
L

L-Alpha-Acetyl-Methadol

Synonyms

LAAM

Definition

LAAM is an opioid drug with limited usage in opioid agonist maintenance therapy. It is a derivative of, and has a similar mode of action to, ► [methadone](#) but has a longer half-life (with two active metabolites) of up to 72 h. Because of a number of adverse events with LAAM, it has been withdrawn from the European and American markets.

Lamotrigine

Definition

Lamotrigine acts on ► [GABA](#) receptors to produce an anticonvulsant action. There are also positive findings in the treatment of bipolar depression. The half-life is around 30 h, and it is metabolized primarily by glucuronic acid conjugation. Serious, potentially life-threatening dermatological adverse events have been reported, albeit very rarely.

Lanreotide

Synonyms

BIM-23014; Somatuline

Definition

Lanreotide is a peptide analogue of SRIF, used to treat acromegaly and tumors in the gastroenteropancreatic tract. Lanreotide has high affinity for sst₂ and sst₅ receptors.

Latent Inhibition

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Synonyms

Stimulus preexposure effect

Definition

Latent inhibition (LI) is demonstrated when a previously exposed, inconsequential stimulus



Impact of Psychoactive Drugs

Since LI is a phenomenon of selective attention whereby organisms ignore stimuli that had been irrelevant in the past, and → attentional deficit is a hallmark cognitive deficit of → schizophrenia (Gray et al. 1991; Lubow 2005; Lubow and Weiner 2010), research examining the effects of psychoactive drugs on LI in rodents has focused primarily on the use of LI as an endophenotype of deficient attentional processing in → schizophrenia for the identification of → antipsychotic, and more recently, procognitive, drug activity (Weiner 2003; Weiner and Arad 2009). The link between LI and → schizophrenia is supported by the presence of LI abnormalities in → schizophrenia patients and high schizotypal persons.

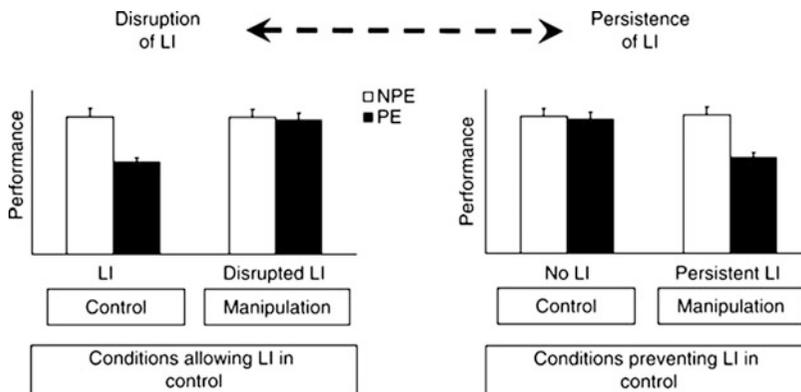
Disrupted and Persistent LI

While drug effects are typically measured as a reduction or an abolition of the target behavior in comparison with its presence in drug nontreated controls, pharmacology of LI has taken a different path from its very inception, focusing on both the disruption and the *induction* of the phenomenon (Weiner 1990, 2003; Weiner and Arad 2009). The latter effect, termed interchangeably LI potentiation, enhancement, or

persistence, is indexed by comparison with the *absence* of LI in drug nontreated controls. Thus, psychoactive drugs can produce two poles of LI abnormality, namely, loss of LI under conditions that lead to LI in normal rats and abnormal persistence of LI under conditions that prevent the expression of LI in normal rats (Fig. 2). It is important to bear in mind that drugs which produce persistent LI *spare* LI under conditions yielding LI in controls. Persistent LI reflects attentional/cognitive inflexibility and thus allows the screening of drugs for their capacity to restore such flexibility, an essential procognitive action (Fig. 2). In addition, pharmacological studies of LI have shown that LI modulation can stem from drug action in the preexposure stage or in the conditioning stage. In addition to unraveling the psychological mechanism by which a given drug affects LI, stage-specific action allows for a refined discrimination between the effects of different drugs.

Models of LI Disruption and Persistence

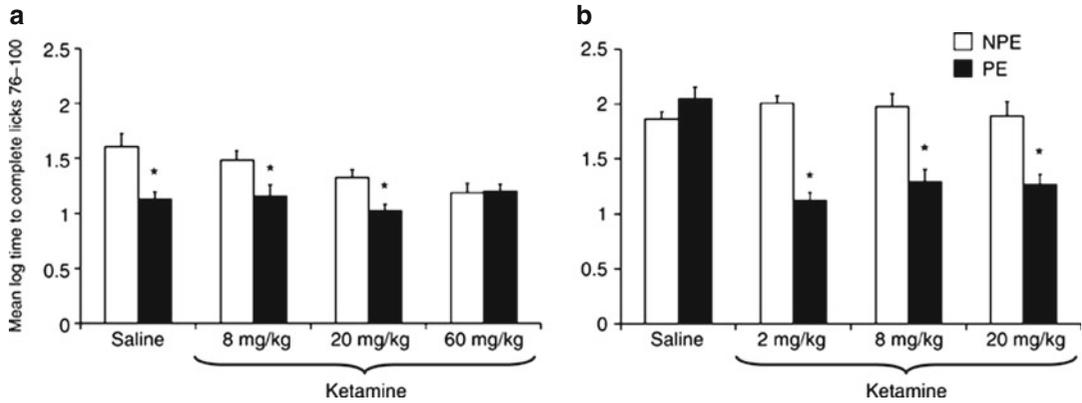
Dopamine (DA) agonists. The notion of a hyperactive dopamine system in schizophrenia is supported by the capacity of the DA releaser, amphetamine, to induce psychosis in healthy humans and exacerbate symptoms as well as



Latent Inhibition, Fig. 2 Two poles of LI abnormality. Based on the view of LI as a window phenomenon, namely, present under very specific and restricted conditions, pharmacological and other manipulations can produce two abnormalities in LI, depending on the status of the phenomenon in control animals: disrupted LI under

conditions yielding LI in controls and persistent LI under conditions preventing the expression of LI in controls. In psychological terms, the former reflects loss of normal ability to ignore irrelevant stimuli, whereas the latter reflects a failure to switch to respond to such stimuli when they become relevant





Latent Inhibition, Fig. 3 Effects of ketamine on LI with weak and strong conditioning. LI was measured in a conditioned emotional response procedure in which rats were either PE to 40 tone presentations or not preexposed (NPE) prior to conditioning with two tone-shock trials (weak conditioning; Fig. 3a) or five tone-shock trials (strong conditioning; Fig. 3b). Time to complete 25 licks in the presence of the tone was used as a measure of fear conditioning to the tone. LI is

manifested in faster times of the PE when compared with the NPE animals. The figures present mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or ketamine. (a) Under conditions yielding LI in vehicle controls, ketamine spared LI at 8 or 20 mg/kg and disrupted LI at 60 mg/kg. (b) Under conditions preventing LI in vehicle controls, ketamine at doses of 2, 8, and 20 mg/kg led to persistent LI

enhance striatal dopamine release in schizophrenia patients. Because amphetamine produces only positive (psychotic) symptoms, amphetamine-induced behavioral abnormalities in animals are considered to model positive symptoms. Consistent with the expectation that the capacity to ignore irrelevant stimuli would be lost in a psychotic-like state, amphetamine disrupts LI in both rodents and humans. Amphetamine-induced LI disruption is due to the drug's action in conditioning stage rather than in preexposure stage, indicating that increased dopamine transmission does not produce a psychotic-like state by increasing stimulus salience but rather by weakening the inhibiting effect of reduced stimulus salience on behavior. Results with repeated amphetamine administration and direct DA agonists are inconsistent.

NMDA antagonists. The hypo-glutamatergic hypothesis of schizophrenia is derived from findings that noncompetitive NMDA antagonists such as phencyclidine (PCP) and ketamine provoke symptoms in human volunteers and exacerbate symptoms in schizophrenia patients as well as abnormalities of glutamate neurotransmission in schizophrenia. Since NMDA antagonists also induce negative symptoms and cognitive

impairments characteristic of endogenous schizophrenia, NMDA antagonist-induced behavioral effects in animals are considered to model negative/cognitive symptoms. Low doses of noncompetitive NMDA antagonists, including PCP, ketamine, and MK801, affect LI in an opposite manner to that of amphetamine, namely, they induce persistent LI (Fig. 3). Importantly, persistent LI is induced by doses of NMDA antagonists that do not produce the well-known deleterious effects of these drugs on associative learning. Higher doses that impair conditioning disrupt LI. NMDA antagonists produce LI persistence via effects in conditioning, indicating that NMDA blockade impairs rats' capacity to switch response based on changed relationships between stimuli and outcomes. The latter is consistent with numerous demonstrations of inflexible behavior following NMDA blockade in rats and humans and supports the relevance of NMDA antagonist-induced persistent LI to cognitive/negative symptoms of schizophrenia, which are characterized by inflexible and perseverative behaviors.

Muscarinic antagonists. Muscarinic antagonists such as scopolamine and atropine induce a

schizophrenia-like syndrome in humans, which includes positive symptoms and cognitive impairments. Recent focus on cognitive impairments in schizophrenia has promoted attention to the cholinergic system because of its well-known role in cognition. Scopolamine can produce both LI disruption and persistence as a function of dose. Low doses of scopolamine disrupt LI via effects at the preexposure stage, whereas high doses induce persistent LI via action in conditioning. Thus, scopolamine mimics both positive and negative/cognitive symptoms by disrupting normal attentional processing, with low doses preventing the development of inattention and high doses producing attentional inflexibility.

Antipsychotics. In rodents, antipsychotic drugs (APDs) are typically investigated for their ability to antagonize the effects of other drugs, but in research concerned with APD effects on LI, their direct influences on LI are also of central importance (Weiner 2003; Weiner and Arad 2009). Specifically, LI in nontreated rodents is used for indexing antipsychotic activity as well as for discriminating between typical and atypical APDs. The former is achieved under conditions of weak or absent LI in controls. Under these conditions, both typical and atypical APDs produce persistent LI via action in conditioning. This effect, produced by a wide range of APDs differing in their *in vivo* and *in vitro* pharmacology, is also obtained in humans and is the most widely used index of antipsychotic action in LI. Although APD-induced LI potentiation is very robust, it does not discriminate between typical and atypical APDs. Such discrimination is manifested under conditions that *produce* LI in controls. Whereas typical APDs do not affect LI, atypical APDs can, depending on the dose and stage of administration, *disrupt* LI. The LI disruptive action of atypical APDs is exerted in the preexposure stage and is likely due to their 5HT_{2A} receptor antagonism. The preexposure-based action of atypical APDs competes with the conditioning-based action of these drugs, so that depending on the dose, atypical APDs can potentiate, spare, or disrupt LI. The latter complexity has critical implications for interpreting the effects of these drugs on LI in animals and

humans as well as for understanding the inconsistencies in their clinical efficacy in general.

In addition, since DA blockade is therapeutic against positive symptoms associated with abnormally increased DA function but is ineffective for and may worsen negative symptoms associated with reduced DA function, dopaminergic blockade-induced persistent LI, as exemplified by haloperidol-induced LI persistence, can model not only alleviation of positive symptoms but also induction of negative symptoms.

Genetic manipulations. In recent years, genetic manipulations increasingly replace pharmacological manipulations to produce schizophrenia-relevant endophenotypes, and both disruption and persistence of LI have been demonstrated using such manipulations (Lipina and Roder 2010). Thus, serotonin transporter knockouts (5-HTT(−/−)) and mice with a point mutation in the DISC1 gene (e.g., Disc1-L100p mutants) show disruption of LI. Conversely, genetic deletion of D1 or D2 dopaminergic receptors and genetic manipulations reducing the activity of the NMDA receptor, including mutations reducing NMDA glycine affinity, deletion or disruption of glycine transporter 1 (GlyT1), or reduction of the glutamate catabolic enzyme glutaminase, produce persistent LI. These results are consistent with pharmacological data, further strengthening the neurobiological validity of the two LI abnormalities and their relevance to schizophrenia.

Reversal of Disrupted and Persistent LI

The four schizophrenia-relevant aberrations of LI, i.e., those induced by amphetamine, NMDA antagonists, and low- and high-dose scopolamine, have been tested with typical and atypical antipsychotics to assess the predictive validity of these models for the identification of clinical treatments for schizophrenia (Weiner and Arad 2009). In recent years, new therapeutic strategies for schizophrenia, considered/hoped to improve negative symptoms and cognitive dysfunction, have emerged. These strategies include, among others, enhancement of NMDA transmission via the glycine B modulatory site on the NMDAR, either directly by agonists such as glycine

Latent Inhibition, Table 1 Summary of representative antipsychotic and other putative treatments tested against models of disrupted and persistent LI

| Model drug | Disrupted LI | | Persistent LI | | |
|------------------------------|----------------|----------|---------------|-----------|-------------|
| | Low amph | Low scop | Low MK801 | High scop | Haloperidol |
| Haloperidol | + | + | — | — | |
| Clozapine | + | + | + | — | + |
| Glycine | + ^a | + | + | + | — |
| Physostigmine | — | + | + | + | — |
| $\alpha 7$ nicotinic agonist | + | ? | + | ? | ? |

+ effective, — ineffective, ? unknown. [COND] acts via conditioning stage, [PREEX] acts via preexposure stage

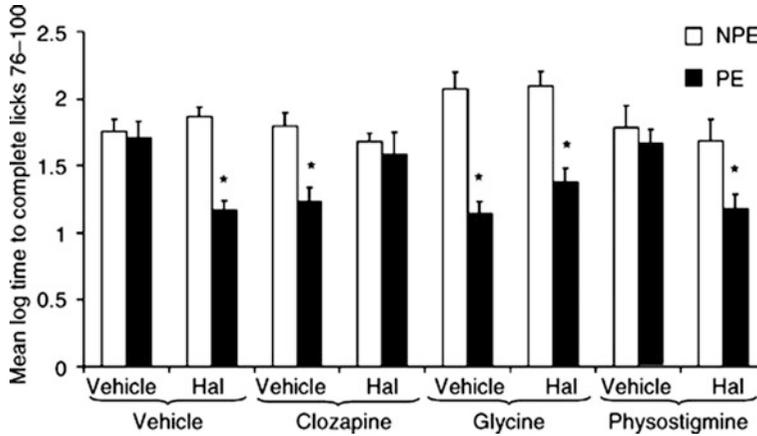
^aThe active compound is Glyt1 inhibitor SSR103800

transporter and D-serine or indirectly by inhibiting the glycine transporter (GlyT1), and enhancement of cholinergic transmission using acetylcholinesterase inhibitors such as physostigmine, muscarinic agonists such as xanomeline, and alpha-7 nicotinic receptor agonists. Table 1 summarizes the distinct responses of five LI models (including haloperidol-induced LI persistence) to typical and atypical APDs, NMDA function enhancers, and cholinergic function enhancers.

Amphetamine- and low scopolamine-induced disrupted LI. Amphetamine- and low scopolamine-induced disrupted LIs, although reflecting distinct psychological processes, are reversed by both typical and atypical APDs as well as by glycinergic enhancers. Intriguingly, genetic deletion of D1, but not D2 dopaminergic receptor, attenuates amphetamine-induced LI disruption. Scopolamine-induced, but not amphetamine-induced, LI disruption is reversed by physostigmine. *MK801-induced persistent LI* is reversed by atypical APDs (e.g., clozapine and risperidone) but not by typical APDs, as found with other NMDA antagonist-induced behavioral deficits and in line with the differential efficacy of typical and atypical APDs in the clinic. MK801-induced persistent LI is also reversed by a wide range of compounds that potentiate NMDA transmission including glycine, D-serine, D-cycloserine (DCS), and GlyT1 inhibitors GDA and ALX5407, and the novel GlyT1 inhibitors SSR103800 and SSR504734. Importantly, MK801 is the only model that discriminates between atypical APDs and

glycinergic compounds as the former reverse this abnormality via effects at preexposure and the latter via effects in conditioning. Finally, the novel alpha7 nicotinic acetylcholine receptor partial agonist SSR180711 (4-bromophenyl-1,4-diazabicyclo(3.2.2)nonane-4-carboxylate-hydrochloride) and the cannabinoid CB1 receptor antagonist AVE1625 are also effective in this model. *Scopolamine-induced persistent LI* is reversed by physostigmine and xanomeline, as well as glycinergic enhancers, but is resistant to both haloperidol and clozapine. While the inefficacy of haloperidol is expected based on its ineffectiveness in models of negative/cognitive symptoms including MK801-induced persistent LI, the inefficacy of clozapine is unexpected and sets this abnormality apart from MK801-induced as well as all other known instances of drug-induced LI persistence. *Haloperidol-induced persistent LI* is reversed by atypical APD clozapine and risperidone but is resistant to glycine and physostigmine (Fig. 4). In addition, haloperidol-induced persistent LI is the only persistent LI that is alleviated by amphetamine, like negative symptoms in the clinic.

Reversal of abnormal LI in mutants. LI disruption in Disc1-L100p mutants is reversed by haloperidol and clozapine as well as inactivation of glycogen synthase kinase-3 (GSK-3). Abnormally persistent LI in Grin1(D481N) mice with reduced NMDA affinity is reversed by glycinergic NMDA enhancers, and by clozapine, further supporting the mechanistic similarity between pharmacological and genetic manipulations.



Latent Inhibition, Fig. 4 Effects of clozapine, glycine, or physostigmine on haloperidol-induced persistent LI. Mean times (logarithmically transformed) to complete 25 licks in the presence of the tone of PE and NPE rats treated with vehicle or haloperidol (*hal*) and pretreated with clozapine (5 mg/kg), glycine (800 mg/kg), or

physostigmine (0.15 mg/kg). No LI was evident in the vehicle control but there was LI in rats treated with haloperidol. Haloperidol-induced persistent LI was antagonized only by clozapine. Clozapine and glycine but not physostigmine led to LI persistence in vehicle-treated rats

Latent Inhibition, Table 2 Five pharmacological LI models proposed to model five domains of pathology of schizophrenia

| Model pharmacological response | Disrupted LI | | Persistent LI | | |
|--------------------------------|--|--|---------------------------|------------------------------------|---------------------|
| | Amphetamine | Scopolamine | Scopolamine | MK801 | Haloperidol |
| Reversed by | Typical and atypical APDs and some cognitive enhancers | Typical and atypical APDs; cognitive enhancers | Cognitive enhancers | Atypical APDs; cognitive enhancers | Atypical APDs |
| Resistant to | Some cognitive enhancers | | Typical and atypical APDs | Typical APDs | Cognitive enhancers |
| Symptom domain | Positive | | Cognitive | Negative/cognitive | Negative |

Using Pharmacology of Disrupted and Persistent LI to Model Domains of Pathology in Schizophrenia

Disrupted and persistent LI can be seen as two poles of dysfunctional attentional control, namely, a failure to inhibit attention to irrelevant stimuli and a failure to redeploy attention when previously irrelevant stimuli become relevant. The former would likely give rise to the aberrantly increased salience perception and distractibility/attentional overshooting that are associated with psychotic symptoms, whereas the latter would result in the cognitive inflexibility and impaired attentional shifting that are associated with negative/cognitive

symptoms. Indeed, both disrupted and excessively strong LI are found in schizophrenia patients, the former associated with acute psychosis and the latter associated with predominance of negative symptoms.

Based on their distinct pharmacological profiles, LI abnormalities produced by amphetamine, haloperidol, NMDA antagonists, and scopolamine can be seen as representing four domains of pathology in schizophrenia (Table 2; Barak and Weiner 2011). *Amphetamine- and scopolamine-induced disrupted LI* represents the domain of positive symptoms, the only domain responsive to both typical and atypical APDs.

Notably, disrupted LI is responsive to APDs irrespective of the manipulations used to induce disruption and the mechanisms underlying the disruption. *NMDA antagonist-induced persistent LI* represents a (hypoglutamatergia-driven) domain of negative/cognitive symptoms that respond to atypical APDs and cognitive enhancers but not to typical APDs. *Scopolamine-induced persistent LI* represents a domain of cognitive impairments that are resistant to APDs. This model may have utility in identifying effective treatments for APD-resistant cognitive impairments in schizophrenia. However, given its insensitivity to APDs, the model is likely to represent a class of behavioral inflexibility that is common to a variety of neuropsychiatric disorders, including Parkinson's disease (PD) and obsessive compulsive disorder (OCD). Indeed, both PD and OCD patients display abnormally enhanced LI. Finally, *haloperidol-induced persistent LI* represents a domain of (hypodopaminergia-driven) negative symptoms that are treatable by atypical antipsychotics but are resistant to cognitive enhancers. This abnormality may represent a class of cognitive/behavioral inflexibility that is selective to schizophrenia. The domain-specific LI model fits the currently advocated directions of psychiatric drug development, which uses polypharmacy strategies, with independent therapeutic agents for different, intra- or transdiagnostic domains of pathology.

Cross-References

- ▶ [Acetylcholinesterase and Cognitive Enhancement](#)
- ▶ [Amphetamine](#)
- ▶ [Classification of Psychoactive Drugs](#)
- ▶ [Attention](#)
- ▶ [Cognitive Enhancers: Role of the Glutamate System](#)
- ▶ [Excitatory Amino Acids and their Antagonists](#)
- ▶ [Muscarinic Cholinergic Receptor Agonists and Antagonists](#)
- ▶ [Nicotinic Agonists and Antagonists](#)
- ▶ [Schizophrenia](#)
- ▶ [Schizophrenia: Animal Models](#)

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Latin Square Design

Definition

A systematic way of controlling the order of administration of treatments within a test session and of balancing treatments between repeated test sessions. The design enables the uncontrollable effects of unexpected events to be distributed evenly between the treatment conditions.



Laxatives

Definition

Drugs taken to induce bowel movements or to loosen the stool, most often used to treat constipation.

Leadén Paralysis

Definition

A feature of atypical depression, leadén paralysis refers to severe fatigue creating a sensation of extreme heaviness of the arms or legs.

Learned Helplessness

Definition

First described by Seligman and colleagues in the 1970s, learned helplessness describes the impairment of learning that follows exposure to uncontrollable stress. The term “learned helplessness” implies that animals learn that they are helpless to control their environment. In the “yoked control” design, two groups of animals receive the identical pattern and intensity of stress, typically footshocks, but in one group the stress is controllable, while in the other group (the yoked controls), it is not. Typically, behavioral deficits are seen only in the “yoked control” group, for which the stress is uncontrollable.

Cross-References

► [Animal Models for Psychiatric States](#)

Learning

Definition

In its broadest sense, the fact or process of change that occurs in the relationship between a stimulus and a response as a result of experience. Also referred to as acquisition. The “black box” that relates the stimulus to the response usually refers to a whole organism but may also refer to part thereof or to an isolated biological system. Learning concerns cognitive but also sensory, motor, emotional, and mood-related life events or items.

Learning and Memory: Molecular Mechanisms

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Definition

Alterations in gene expression have been proposed to underlie key aspects of learning and memory in diverse systems. The mechanisms by which behavioral experiences, via alterations in synaptic transmission, induce changes in gene expression in specific brain regions are reviewed. Such mechanisms include alterations at the level of chromatin structure, which might be expected to mediate particularly long-lasting adaptations. There are many examples of psychotropic drugs that regulate learning and memory via their effects on gene expression.

Impact of Psychoactive Drugs

The ability of an organism to learn and remember, sometimes for extended periods of time, indicates that environmental experience can induce long-lasting changes in the brain. The nature of these changes, at the molecular and

cellular levels, has accordingly been intensively studied for several decades. This work has provided an impressive appreciation of the types of adaptations that occur in the brain in association with many types of learning and memory. It also has been possible to directly demonstrate the importance of a given molecular or cellular mechanism in mediating a particular aspect of learning and memory. However, despite these important gains, we still know relatively little about how these molecular and cellular adaptations actually summate to create a behavioral memory or enable its long-term storage and retrieval. This latter level of understanding, which represents perhaps the greatest remaining challenge in the neurosciences, requires a neural circuit level of analysis that is not yet available.

This entry provides a brief overview of the types of molecular and cellular adaptations in the brain that have been implicated in learning and memory and focuses on changes achieved at the level of gene expression or gene transcription, which have been thought for over a decade to provide the long-lasting mechanisms underlying stable behavioral change.

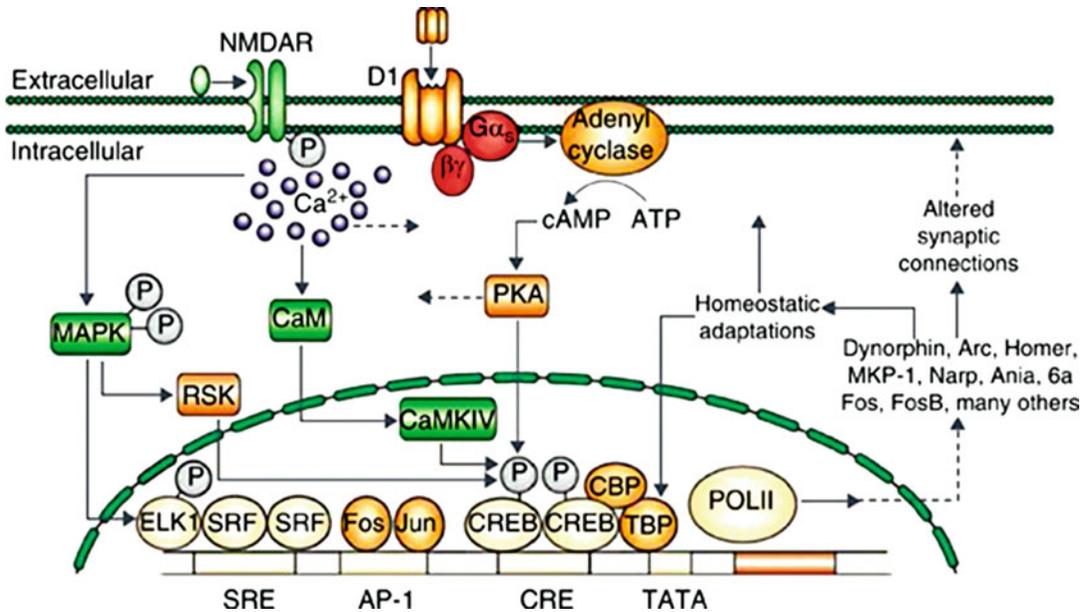
From Synapse to Nucleus

Synaptic transmission is best understood as the effects that a neurotransmitter, released by one nerve cell, exerts on a second nerve cell by virtue of its binding to a specific receptor. The activation of a receptor by its neurotransmitter triggers chemical changes inside the second nerve cell that alter its electrical activity. This occurs on the timescale of milliseconds to seconds. Operating on a much slower timescale, on the order of minutes to hours, are more complex chemical changes triggered by that very same neurotransmitter-receptor interaction. Thus, in addition to regulating ion channels, such interactions initiate cascades of chemical changes that eventually signal to the nerve cell's nucleus, where changes in gene expression – alterations in the amounts and types of proteins expressed by that cell – are induced. For example, synaptic transmission can alter the levels of ion channels or receptors expressed by a nerve cell. Consequently, at some later time point, when the first

nerve cell again releases neurotransmitter onto that second nerve cell, the second nerve cell shows an altered response due to these changes in gene expression. This represents a unit of “molecular memory.” Somehow, by summing these changes across the trillions of synapses in the brain and integrating them over time, an organism learns and remembers and thereby adapts and responds to its environment.

We now know a great deal about the mechanisms by which synaptic transmission alters gene expression. The most important mechanism involves the activation of a class of proteins termed transcription factors (TFs), which bind to regulatory regions (called promoters) of specific genes and thereby increase or decrease the rate by which those genes are expressed. Hundreds of TFs are known, which exhibit three general mechanisms for their activation by synaptic transmission. Some TFs, expressed in nerve cells under basal conditions, are activated by cascades of second messenger and protein phosphorylation pathways that are stimulated (or inhibited) when neurotransmitters bind to their receptors. A prototypical example is CREB (cAMP response element-binding protein), which can be phosphorylated and activated by a wide range of second messenger cascades illustrated in Fig. 1. For example, in the striatum, dopamine (via the activation of the cAMP pathway) and glutamate (via the activation of Ca^{2+} pathways) activate several different protein kinases, each of which phosphorylates CREB on the same serine residue, resulting in the activation of its transcriptional properties. The TFs Elk1 and SRF (serum response factor) are regulated via similar mechanisms (Fig. 1). A related mechanism exists for another TF, termed NF- κ B (nuclear factor- κ B). At baseline, NF- κ B is bound to an inhibitor protein, I- κ B (inhibitor of κ B), which sequesters NF- κ B in the cytoplasm. Upon the activation of certain second messenger cascades, I- κ B is phosphorylated, leading to its degradation and the freeing up of NF- κ B to enter the nucleus where it exerts its transcriptional effects.

Other TFs are expressed at very low levels under normal conditions but are induced in



Learning and Memory: Molecular Mechanisms, Fig. 1 Regulation of CREB activity in the striatum. Stimulation of D1 dopamine receptors and glutamate receptors on striatal neurons activates several second messenger cascades. Not shown is the ability of several growth factor-associated receptors to stimulate some of the same cascades, for example, MAPK. Depicted in the cell nucleus is a model of binding sites from the c-Fos

promoter including a serum response element (*SRE*), activator protein-1 (*AP-1*) element, and a cyclic AMP (*cAMP*) response element (*CRE*). *CBP* CREB-binding protein, *CREB* cAMP response element-binding protein, *MAPK* MAP kinase, *NMDAR* NMDA receptor, *PKA* protein kinase A, *TBP* TATA-binding protein (From McClung and Nestler 2008)

nerve cells in response to neurotransmitter-receptor interactions. Examples include Fos (e.g., c-Fos, FosB) and Egr (early growth response) families of TFs. These TFs are induced because their promoter regions contain target sites for preexisting TFs such as CREB and SRF (see Fig. 1).

The third paradigm of TF activation operates for the steroid hormone receptor family of proteins (also called the nuclear receptor family), which are activated upon binding their respective hormone (e.g., glucocorticoids, gonadal steroids, etc.) and can therefore be viewed as ligand-activated TFs. Under basal conditions, steroid hormone receptors are bound by chaperone proteins which keep them in the cytoplasm. Steroid hormones, which readily permeate cell membranes, bind to the receptors and trigger their release from the chaperones and their movement to the nucleus. Once in the nucleus, the steroid

receptors bind directly to responsive genes or bind to and inhibit other TFs (e.g., CREB, c-Fos).

An important principle of TF action is that most bind to DNA as dimers. Some bind as homodimers (e.g., CREB), whereas others must complex with distinct families of TFs: Elk1 dimerizes with SRF, Fos family proteins dimerize with Jun family proteins (to form an AP-1 (activator protein-1) complex), and so on. Together, this results in a highly complex array of transcriptional regulation during the normal process of synaptic transmission.

Implicating TFs in Learning and Memory

An important role for all of the aforementioned TFs, and many others, in diverse types of learning and memory has been established over the past decade. Investigators have demonstrated the activation of specific TFs in a given brain region in response to an environmental challenge in tight

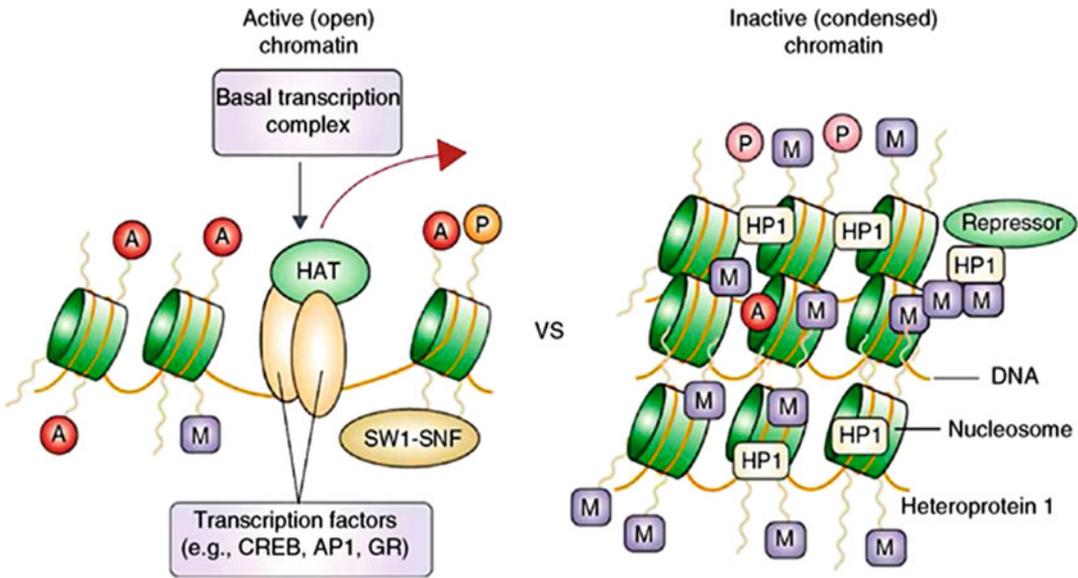
temporal correlation with a form of behavioral plasticity. Examples include the phosphorylation and activation of CREB and the induction of c-Fos and Egr, in the hippocampus and amygdala in parallel to aversive learning (e.g., fear conditioning), in some cases in parallel to a specific facet of aversive learning such as acquisition, consolidation, or extinction, among others. Likewise, exposure to a drug of abuse activates each of these TFs in drug-responsive regions (e.g., striatum, amygdala, prefrontal cortex), and such activation has been correlated with different aspects of drug-induced plasticity, such as locomotor sensitization, reward tolerance, or sensitization. An interesting variation in this theme is the induction of Δ FosB, a truncated splice variant of the *fosB* gene, uniquely by chronic drug exposure. Δ FosB, normally present at very low levels in nerve cells, is induced via CREB and SRF, but unlike all other Fos family members (which are highly unstable and therefore degrade to low basal levels shortly after the stimulus), Δ FosB is highly stable which enables it to accumulate to high levels in response to chronic stimuli. In this way, Δ FosB could mediate some of the longer-lasting effects of drug exposure on behavior.

The second key step in implicating a TF in learning and memory is to manipulate that TF and demonstrate an effect on behavior. This causal information came initially from gene knockout studies, where deletion of CREB or another TF of interest was shown to obliterate an aspect of learning and memory. However, the interpretability of these early experiments was limited by the fact that the TF was knocked out from all brain regions (indeed all tissues) from the earliest stages of development, making it difficult to conclude that the TF was required in a given brain region of an adult. Such limitations have been overcome in recent years with the advent of powerful genetic and viral tools, where a TF of interest – or an inhibitor (sometimes referred to as a dominant-negative antagonist) – can be overexpressed in a given brain region of an adult animal or can be knocked out selectively from that region of an adult animal. Such methods have greatly strengthened the level of proof for a TF's role in learning in memory.

Overexpression of CREB specifically in the hippocampus or amygdala promotes aversive learning, while overexpression of a CREB antagonist has the opposite effects. Likewise, CREB overexpression in the striatum dampens an animal's sensitivity to the rewarding effects of a drug of abuse, with a CREB antagonist having the opposite effect. These latter data support the hypothesis that CREB induction by drugs of abuse represents a homeostatic mechanism mediating tolerance and dependence. Conversely, Δ FosB overexpression in the striatum increases the rewarding effects of a drug of abuse, while its antagonist reduces drug reward, supporting the notion that Δ FosB induction represents a mechanism of sensitization.

From TF to Chromatin

In recent years, analyzing transcriptional mechanisms in the brain has been extended to chromatin structure, where the covalent modification (e.g., acetylation or methylation) of histone proteins, around which DNA is wound in the cell nucleus, and methylation of the DNA itself have profound effects on the ability of genes to be expressed. Chromatin exists in a continuum from a permanently inhibited (closed) state to a constitutively active (open) state (Fig. 2). Genes in closed chromatin are not expressed because they are not accessible to the cell's transcriptional machinery, whereas other genes exist in permissive chromatin where the genes are accessible to transcriptional machinery. This explains, for example, why CREB cannot induce neural gene targets in peripheral tissues where the genes exist in silenced chromatin, but can in nerve cells where the genes exist in permissive chromatin. TFs induce genes in permissive chromatin by recruiting to those genes many types of coactivator proteins. TFs recruit histone acetyltransferases, enzymes that acetylate histones; such acetylation further opens the chromatin. TFs also recruit many types of chromatin-remodeling proteins, such as the so-called SWI-SNF factors, proteins that provide the molecular motor for histones to move across a strand of DNA as it is being actively transcribed.



Learning and Memory: Molecular Mechanisms, Fig. 2 Differential states of chromatin. Chromatin exists in a continuum of states from being open (i.e., active, allowing gene expression) to condensed (i.e., inactive, repressing gene expression). Changes across this continuum are mediated in part by modifications to core histone proteins. Histone acetylation (A) is associated with chromatin relaxation and the binding of TFs and coactivators,

such as *HATs* (histone acetyltransferases) and SWI-SNF proteins that mediate the movement of histone complexes along a strand of DNA. Histone methylation (M) at certain sites results in condensed chromatin and transcriptional repression (*REP*). Methylation of the DNA itself also generally results in condensed, repressed chromatin (From McClung and Nestler 2008)

This knowledge of chromatin biology has now begun to inform our understanding of gene expression regulation in the brain and, in particular, its role in learning and memory. First, changes in histone acetylation and methylation and in DNA methylation have been shown to occur in the hippocampus in parallel to aversive learning. These findings are striking because they emphasize the degree to which fundamental mechanisms of gene regulation are affected during the course of normal synaptic transmission – on a timescale of hours. Similar changes in chromatin have been demonstrated in the striatum in response to drugs of abuse. Second, it has been possible to directly implicate the mechanisms of chromatin regulation in aversive learning and drug addiction by demonstrating that direct manipulations of histone or DNA modifications have profound effects on behavior. Inhibitors of histone deacetylases (enzymes that remove acetyl groups from

histones and thereby inhibit gene expression) or of DNA methyltransferases (enzymes that add methyl groups to DNA and thereby inhibit gene expression) promote hippocampal-dependent memory as well as the rewarding effects of drugs of abuse. In contrast, overexpression of these inhibitory enzymes in specific brain regions exerts the opposite effects. A similar important role for histone methyltransferases (enzymes that add methyl groups to histones and thereby activate or inhibit gene expression depending on the site undergoing methylation) in learning and memory phenomena has also been established.

The Future

One of the major challenges of current research is to identify the target genes through which a given TF exerts its particular effects on behavioral plasticity. Small numbers of target genes have been identified for all of the TFs mentioned above;

however, some TFs may regulate hundreds of targets. This has been demonstrated by the use of gene expression arrays and more recently of RNA-seq (sequencing) (which measure levels of all mRNAs in a tissue) and ChIP (chromatin immunoprecipitation)-chip or ChIP-eq methods (which measure levels of chromatin modifications across the entire genome). Understanding how the coordinated regulation of such large numbers of genes summates to produce the net functional effects of a TF and how the effects of multiple TFs are summated remains a great technical challenge.

Ultimately, it is essential to define the many ways in which brain function is altered by transcriptional and chromatin regulation to mediate the behavioral plasticity associated with learning and memory. In addition to altering levels of ion channels and neurotransmitter receptors and many related second messenger proteins, as stated at the outset, there is increasing evidence that environmental experience produces more profound changes in nerve cells, including alterations in their overall size and shape and the extent of their dendritic arborizations and synaptic inputs. Work is beginning to define the changes in gene expression and the specific TFs and chromatin-modifying enzymes that underlie this long-lasting reordering of nerve cells. As we build this increasingly complete view of molecular and cellular changes that occur in concert with behavioral plasticity, it is essential to then understand at a circuit level how such changes mediate behavioral memory.

Cross-References

- ▶ [Addictive Disorder: Animal Models](#)
- ▶ [Chromatin Remodeling](#)
- ▶ [Gene Expression, Gene Transcription](#)
- ▶ [Long-Term Depression and Memory](#)
- ▶ [Long-Term Potentiation and Memory](#)
- ▶ [Spatial Learning in Animals](#)
- ▶ [Synaptic Plasticity](#)

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Learning Set

Definition

A learning set (and the closely related concept, task set) is present when a learned rule is generalized so that there is facilitation of learning a new discrimination or task; it occurs when a previously learned rule or principle applies to the new situation (see Harlow 1949). There is a corresponding impairment of new learning when a previously

learned rule or principle does not apply, as exemplified by the “Einstellung effect” (Luchins 1942).

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Legal Aspects of Psychopharmacology

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Synonyms

Allowable; Constitutional; Lawful; Legitimate (aspects of psychopharmacology)

Definition

“Legal” as a topic means falling within the province of the law and its study. It also has the more specific connotation of such as is required by the law and not falling outside what is permitted.

Current Concepts and State of Knowledge

Introduction

Human societies are governed by social rules that moderate our basic biological instincts. Moreover, such social rules reflect moral and ethical principles (Harris 2002). These social institutions and conventions are governed by the rules of law. These can be complex, with codes of law extending to numerous tomes, written in technical legal language. In a complex society, it is almost impossible to find any human activity that is not touched in some way by the law.

Psychopharmacology, a branch of science that involves the activities of the most complex human organ, the brain, is particularly affected by rules, regulations, and the panoply of the law. Both criminal and civil laws contain swathes of material directly relevant to psychopharmacology. Rules of law may forbid certain activities or specify certain conditions that must be carried out. Rules are normative (what ought to happen), rather than factual (what actually does happen). Laws lay down rules of behavior to which we are expected to conform. If we do not, the law can apply sanctions, ranging from a censure, a fine, or restriction of liberty, right through to the death penalty, still imposed in a minority of countries.

Durkheim (1964) regarded society as ranging from relatively simple, technologically undeveloped aggregates of people to advanced, mobile, sophisticated social structures. The purpose of laws was to maintain social cohesion by striving for an equitable balance between competing ideas and interests. If members of a group perceive a law as failing to recognize a strongly held belief, they may in desperation adopt extra-legal measures, as evidenced, for example, by some animal rights activists or those opposed to genetically modified crops.

Legislation to Morality

This raises the question of the complex relationship between the law and views of morality. A society’s code of morality is the set of beliefs, values, principles, and standards of behavior adhered to by most members of the society. In a homogeneous society, the set of morals tends to be fairly consensual. In a multicultural society, moral values may differ greatly and even conflict. To accommodate these disparate views, the law which formalizes such moral principles may have to introduce special cases, exemptions, and exceptions. Even so, some members of the society may feel unable to abide by the law, as, for example, in the case of individuals who believe that human embryo research clashes with the imperatives of their religious tenets.

One cardinal example in psychopharmacology concerns the complex laws relating to the use of

probably the oldest of psychotropic substances, alcohol. Laws outlawing alcohol in the USA (“Prohibition”) were in response to pressures from those in society who took the moral high ground after the First World War. These groups were organized into religious and temperance organizations that emphasized both the moral shortcomings of heavy drinking and its medical and social toll. The moral disadvantages and legal injustice of penalizing moderate and occasional social drinkers were submerged under the tsunami of moral temperance rectitude. The Prohibition Laws failed because they were too draconian, and large numbers of US citizens flouted them without considering themselves to be criminals. But, in many countries, achieving a just balance in the licensing of alcohol still remains a distant objective, viz., binge drinking in the United Kingdom.

Legal Instruments

It is impossible to even outline the different forms of jurisdiction. Most European countries rely on systems of law based on the Roman model and codified by Napoleon. The United States and England (but not Scotland) use a common law system, in which judges interpret and modify legislation. Some countries maintain tight central control; others devolve to the periphery. Some have both, such as Federal and State laws in the United States, the relationship between which is being constantly adjusted. In some countries, religious law such as sharia is paramount; in others it exists in parallel and may be resorted to by religiously observant people. In the European community, national laws have yielded precedence to EC laws, regulations, and directives. International courts with supranational jurisdictions, such as those in The Hague, have become increasingly recognized.

Research

Legal systems, under pressure from animal rights activists, have long introduced measures to regulate the treatment of animals. As these activists vary in their attitudes from country to country, so do the regulations. Many countries have a set of rules rather than guidelines. In some, registration

of laboratories, projects, and individual experimenters is required. Particular stringency is often applied to studies on primates. Research using the Great Apes may be prohibited altogether, as may that on species deemed at risk of extinction even if they are not primates (► [Ethical Issues in Animal Psychopharmacology](#)).

In the human sphere, a series of declarations followed the unspeakably abhorrent practices of the Nazis. The Declaration of Helsinki (1964) states that, “It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.” Ethical committees were set up, in the USA and then in other countries, to regulate human research, first voluntarily but increasingly under statute (► [Ethical Issues in Human Psychopharmacology](#)). Considering a detailed protocol provided by the investigators, a properly constituted ethical committee containing both professional and lay members reviews the proposal, modifies it if necessary, and ensures that it is adhered to. Such committees have a special (fiduciary) duty to act properly and responsibly. Any researcher failing to submit an appropriate protocol could, depending on the jurisdiction, be subject to the criminal code for inflicting bodily harm or to financial redress under the civil code for causing a personal injury (“tort”) or expulsion from the relevant professional body. With psychotropic drugs, psychological harm could be the basis for a court action (Carson and Bull 2003).

Informed consent is typically a sine qua non for the recruitment of experimental subjects. This entails that each potential participant be adequately informed of the purpose of the study, its methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researchers, the expected risks and potential benefits of the study, and the anticipated discomfort. The presence of a neutral witness is a useful safeguard. The volunteer should be informed of the right to withdraw from the study at any time without explanation. The investigator and the independent witness must be sure that the potential subject has understood the information and has been encouraged to ask questions. Consent should be in writing wherever possible.



Special rules generally pertain to subjects who suffer from a severe psychiatric disorder or lack mental capacity to give informed consent and to children. Recently, the question of genetic privacy has been raising concern.

Two European directives, Clinical Trials Directive (2001) and Good Clinical Practice (2005), initiated changes in medical research procedures across Europe to varying extents (Brazier and Cave 2007). A directive sets out the broad goals of the legislation but allows each EU country to determine the form and precise content of that legislation (► [Randomized Clinical Trials](#)).

Therapeutics

It is a truism that each administration of a therapeutic substance is essentially an experiment. If that usage in a patient is grossly negligent, criminal proceedings may follow. If it falls short of that, then the injured party generally has to show that the drug administration was below acceptable clinical standards and that it caused an injury that can be assessed, at least in financial terms (“quantum of damage”). Standard rates are applied to gross physical injuries such as an amputation, but psychological or psychiatric damage is difficult to quantify. Often, the functional impairments are evaluated, as well as symptomatic complaints.

Psychotropic drugs may be associated with some special considerations. First, in psychiatric clinical practice, a treatment may be administered compulsorily: stringent safeguards are essential. Second, some medications have a low therapeutic index and must be monitored according to stringent specified protocols (e.g., lithium salts, clozapine).

No consensus exists between various jurisdictions with respect to topics such as withdrawal syndromes, neuroleptic malignant syndrome, and tardive dyskinesia. Currently, much concern is being expressed with regard to suicidal phenomena with selective serotonin reuptake inhibitors (SSRIs), especially in adolescents, for whom evidence for efficacy is often scanty. Another area of concern is the widespread use of antipsychotic medication in people with dementia (Banerjee 2009).

In most jurisdictions, the development of an adverse effect, ipso facto, does not constitute a basis for action as long as the drug was administered in accord with accepted clinical standards. These can change over time, and regulatory bodies may suggest different practices. Prescribers must be aware of the latest developments and even trends.

Regulatory Affairs

How medicines are developed and licensed is dealt with elsewhere (“Licensing and Regulation of Drugs”). Randomized clinical trials raise particular concerns.

Consumer Protection

Various jurisdictions (including the EU) have brought in legislation to protect consumers from defective products – those that are unfit for purpose or those that are not of a quality that a reasonable consumer has a right to expect. Medicinal products are usually subject to such control. A group of consumers who believe that a product is defective and that they have suffered from using the product may bring an action and may subsequently recover damages. The manufacturer’s usual defense is to try and prove that the product is not defective or that scientific knowledge at the relevant time was not sufficiently developed for a reasonable manufacturer to have been able to detect the defect.

Misuse of Drugs

One area where psychopharmacology is closely involved with the law is in the area of drug misuse. This can relate to drugs which have no official recognized therapeutic properties, such as LSD, and therefore whose use can only be a misuse, or to products that have a licit indication, such as morphine, but can be misused (Glaser and Warren 1999). A controversy attends the use of cannabis products, where some products have been licensed in some countries to establish a legitimate therapeutic usage in pain and nausea.

Jurisdictions differ widely in both the form and content of the illicit drug “scheduling”

legislation. The classification of drugs of dependence is usually into several categories, and maximum penalties for use, possession, and supply vary according to the category. For example, sanctions, often severe, are imposed with respect to heroin and cocaine; at the other end of the spectrum, penalties are minimal with benzodiazepines, which may not even be scheduled in some countries. Cannabis is controversial and debates continue as to how it should be classified. Chemical precursors and intermediates can be scheduled. The proliferation of synthetic compounds with psychoactive properties is presenting an increasing challenge to authorities, both national and international.

The available penalties cover a range of unlawful activities – producing a controlled/scheduled drug, supplying or offering to supply one to another person, possessing a controlled/scheduled drug, and, in some countries, cultivating any plant of the opium or cannabis type. Exemption is available for legitimate purposes, for example, the manufacturers of morphine, the pharmacists who store and supply it, and the medical, dental, and veterinary practitioners who prescribe and administer it. Special dispensations for research purposes can be applied for but are often notoriously difficult to facilitate. Most jurisdictions lay down strict rules for safe custody.

The misuse of controlled drugs is further regulated in various ways. In professional circles, the prescription of a controlled drug usually has to follow a strictly applied proforma, and careful records are mandatory. Addicts may have to be reported to a government department or agency. Some controlled drugs such as heroin can only be prescribed by specially recognized doctors. Irresponsible prescribing is penalized.

Various crimes are established under legislation and involve the criminal law system, police, judges, the prison system, and customs and excise departments. Much of this is governed by the Single Convention on Narcotic Drugs signed in New York on March 30, 1961, and by the 1971 Convention covering drugs more widely. Searches of individuals, possessions, and premises can usually be authorized.

Sales Outlets

Jurisdictions generally recognize various ways by which medicinal products can be provided (Appelbe and Wingfield 2005). The most restricted is a prescription-only medicine, prescribed by a recognized medical, dental, or veterinary practitioner. The least restricted is a general sale medicine which can be sold in shops and supermarkets. Some countries have an intermediate category of drugs which are available without prescription under the supervision of a pharmacist.

Many remedies are “alternative,” the most widely used being herbal and homeopathic compounds. Countries vary enormously with respect to whether or how these are regulated. Finally, concoctions that are used as folk remedies are rarely encountered in legal systems unless poisonous effects are produced. Alternative medicines may also raise problems with toxic constituents (► [Herbal Remedies](#)).

Alcohol is also subject to regulation. The Scandinavian countries are typically the most stringent. Some states in the United States are also quite restrictive. The minimum age for purchasing and drinking alcoholic beverages may be 21, and the bottles containing alcohol cannot be openly displayed.

Cross-References

- [Ethical Issues in Animal Psychopharmacology](#)
- [Ethical Issues in Human Psychopharmacology](#)
- [Herbal Remedies](#)
- [Randomized Controlled Trials](#)

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Leptin

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Synonyms

OB protein

Definition

A hormone produced in and secreted primarily by adipose tissue that regulates appetite, body weight, and neuroendocrine functions.

Pharmacological Properties

History

The hormone leptin was discovered in 1994; its name is derived from the Greek word for thin, *leptos*. Like other hormones, leptin is secreted in a pulsatile manner and shows a diurnal variation with a peak during the night. Lack of leptin signaling due to a mutation of *leptin* (e.g., *ob/ob* mouse) or the leptin receptor (*lepr*) (e.g., *db/db* mouse) in rodents and humans results in increased food intake, reduced energy expenditure, and severe obesity.

Mechanisms of Action

Leptin has been implicated in activating a variety of intracellular signaling cascades primarily

through one isoform of the leptin receptor, LepR or ObR. The LepR contains a single transmembrane domain and is structurally similar to the class 1 cytokine receptor family. There are multiple LepR isoforms, all of which are products of a single *lepr* gene containing 17 common exons and several alternatively spliced 3' exons. In mice, the six distinct LepR isoforms that have been identified are designated LepRa–LepRf. LepR isoforms can be divided into three classes: secreted, short, and long forms. The secreted form (LepRe) contains only extracellular domains that bind circulating leptin, perhaps regulating the concentration of free leptin. Short forms (LepRa, LepRc, LepRd, and LepRf) and the long form LepR (LepRb in mice) have identical extracellular and transmembrane domains as well as the same first 29 intracellular amino acids, but diverge in sequence thereafter due to the alternative splicing of exons. Unlike the other LepR isoforms, the long form LepRb contains a 302-amino acid cytoplasmic domain that includes motifs for binding of intracellular signaling molecules, and therefore LepRb is crucial for leptin action. The *db/db* mice are deficient in LepRb, but not other LepR isoforms, as a consequence of a mutation that causes mis-splicing of the LepRb mRNA. These mice display a phenotype that is indistinguishable from that of mice which are deficient in all LepR isoforms (*db^{3J}/db^{3J}* mice) and of leptin-deficient *ob/ob* mice. The function of short form LepRs is less clear, although proposed roles include the transport of leptin across the blood–brain barrier (BBB).

It is currently accepted that leptin receptor-bearing neurons within the hypothalamus are responsible for mediating a concerted response to fluctuations of body energy stores. Before leptin reacts with its target cells in the hypothalamus, leptin must first cross the BBB. This step is facilitated by a transporter that is an alternatively spliced product (LepRe) of the leptin receptor gene present in brain endothelial cells. Long form leptin receptors, LepRb, are expressed in the central nervous system (CNS), and leptin injection induces neuronal activation. Substantial evidence suggests that the brain mediates the

majority of leptin's action on energy homeostasis. Intracerebroventricular injection of leptin decreases food intake and body weight. Mice with a specific deletion of LepRb in the brain are obese, but the deletion of peripheral leptin receptors does not change the normal phenotype of the animal. Expression of LepRb in neurons of LepRb-deficient mice leads to an amelioration of their obesity.

Among the various brain areas that express LepRb, the mediobasal hypothalamus is implicated as playing an especially important role. There are two primary populations of neurons that express LepRb and exert potent, opposing effects on food intake and body weight in the arcuate nucleus (ARC) of the hypothalamus. Leptin stimulates the production of proopiomelanocortin (POMC) and its derived products including α -melanocyte stimulating hormone (α -MSH), which act on melanocortin 4 receptor (MC4R). Leptin also stimulates the production of cocaine amphetamine-regulated transcript (CART). Both α -MSH and CART inhibit feeding as appetite suppressants. In another type of ARC neuron, leptin inhibits the production of agouti-related peptide (AGRP), an endogenous antagonist that acts on MC4R, and neuropeptide Y (NPY). AGRP and NPY are potent stimulators of feeding as appetite stimulants. Thus, leptin decreases food intake and increases energy expenditure by simultaneously stimulating the production of α -MSH and CART and inhibiting the production of NPY and AGRP in the ARC. These neuropeptides are transmitted to and interact with receptors in neurons of the paraventricular nucleus (PVN) of the hypothalamus. These PVN neurons, in turn, generate outputs that coordinate feeding behavior and energy expenditure and send these outputs to the hind-brain. Deletion of LepRb only in POMC neurons leads to a mild obesity, and restoration of ARC LepRb signaling attenuates obesity and hyperphagia in leptin receptor-deficient animals. These findings constitute direct evidence that LepRb signaling in the ARC is required for normal energy homeostasis (Varela and Horvath 2012).

A number of signaling pathways are involved in mediating the diverse functions ascribed to leptin. These signaling pathways include the Jak kinase family (JAK)–signal transducer and activator of transcription (STAT), the mitogen-activated protein kinase (MAPK) family, the phosphatidylinositol 3-kinase (PI3K)/Akt, the AMP-activated protein kinase (AMPK), the mammalian target of rapamycin complex 1 (mTORC1), and the forkhead transcriptional factor subfamily forkhead box O1 (FoxO1 or Fkhr). STAT3 plays a major role in mediating leptin signaling in the hypothalamus. Upon leptin binding, activated Jak2 phosphorylates itself and residues Tyr985, Tyr1077, and Tyr1138 within the intracellular tail of LepRb. Tyr1138 recruits and phosphorylates STAT3 proteins, which then dimerize and translocate to the nucleus and activate a specific program of gene transcription. A knockout mouse that leaves the leptin receptor intact but specifically disrupts the LepRb–STAT3 signal is hyperphagic and obese. These findings indicate that the cytoplasmic tyrosine residue (Tyr1138) is necessary for proper LepRb–STAT3 signaling in the hypothalamus after leptin stimulation. STAT3 mediates the transcription of suppressor of cytokine signaling 3 (SOCS3) which then binds to Tyr985 of LepRb to inhibit LepRb–STAT3 signaling. Protein-tyrosine phosphatase 1B (PTP1B) dephosphorylates activated Jak2 and STAT3. Thus, both SOCS3 and PTP1B function as negative regulators of leptin signaling in the hypothalamus (Varela and Horvath 2012).

Metabolic Effects of Leptin

The finding that leptin deficiency causes obesity raised the possibility that leptin replacement therapy may ameliorate obesity. Leptin treatment reverses many of the phenotypes of leptin-deficient mice and humans. Lipodystrophy and type 1 diabetes are characterized by low plasma leptin levels. Severe insulin resistance and hyperglycemia were improved by leptin treatment in rodent models of and patients with lipodystrophy. Leptin treatment caused an improvement in glycemia in rodent models of type 1 diabetes and patients with the combination of type 1 diabetes

and acquired generalized lipodystrophy. However, it was quickly apparent that an absolute leptin deficiency is an extremely rare cause of human obesity. Plasma leptin levels are elevated, rather than reduced, in the majority of obese subjects, and plasma leptin levels are highly correlated with total fat mass. Leptin treatment failed to reverse obesity and insulin resistance in animal models of and patients with leptin-resistant obesity and diabetes. Importantly, a proportion of type 2 diabetes patients are not highly obese and are not associated with hyperleptinemia. These patients can respond to the metabolic actions of exogenously administered leptin. Thus, leptin treatment is an effective therapy to improve obesity and insulin resistance in patients with no leptin or very low levels of leptin. In contrast, leptin treatment has a limited effect in the vast majority of leptin-resistant obese patients (Coppari and Bjorbaek 2012).

Leptin Resistance and Obesity

Since leptin resistance appears to be the major cause of human obesity, a great effort has been made to identify the mechanism of leptin resistance. One possible mechanism for leptin resistance is a defective leptin transport across the BBB. The transportation of leptin into the brain is mediated via a specific transport mechanism across the BBB and/or via the circumventricular organs. Leptin is transported across the BBB by a saturable transport system that may be in part mediated by the short form of leptin receptor, LepRe. Leptin transport rate is reduced in animal models of leptin resistance, such as diet-induced obese (DIO) rodents. Another possible mechanism for leptin resistance is impairments in intracellular LepRb signaling system. Leptin-resistant DIO mice do not respond to peripherally administered leptin, but they partially respond to central injection of leptin, suggesting that the downstream signaling pathways are partially capable of mediating leptin action. This also indicates that the ability of leptin to activate hypothalamic signaling is impaired in leptin-resistant animals. Leptin-induced activation of signaling pathways (e.g., STAT3, PI3K, and mTORC1) and

inhibition of AMPK signaling is reduced in the hypothalamus of DIO animals. These data indicate that impairments in these LepRb signaling contribute to the development of leptin resistance. SOCS3 and PTP1B are important physiological determinants of leptin signaling strength by acting as negative regulators of leptin signaling in the hypothalamus. The LepRb–STAT3 pathway stimulates SOCS3 expression, and SOCS3 expression levels correlate with the attenuation of LepRb signaling. Thus, high levels of leptin may induce SOCS3 expression and thereby attenuates leptin signaling in obesity (Konner and Bruning 2012).

Leptin and Psychological States

Metabolic diseases such as obesity and diabetes are associated with psychological abnormalities. Leptin deficiency or leptin receptor deficiency is associated with not only obesity but also anxiety and depression. Deletion of LepRb in specific neuronal populations causes anxiety-like and depression-like behaviors in mice (Guo et al. 2013). Leptin treatment produces antidepressant-like effects in rodents. Treatment with leptin also reduces body weight and improves anxiety-like behavior in leptin-deficient *ob/ob* mice. These beneficial effects of leptin on psychological well-being may be mediated via alterations in dopaminergic activity in the amygdala and increased neurogenesis in the hippocampus. These findings in animal models suggest the possibility that leptin treatment may be beneficial in ameliorating both metabolic and psychological abnormalities.

There is a strong association between obesity and schizophrenia. Patients with schizophrenia are at greater risk for obesity than other individuals. This may be partly due to side effects of antipsychotic drugs. Although there are some exceptions, a majority of study reported that antipsychotic treatment is associated with both an increase in circulating leptin levels and an increase in body weight, indicative of leptin resistance in schizophrenic patients. The effects of antipsychotics are mediated via a number of neuronal systems involving serotonin, dopamine,

and histamine which also mediate the metabolic effects of leptin (Panariello et al. 2012).

Conclusion

Leptin serves to communicate the state of body energy stores to the CNS in order to maintain normal metabolic and neuroendocrine functions. Leptin also plays a role in the maintenance of psychological well-being. These actions of leptin require its transportation to the CNS across the BBB and its binding to the long form LepRb, followed by the activation of diverse intracellular signaling pathways. Leptin therapy is effective in reversing metabolic impairments in obese/diabetic patients without leptin resistance. However, the vast majority of patients with obese and type 2 diabetes are characterized by hyperleptinemia and leptin resistance, and leptin therapy has a limited effect in these patients. Leptin treatment may be also beneficial to relieve anxiety and depression.

Cross-References

- ▶ [α-Melanocyte-Stimulating Hormone](#)
- ▶ [Agouti-Related Peptide](#)
- ▶ [Antipsychotic](#)
- ▶ [Anxiety](#)
- ▶ [Appetite Stimulants](#)
- ▶ [Appetite Suppressants](#)
- ▶ [Blood–Brain Barrier](#)
- ▶ [Circumventricular Organs](#)
- ▶ [db/db Mouse](#)
- ▶ [Depression](#)
- ▶ [Dopamine](#)
- ▶ [Hyperphagia](#)
- ▶ [Hypothalamus](#)
- ▶ [Neuropeptides](#)
- ▶ [Neuropeptide Y](#)
- ▶ [ob/ob Mouse](#)
- ▶ [Rapamycin](#)
- ▶ [Satiety](#)
- ▶ [Schizophrenia](#)
- ▶ [Serotonin](#)

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Leucoplakia

Synonyms

Leukoplakia

Definition

A white-coloured thickened patch in the mucosa of the oral cavity. This lesion is primarily caused by chronic irritative stimuli such as tobacco use or friction and may potentially evolve in cancer.

Levodopa, L-DOPA

[*L-3,4-Dihydroxyphenylalanine* or *3-Hydroxy-L-Tyrosine*]

Synonyms

Larodopa (levodopa), in combination with carbidopa or bensezaride, or entacapone: Aktipar, Atamet, Carbilev, Ceredopa, Dopaflex, Dopar,

Doparkin, Eldopal, Madopar, Madopark, Parcopa, Prolopa, Sinemet, Stalevo, Zimox, and others

Definition

Dopamine precursor, antiparkinsonian L-DOPA is used in the treatment of Parkinson's disease, since it is a precursor of dopamine. L-DOPA can cross the blood-brain barrier but tends to be metabolized peripherally by both aromatic L-amino acid decarboxylase or DOPA decarboxylase (DDC) and catechol-O-methyltransferase (COMT). Therefore, L-DOPA is often associated with a DDC inhibitor (e.g., carbidopa) or a COMT inhibitor (entacapone) as double combinations or even with both a DDC inhibitor (e.g., carbidopa) and a COMT inhibitor (entacapone) as a triple combination. The combinations are used to prolong the plasma half-life of L-DOPA but also to avoid its conversion into dopamine in the periphery, thus avoiding peripheral dopaminergic side effects. Once in the brain, L-DOPA is converted to dopamine, since the DDC inhibitors do not cross the brain barrier, and dopamine will then activate dopamine receptors; this is the basis for the treatment of Parkinson's disease or dopamine-responsive dystonias. Unfortunately, L-DOPA treatment response diminishes over the years, at which point various combination therapies must be started. Also, long-term treatment with L-DOPA may be accompanied by the "on-off" phenomenon, patients oscillating between symptom improvement and abrupt onsets of akinesia.

Cross-References

► [Anti-Parkinson Drugs](#)

Levomepromazine

Synonyms

Methotrimeprazine

Definition

Levomepromazine is a ► [phenothiazine](#) antipsychotic with a plasma half-life of 16–78 h. It is mainly metabolized by 1A2 and 2D6 CYP450 isoenzymes. It is said to have strong sedative properties, probably due to strong histamine H1 receptor blockade.

Cross-References

► [First-Generation Antipsychotics](#)

Lewy Bodies

Definition

Globular protein-rich inclusions in cell soma that are characteristic of a number of diseases, in particular Parkinson's disease (PD) and certain dementias. Although dopamine depletion can occur in a number of disorders, the presence of Lewy bodies in the dopaminergic neurons of the ventral midbrain is considered as defining idiopathic PD. The principal molecular component of the Lewy body is α -synuclein, and several of the mutations associated with familial PD involve disturbance in the α -synuclein gene or in the genes encoding-related interacting proteins.

Lewy Body Dementia

Synonyms

Dementia with Lewy bodies; DLB

Definition

Lewy body dementia is characterized by distinct cognitive impairment with fluctuating confusion, disturbance of consciousness, visual hallucinations, delusions, falls, and significant parkinsonism. The hallmark feature is the widespread Lewy bodies throughout the cortex with the presence of Lewy body and cell loss in the subcortical nuclei.

Liberation

Definition

Liberation is the process of releasing a drug from its formulation.

Cross-References

- ▶ [Absorption](#)
- ▶ [Distribution](#)
- ▶ [Excretion](#)
- ▶ [Metabolism](#)
- ▶ [Pharmacokinetics](#)

Libido

Definition

The desire or drive for sexual activity.

Cross-References

- ▶ [Agoraphobia](#)
- ▶ [Sexual Disorders](#)
- ▶ [SSRIs and Related Compounds](#)

Licensing and Regulation of Medicines in the UK

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Synonyms

Drug licensing; Medicines control; Medicines regulation

Definition

The licensing and regulation of medicines in the UK is the statutory responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA), based in London. Before any medicine can be prescribed or sold in the UK, it must have a marketing authorization (previously known as a product license). The marketing authorization specifies precisely the summary of product characteristics (SPC), along with the labeling and package leaflet for the product. The regulation of medicines, and the overall responsibilities of the MHRA, involves considerably more than a “once only” marketing authorization. Regulation also entails post-licensing surveillance of safety and scrutiny of any proposed variation to the clinical indications for the medicine, any changes in availability, the ongoing quality of the production process, and the enforcement of regulations when required, all in respect of the Agency’s principal aim, which is to safeguard the public health. Marketing authorization is given or refused on the grounds of safety, quality, and efficacy. Financial cost plays no part in regulatory decisions. The regulatory process is



separate from the work of the National Institute for Health and Care Excellence (NICE) which has the role of assessing the clinical and cost-effectiveness of new medicines.

Current Concepts and State of Knowledge

Status and Function of the MHRA

The legal context within which MHRA operates is described in the Medicines Act of 1968, which became operational in 1971. The act designated the Secretary of State for Health in England (and equivalents in Scotland, Wales, and Northern Ireland) the Licensing Authority for Human Medicines in the UK. This is a retained authority within the UK. In 2003, the then Medicines Control Agency was reestablished as the MHRA, which became responsible not only for the regulation of medicines but also medical devices and, more recently, blood and blood products. Many of the provisions of the 1968 act have now been superseded by regulations implementing European legislation on medicines. A diminishing number of medicines are licensed on a national basis by MHRA, solely for use in the UK. Most medicines are now authorized through European procedures to ensure that they are available to, and used in the same way across, all the member states of the European Union (EU). This is either through agreement of identical national authorizations in all member states, based on the assessment of a lead member state (a mutual recognition or decentralized authorization) or through a single EU authorization issued by the European Medicines Agency (EMA) (centralized authorization). Under the “mutual recognition or decentralized” procedures, all EU countries in which marketing permission is sought receive the full marketing authorization application, and any objections are considered and resolved through the EMEA’s scientific advisory committee, the Committee for Medicinal Products for Human Use (CHMP). The centralized approval system is compulsory for biotechnology products and has expanded in scope to cover drugs for

AIDS, cancer, neurodegenerative diseases, and diabetes. Often the MHRA will be asked to take the lead on the licensing process in Europe, particularly for biological and biotechnology treatments, such as a gene therapy.

The Marketing Authorization Process

Authorization to market a medicine is based on detailed requirements and elaborate processes, the scope of which is constantly changing. However, the core elements of medicines control remain essentially unchanged, the primary focus being on the evaluation of pre-licensing data (from nonclinical tests and phases 1–3 clinical trials) on safety, quality, and efficacy generated or commissioned by companies and submitted for approval in a Marketing Authorization Application. A medicine progresses “from bench to bedside” over a period of many years, and innovation usually involves the discovery, development, and bringing to market of a new molecular entity (NME). Often the NME is original, such as the first SSRI or atypical antipsychotic, but it may also be a relatively minor molecular modification of an existing drug. The preclinical and nonclinical assessment involves necessary animal and bench testing before administration to humans. Phase 1 clinical trials are also known as “first time in man” studies and are conducted usually with healthy volunteers. Phase 2 clinical trials are for “proof of concept,” evidence of efficacy, and safety in patients with the target condition. Phase 3 clinical trials represent the main clinical reference point upon which marketing authorization may be granted. These are usually large trials (involving many thousands of patients suffering from the target condition); they usually involve comparison of clinical benefits and risk between randomized samples of the target population given either the active drug or a placebo and/or active comparator, and the results inform the labeling and patient information for the medicine when it is marketed. The benefits recorded in phase 3 clinical trials represent the main database on “efficacy.” Phase 4 trials are conducted post-marketing, the principal aim being to provide ongoing, structured safety

information. Benefits recorded in Phase 4 trials are usually more appropriately termed the medicine's "effectiveness" and more faithfully reflect every day clinical practice in that they derive from patients who have not been so strictly selected or supervised as those involved in Phase 3 studies.

Clinical Trial Authorization

Clinical trials are conducted according to Guidelines on Good Clinical Practice (GCP) as described in EU Directive 2001/20/EC, Article 1, Clause 2, which deal with ethical and scientific issues relating to the design, conduct, recording, and reporting of clinical trials that involve human subjects. The principles of GCP are outlined in Articles 2–5 in the EU Directive 2005/28/EC. The serious side effects experienced by volunteers taking part in a trial of TGN1412 in March 2006 at Northwick Park Hospital are extremely rare but indicate the importance of thoroughly testing a treatment before widespread use. Another regulatory responsibility of MHRA is to authorize any clinical trial of a medicinal product in the UK. Information on the quality of the product and its nonclinical safety will have been obtained before Clinical Trial Authorization can be obtained and any clinical trial program commencing.

Judging the Balance of Risks and Benefits

Evidence in pursuit of authorization is submitted by the applicant (normally a pharmaceutical company) either in paper form or electronically. Thorough assessment of all of the clinical and preclinical data is conducted in-house by MHRA assessors, and a recommendation is then made to one or more elements of the agency's expert advisory structure. The main independent, expert, group advising the agency is the Commission on Human Medicines (CHM), which came into being in October 2005. The commission has three statutory, standing, Expert Advisory Groups in (1) pharmacovigilance; (2) chemistry, pharmacy, and standards; and (3) biologicals and vaccines. The chairs of the Expert Advisory Groups are members of the commission. In addition, there are a number of established Expert

Advisory Groups covering a range of specific therapeutic areas such as psychiatry and old age psychiatry. The commission is charged with the responsibility to advise ministers, through the MHRA, on matters relating to human medicinal products.

The Life Cycle of a Medicine

Marketing authorizations are granted for periods of up to 5 years, when they then have to be renewed. On renewal each marketing authorization must reflect all current knowledge about the product, including any necessary action from the most recent periodic safety update report (PSUR) submitted by the applicant. Once renewed, the marketing authorization will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, when it may become necessary to proceed with one additional 5-year renewal. Variations to marketing authorizations must be approved before introducing any changes. They take account of technical and scientific progress, introduce additional safeguards, or reflect evolving therapeutic indications. It is common practice for new products to be varied many times, particularly in the first 2 years after marketing. Once licensed, a medicine is normally under patent protection for 10 years. Once that period has expired, the originating pharmaceutical company is deemed to have been rewarded for the costs and risks of innovation, and generic versions of the medicine may then enter the market. Such generic medicines contain the same active ingredients as the original product, and the regulatory standards for safety, quality, and efficacy are the same as for branded products, and marketing authorization must be obtained before the generic medicine is allowed on to the market.

Safety Monitoring

No medicine is completely free of risk, but sound evidence underpins all of the MHRA's decisions to ensure that an acceptable balance exists between risks and benefits. Companies applying for a marketing authorization are required to submit a risk management plan which states what is known about the medicine, identifies any gaps in



knowledge about safety, and outlines plans to collect data in the post-marketing period to fill those gaps. The MHRA monitors safety and quality standards by a number of means. It conducts regular inspections of good and safe practice including medicines manufacture and supply; carries out routine sampling of marketed medicines at manufacturers' premises; considers ongoing reports from health professionals, patients, and manufacturers (such as the Yellow Card Scheme, see below); reviews important new evidence on products (such as the SSRIs); and assesses misleading or incorrect information contained in advertisements, product labeling, or product information leaflets (PILs).

Pharmacovigilance is the process of detection, assessment, understanding, and prevention of adverse effects of medicines, against which benefits must be weighed in coming to any decision about the need to modify, restrict, or withdraw marketing authorization. By law, manufacturers must report to the MHRA any important defects in the quality (chemical identity and purity) or clinical safety of a medicine. Any action taken by MHRA is determined by the scale of the threat posed to the public health. If a new side effect is identified, MHRA can seek advice from its external experts and/or commission further research to illuminate the issues. A number of options are available to the agency short of requiring withdrawal of the product, and any modifications to clinical usage are reflected in the SPC. Health professionals are informed of important new information and advice in relation to medicines via a letter sent by the manufacturer or via a direct communication from the MHRA through the Department of Health Central Alerting System. The MHRA also issues a monthly bulletin "Drug Safety Update" which includes the latest advice for users of medicines and is available on the Agency's website; www.mhra.gov.uk/mhra/drugsafetyupdate The MHRA has for a number of years operated a "Black Triangle Scheme" under which all new medicines, and established medicines newly authorized for a different patient population, are intensively monitored for the first few years of marketing. Products monitored under this scheme are denoted by an

inverted black triangle which appears on any advertising material and in the British National Formulary (BNF). The Black Triangle Scheme has been adopted in all EU member states following the implementation of new Pharmacovigilance Legislation in July 2012. The aim of the scheme is to highlight new medicines to prescribers and patients and encourage reporting through the Yellow Card Scheme. "Yellow Card" Scheme is run by the MHRA and the CHM and is used to collect information submitted spontaneously from health professionals and the general public on suspected side effects or adverse drug reactions (ADRs). Prescribers and users need not be certain about causality, and the golden rule is "if in doubt, report." Reports can be made through the MHRA website www.yellowcard.gov.uk, and paper copies of yellow cards are attached at the end of the BNF. A rich source of data on marketed medicines comes from the Clinical Practice Research Datalink (CPRD – previously the General Practice Research Database), the management of which is entrusted to the MHRA. The CPRD is a new NHS observational data and interventional research service which aims to maximize the way anonymized NHS clinical data can be linked to enable many types of observational research. It is used worldwide for research by the pharmaceutical industry, clinical research organizations, regulators, government departments, and leading academic institutions and is an internationally recognized source of information on the safety and effectiveness of licensed medicines.

The potential for selective serotonin reuptake inhibitors (SSRIs) to cause withdrawal reactions, dependence, and suicidal thoughts and behavior has been the subject of controversy and public concern since the late 1980s. The safety of SSRIs was closely monitored leading to updates to the SPC and patient information as evidence accumulated. An Expert Working Group of the Committee on Safety of Medicines (predecessor of CHM) established in 2003 conducted a detailed investigation of clinical trial data, data from the Yellow Card Scheme, and from GPRD. Their recommendations were published in 2004 and fed into the NICE clinical guideline on

depression. In 2005, analyses of 17 placebo-controlled studies found that atypical antipsychotics were associated with an increased risk of death in elderly people with dementia. The product information for these medicines was updated to include warnings about this risk. There is increasing awareness of psychiatric adverse effects of nonpsychiatric medicines. Rimonabant (Acomplia) was withdrawn from the market in the EU in 2008 because the risk of psychiatric disorders, particularly depressive reactions, was considered to outweigh its benefits in the management of obesity.

Herbal Medicines

The regulation of herbal medicinal products also falls within the remit of MHRA. There are three possible regulatory routes by which a herbal remedy can reach a consumer as an unlicensed, registered, or licensed herbal medicine. As of April 2011 all manufactured herbal medicines are required to have either a traditional herbal registration or a product license. The simplified registration scheme (the Traditional Herbal Medicines Registration Scheme) began in October 2005. Registered products are required to meet specific standards of safety and quality and to be accompanied by agreed indications based on traditional usage. To be licensed a herbal medicine requires to demonstrate safety, quality, and efficacy (or effectiveness) and to be accompanied by the necessary information for safe usage. As with conventional medicines, herbal remedies may be the subject of Yellow Card reports.

Counterfeit Medicines

The detection and confiscation of counterfeit medicines represents a growing activity for MHRA. The World Health Organization (WHO) estimates that up to 1 % of medicines available in the developed world are likely to be counterfeit, and this figure rises to 10 % globally. Therapeutic psychoactive drugs are no exception – counterfeit Zyprexa (olanzapine) was detected and recalled in the UK by the MHRA in 2007. Counterfeit medicine is commonly available to consumers via Internet online

pharmacies, WHO estimating that 50 % of medicines available from such sites which conceal their physical address are counterfeit. Counterfeits discovered in the UK typically contain a reduced amount of the active pharmaceutical ingredient, although the wrong ingredient or no ingredient at all have been found less frequently; therefore, all counterfeit medicines are potentially dangerous.

Medicines Availability

Marketing authorization of a medicine may specify whether it can be made available either on prescription (prescription only medicines (POM)), available in a pharmacy without prescription under the supervision of pharmacist (P), or on general sale (GSL). Prescriptions can be issued by doctors, dentists, nurse independent prescribers, pharmacist independent prescribers, and supplementary prescribers. Before restrictions on the supply of a medicine can be downgraded from POM, ministers, advised by MHRA, must be satisfied that it would be safe to allow it to be supplied without prescription. Similarly, switching from P to GSL requires demonstration of acceptable safety if sold or supplied otherwise than by or under the supervision of a pharmacist.

Orphan Drugs

The pharmaceutical industry has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients (“orphan drugs”), and the EU offers a range of incentives to encourage the development of these medicines, including reduced licensing fees. In that case, the company applies to the EMEA requesting “orphan designation” for their product.

Powers

When regulations have been breached, the MHRA has the power to prosecute. Courts can impose fines or prison sentences when the law has been broken, and the agency has the power to require unlicensed/illegal products to be withdrawn from the market.

Cross-References

- ▶ [Herbal Remedies](#)
- ▶ [SSRIs and Related Compounds](#)
- ▶ [Suicide](#)
- ▶ [Withdrawal Syndromes](#)

Ligands

Definition

Substances that bind to receptors and alter the three-dimensional shape of selected receptor proteins. The shape of a receptor protein determines the functional state of a receptor. Ligands include substrates, inhibitors, activators, and neurotransmitters, thereby embracing the majority of psychoactive drugs.

Liking and Wanting

Definition

Liking is the hedonic quality of food and the pleasing experience of consumption, while wanting is the desire to consume food and its motivational salience. The two are distinct as we can like a food without wanting it and vice versa; however, both are probably intrinsic components of palatability. In terms of animal behavior, the strength of initial feeding response is held to indicate liking, while later feeding behavior, including returning to food source, indicates the desire to consume. A similar distinction has been applied in some theoretical formulations of processes underlying drug dependence and addiction.

Cross-References

- ▶ [Palatability](#)

Lipophilic

Synonyms

Fat soluble; Lipid soluble

Definition

Lipophilic substances are those that dissolve in fats, oils, lipids, and nonpolar solvents (i.e., accumulate in lipid stores in the body).

Cross-References

- ▶ [Blood–Brain Barrier](#)
- ▶ [Lipophilicity](#)
- ▶ [Sex Differences in Drug Effects](#)

Lipophilicity

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Synonyms

Hydrophobicity; Nonpolarity

Definition

Lipophilicity, or “fat friendly” as derived from the Greek, is described as the degree to which an organic molecule dissolves in fat, oil, or nonpolar organic solvents (i.e., hexanes), as opposed to polar solvents (i.e., water). Of all the physiochemical properties measured and monitored in a chemical optimization program en route to a drug candidate, lipophilicity is the

most important, as it influences ligand–target binding interactions, solubility, ADME (absorption, distribution, metabolism, and elimination) properties, as well as in vivo toxicological outcomes, and, therefore, the overall quality of the drug candidate. Historically, LogP, the partition coefficient of a molecule between octanol (lipophilic phase) and water (hydrophilic phase), was used to measure lipophilicity; however LogD, the LogP at pH 7.4 (the physiological pH of blood serum), is now often employed to more accurately account for charged molecules. Recently, studies with marketed drugs and clinical candidates demonstrate robust correlations between lipophilicity and clinical success, especially in the case of central nervous system (CNS) therapeutics.

Current Concepts and State of Knowledge

Background

Since the late nineteenth century, the key role of lipophilicity on the pharmacological responses of molecules was well established qualitatively, and with further refinements in the 1960s by Hansch, quantitative relationships between lipophilicity and structure–activity relationships (SAR) rose into prominence throughout the twentieth century (Hansch 1969; Keseru and Makara 2009; Waring 2010). In drug discovery, the most common method for quantifying lipophilicity is derived from the octanol/water partition coefficient, or logP (Fig. 1). For ionizable compounds, logD is a better descriptor and employs buffered water at a given pH (i.e., pH of 7.4, the physiological pH of blood serum). Today, logP or logD is rarely experimentally measured, and instead chemists rely on calculated values, i.e., clogP. However, numerous studies have shown an error of >1 log unit, due to the composition of the training sets employed, and since the logP range of interest is ~1–3, an error of >1 log unit is of serious concern, as are errors inherent in computationally derived pK_as (acidity measure) for logD calculations. Therefore, more accurate clogP estimates

$$\log P = \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{neutral water}}}$$

$$\log D_{7.4} = \frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{ionized water}} + [\text{solute}]_{\text{neutral water}}}$$

Lipophilicity, Fig. 1 Equations to calculate logP and logD. For logD, the pH must be specified

require experimentally determined logPs within a given chemotype to be employed in the computational training set (Waring 2010).

In 1997, Pfizer scientist Lipinski put forth the Rule of 5, defining key physiochemical properties that accounted for ~90 % of successful phase II oral clinical candidates: molecular weight (MW) <500, cLogP < 5, hydrogen bond donors <5, and hydrogen bond acceptors <5 (Lipinski et al. 1997). Of these parameters, logP is essential for optimal solubility and permeability across membranes, both in the gut and CNS (blood–brain barrier). Gleeson suggested more stringent parameters in support of a logP < 4 and MW <400 for optimal clinical outcomes (Gleeson 2008). More recent studies with successful CNS clinical candidates and drugs further refine these values to a more narrow logP range of ~1–3, with a logP of 2.8 or a logD of 1.7 being optimal, along with additional refined physiochemical values (molecular weight = 305.3, hydrogen bond donor = 1, total polar surface area (TPSA) = 44.8, and pK_a = 8.4) (Wager et al. 2010a, b). Clearly, clinical success of CNS agents is tied to physiochemical properties, and lipophilicity is among the most important.

Efficiency Metrics and Lipophilicity

Recently, new composite parameters have been developed to assess efficiency metrics in chemical optimization, and most utilize lipophilicity as a major determinant of enthalmic optimizations (Wager et al. 2010a, b; Waring 2010; Shultz 2013). These composite parameters correlate potency, size, and lipophilicity (Fig. 2). Ligand efficiency (LE) is a term used to qualify the



$$LE = \frac{-1.4 \log(K_i [M])}{\text{number of heavy atoms}}$$

$$LLE = -\log(K_i [M]) - \text{clogD}$$

$$LELP = \frac{\text{clogP}}{LE}$$

$$\text{LipE} = \text{pIC}_{50} - \text{clogP}$$

Lipophilicity, Fig. 2 Composite parameters used to quantify efficiency metrics, and lipophilicity is a key parameter

efficiency of binding with respect to heavy atoms, and this was later refined into the ligand-lipophilicity efficiency (LLE) to maximize lipophilic efficiency. A new descriptor, ligand-efficiency-dependent lipophilicity (LELP), factors in both size and lipophilicity. Out of a collection of 119 marketed drugs, 95 (80 %) possessed median LE, LLE, and LELP values of 0.52, 6.3, and 5.9, respectively. In 2013, Schultz introduced a new composite parameter lipophilic efficiency (LipE) that displayed a strong correlation with enthalpy-driven receptor–ligand binding interactions (Schultz 2013).

Impact of Lipophilicity on Solubility, Permeability, and Target Engagement

A direct correlation exists between lipophilicity and compound solubility, and the general solubility equation derives compound solubility as a function of logP (Fig. 3). Once a compound reaches the acidic aqueous environment of the stomach and small intestine, solubility is a major determinant of oral bioavailability (Waring 2010). Indeed, numerous studies have demonstrated that solubility increases with decreasing lipophilicity (logP). For example, for a set of 711 compounds possessing MW of 500 and a desired kinetic solubility of >500 μM, only 1 % met solubility criteria when logP > 3, but ~50 % displayed kinetic solubility of >500 μM when logP < 3; moreover, additional studies showed improved solubility when logP < 3 (Gleeson 2008; Waring 2010). Similarly, selective partitioning into octanol can be

$$\log\text{Sol}_{\text{aq}} = 0.5 - \log\text{P} - 0.01(\text{MP} - 25)$$

Lipophilicity, Fig. 3 General solubility equation directly relates aqueous solubility to logP. MP is the melting point

viewed as a crude surrogate for a compound partitioning into a cell membrane from an aqueous environment, thus mimicking cell/membrane permeability. While not linear, it is well established that cell permeability decreases with lower logP. A similar trend is present for passive permeability into the CNS across the blood–brain barrier. Compounds with logP < 1 typically display poor permeability into the CNS, while compounds with logP > 2 typically display good CNS permeability (Summerfield et al. 2007; Gleeson 2008; Wager et al. 2010a, b; Waring 2010). Finally, increasing logP can often increase binding potency (target engagement) when lipophilic ligand–receptor interactions are important. However, compounds with high logPs often engender a high degree of promiscuous pharmacology due to off-target lipophilic interactions and hydrophobic collapse. Thus, as chemical optimization efforts typically increase logP, while increasing desired on-target potency, this can often lead to enhanced and undesired ancillary pharmacology (Waring 2010).

Impact of Lipophilicity on ADME Properties

The *in vivo* clearance of a candidate compound is directly related to its lipophilicity (logP). For polar compounds (logP < 1), clearance of the parent compound through renal mechanisms dominate and exceed 50 % when logP and/or D < 0. More lipophilic compounds are cleared by cytochrome P450 (CYP) enzymes, which are lipophilic in nature and thus more affectively bind and oxidize lipophilic compounds (logP/D ~2 to 5). Thus, not unexpectedly, for a set of ~12,000 compounds, *in vivo* clearance in rats increased with increasing logP (Gleeson 2008; Waring 2010). These data also reflect plasma protein binding and general distribution of compounds, intrinsically tied to lipophilicity. A major factor governing plasma protein binding is

lipophilicity, and direct correlations between logP and human serum binding logK values have been shown, as well as correlations with other nonspecific tissue binding in vivo (volume of distribution, compounds depotting in fat and muscle when $\log P > 3$). This is the free drug principle, which states that only free drug, not bound to plasma proteins or other tissues, is free to bind a molecular target and elicit pharmacological effects (Summerfield et al. 2007; Gleeson 2008; Waring 2010).

For CNS agents, lipophilicity also governs access across the blood–brain barrier (Summerfield et al. 2007; Wager et al. 2010a, b; Waring 2010). A recent study of 50 marketed CNS drugs indicates that 75 % possess logPs > 2 , and brain permeability is not linear but plateaus with logPs between 2 and 3 (recall optimal logP for CNS drugs is 2.8). Furthermore, transporters, such as P-glycoprotein (P-gp), at the blood–brain barrier pump out polar compounds (logPs < 1.5), further reducing CNS penetration, while compounds with logP > 2 trend toward not being substrates for P-gp and thus afford enhanced exposure to the CNS. Like plasma protein binding, highly lipophilic compounds (logP > 3) may gain entry into the CNS but often show high levels of binding to brain tissue, rendering them unavailable to engage the molecular target (free drug principle). Moreover, numerous studies have shown that molecules with optimal CNS exposure have logD values between 1 and 3, a profile virtually identical for drugs with optimal oral bioavailability (Summerfield et al. 2007; Wager et al. 2010a, b; Waring 2010). Of course, achieving good bioavailability relies on high solubility and permeability to enable absorption, as well as low hepatic (CYP-mediated) first-pass metabolism – all of which are governed by compound lipophilicity. As eluded to, optimal logD values range ~ 1 –3 for oral drugs, while optimal logP values range from 0 to 3, and in several studies, 99 % of compounds that display > 80 % oral bioavailability fall within this narrow range (Summerfield et al. 2007; Wager et al. 2010a, b; Waring 2010).

Impact of Lipophilicity on Toxicological Outcomes

A major driver of ligand affinity for any molecular target is lipophilicity, and clear trends show that more lipophilic compounds (logP > 4) are more promiscuous and engender various toxicological outcomes during lead optimization (Hughes et al. 2008; Waring 2010). Of these, drug–drug interactions are a major issue for CNS drug discovery efforts, and avoiding CYP inhibition is a major program objective due to the many concomitant medications often prescribed. Here too, lipophilicity plays a major role in determining the degree of CYP inhibition. Analysis of a collection of $> 44,000$ compounds showed that inhibition of the five major CYP isoforms (3A4, 1A2, 2D6, 2C9, and 2C19) increased with increasing logP and was generally lower ($IC_{50s} > 10 \mu M$) when logP < 3 . In addition to CYP inhibition, Cerep (now Eurofin) released data showing that general promiscuity in a panel of radioligand binding assays across a wide range of targets increased dramatically when logP > 3 , leading to undesired events in vivo. Furthermore, a study by Pfizer showed a direct correlation between logP and toxicity in rat and dog in vivo tolerability studies. In this case, compounds with a logP > 3 and a PSA $< 75 \text{ \AA}^2$ were 2.5 times more likely to be toxic than compounds with a logP < 3 and a PSA $> 75 \text{ \AA}^2$.

Two other toxicities that hinder optimization programs, hERG (the human Ether-a-go-go-Related Gene, the $K_v11.1$ potassium channel) binding and phospholipidosis, are both strongly associated with lipophilic, basic compounds (Waring 2010). As we are discussing, basic, i.e., ionizable compounds, logD is a more appropriate measure. hERG binding underlies the QT interval (measure of the time between the start of the Q wave and the end of the T wave in the heart's sinus rhythm), and compounds that inhibit hERG ($IC_{50s} < 10 \mu M$) engender serious cardiovascular toxicology that has led to both clinical failures and the withdrawal of marketed drugs. Multiple studies have shown that a 70 % chance of maintaining hERG binding above $10 \mu M$ requires a logD of < 3.3 for neutral molecules and a logD



of <1.4 for basic compounds. Highly lipophilic bases ($\log D > 4$) are generally potent hERG binders and result in QT syndrome. In the case of phospholipidosis, risk increases if the sum of $\log P^2$ and pK_a^2 is >90 ; therefore, for a basic compound with a pK_a of 9.0, a $\log P < 3$ (and others state $\log P$ should be less than 2.75) reduces the risk of phospholipidosis (Waring 2010).

Summary

More so than any other physiochemical parameter, lipophilicity, quantified by $\log P$ or $\log D$, determines ligand–target binding interactions, solubility, ADME (absorption, distribution, metabolism and elimination) properties as well as in vivo toxicological outcomes, and, therefore, the overall quality of the drug candidate. For oral drugs launched since 1983, $\log P$ values have remained fairly consistent with $\log P$ values between 2.3 and 2.6 and oral CNS agents averaging $\log P$ values of 2.8. As discussed, the properties of a compound and its clinical success are compromised at both extremes of the lipophilicity scale, engendering adverse disposition and/or toxicology. High lipophilicity ($\log P > 3$) can lead to problems with compound solubility, metabolism, diminished free drug concentration, and increased ancillary pharmacology; in contrast, low lipophilicity ($\log P < 1$) can lead to poor membrane permeability and high renal clearance of un-metabolized parent. Surprisingly, optimal lipophilicity for therapeutic agents lies in a very narrow range of $\log P \sim 1$ – 3 . Recently, new composite parameters have been developed to assess efficiency metrics in chemical optimization, and most (such as LLE_{AT} , $LLEP$, and $LipE$) utilize lipophilicity as a major determinant in enthalmic optimizations. Historically, lipophilicity is typically increased in the course of a lead optimization effort to enhance target potency and then reduced in late lead optimization to diminish the adverse pharmacology and toxicology of potent, lipophilic leads. In future drug discovery efforts, it would be interesting to see medicinal chemists develop their structure–activity relationships (SAR) within the more narrow, yet optimal, $\log P$ ranges and assess

if successful clinical candidates are arrived at more quickly.

Cross-References

- ▶ Affinity
- ▶ Drug-Drug Interactions
- ▶ Half-Life
- ▶ Metabolism

References

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Liquid Diet for Administering Alcohol

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Definition

This is a technique for feeding alcohol (ethanol) as part of a liquid diet. The technique helps to mimic in experimental animals the effects of chronic alcohol intake in man and is used in research on alcohol effects in experimental animals, especially rodents. It has been used for more than 40 years in many experimental studies that investigate and model the effects of alcohol abuse and dependence in animals.

Proper controls and dietary adequacy pose significant challenges in studies on chronic exposure to alcohol in rodents. Thus, a suitable animal model that mimics the effects of chronic alcohol intake in man has long been sought. The technique of feeding ethanol as part of a totally liquid diet was first reported in 1963 (Lieber et al. 1963). Then, the liquid diet technique became the most preferred and practical method to induce physical dependence on alcohol experimentally since aversions to alcohol can be overcome and the intake is sufficient to sustain high daily alcohol consumption.

The route of drug delivery is an important consideration when evaluating the long-term biobehavioral adaptations occurring in response to chronic drug administration. Before the development of liquid diet technique, alcohol was commonly given to rats as part of their drinking water. Alcohol administration in water is associated with insufficient consumption and heavy weight loss. Insufficient intake of alcohol results in low levels in the blood; on the other hand, if the intake of alcohol is sufficient, there can be significant

liver damage due to an inadequate intake of dietary nutrients rather than to the effects of alcohol (Lieber and DeCarli 1989). Esophageal and gastric ulceration may also appear frequently. Administering alcohol to experimental animals as part of a liquid diet provides an efficient model allowing the investigation of chronic effects of alcohol without irrelevant harmful effects. It is also closer to chronic intake of alcohol in man. In addition to achieving a significant alcohol intake, this technique has the advantage of allowing the study of methods for minimizing alcohol-induced liver injury.

There are several liquid diet formulae available containing a mixture of mainly carbohydrates, oils, proteins, vitamins, and mineral (Lieber and DeCarli 1989). Milk is known to be an essential nutrient for growth of mammals. Cow's milk contains the major ingredients of an ideal liquid diet. It has also been reported that cow's milk may be used as a liquid diet in rats after the addition of 1 % (w/v) sugar (Parale and Kulkarni 1986) or a synthetic sweetener and vitamin A (Uzbay et al. 1995). A modified liquid diet of chronic alcohol administration to rats has also been defined and used (Uzbay and Kayaalp 1995).

Principles and Role in Psychopharmacology

Some Critical Points in Liquid Diet Practice

Liquid diet mixtures with or without alcohol provide 1,000 kcal/L. The liquid diet method for administration of alcohol involves pair feeding of control and treated animals with identical amounts of the same diet to control exposure to putative nutritional deficits. Control rats are paired with an isocaloric liquid diet containing a carbohydrate such as sucrose or dextrin maltose as a caloric substitute for ethanol. It is highly recommended to have a second control group with continuous access to standard laboratory diet and water. If the alcohol-treated group differs from both control groups and the control groups do not differ from each other, effects seen will not be due to limitations in dietary intake or the liquid

Liquid Diet for Administering Alcohol, Table 1 A simple liquid diet formula for studies on alcohol dependence^a

| Ingredients | Liter |
|-----------------|----------|
| Cow's milk | 925 ml |
| Ethanol (96.5%) | 75 ml |
| Vitamin A | 5,000 IU |
| Sucrose | 17 g |

^aUzbay and Kayaalp (1995); 1000.7 kcal/L

diet but rather to alcohol per se (Driscoll et al. 1990).

To prevent decrease in diet intake and weight loss, ethanol (96.5 %, v/v) should be gradually presented in progressively increasing concentrations during a habituation phase. After almost a week's feeding with liquid diet without ethanol, ethanol (about 2.5 % v/v) can be added to the liquid diet for 3–4 days. Then, the ethanol concentration can be increased to approximately 5 % for 3 days and finally to 7.0–7.5 %. When ethanol concentration is increased, a carbohydrate ingredient such as sucrose or dextrin maltose is reduced to maintain isocaloricity of the diet. Then, exposure to ethanol contained in liquid diet (approximately 7 %, v/v) is continued (Uzbay and Kayaalp 1995). A simple formula is shown in Table 1.

Although the liquid diet is meant to be the sole source of fluid and food, decreases in diet consumption can be avoided by giving access to water. Animals which receive water ad libitum lose less weight than groups that do not receive water ad libitum and keep consuming the same amount of liquid diet (Piano et al. 2001).

Daily alcohol consumption and blood ethanol levels are the most critical parameters for testing the validity of a liquid diet as a vehicle for alcohol administration. Above 10 g/kg/day alcohol consumption for a couple of weeks and more than 150 mg/dl blood ethanol concentrations may be adequate for the development of physical dependence on alcohol in rats (Uzbay and Kayaalp 1995). It has been recommended that in an acceptable liquid diet, 36–50 % of total energy should be acquired from the ethanol (Lieber and DeCarli 1989; Uzbay and Kayaalp 1995).

Lieber and DeCarli (1989) found that the alcohol obtained from a liquid diet containing 35 % ethanol provided about 36 % of the daily energy intake, with average ethanol intakes in the range of 10–14 g/kg/day. The associated blood-alcohol levels were over 100 mg/dl when pregnant rats consume the majority of their daily intake. These 100 mg/kg levels were similar to those estimated after human consumption of three drinks in 1 h and produced most major neurobehavioral effects of prenatal exposure to alcohol in their offspring (Driscoll et al. 1990).

Utilization of Liquid Diet Technique in Experimental Practice

Alcohol abuse and dependence remain among the greatest substance abuse problems worldwide. The mechanisms underlying physical dependence to alcohol are poorly understood. Generally accepted criteria for animal models of alcoholism include physical dependence upon and tolerance to alcohol. Tolerance is often inferred when large doses of alcohol have minimal effects on behavioral performance after chronic alcohol exposure. Physical dependence is defined by the appearance of withdrawal signs upon removal of alcohol after a period of intoxication.

The technique for the administration of ethanol as part of a liquid diet is preferable in the animal models for the development of alcohol tolerance and dependence. Alcohol withdrawal syndrome induced by discontinuing chronic ethanol intake is the most important evidence indicating the presence of physical dependence on alcohol (O'Brien 1996). A severe alcohol withdrawal syndrome is produced by the liquid diet technique in rats. Also, this method can be used to assess the pharmacological profile of drugs on the alcohol withdrawal syndrome in rodents (Uzbay and Kayaalp 1995).

The liquid diet technique has been adapted to a number of animal species other than rodents. One of the most successful applications has been the baboon liquid diet. The composition of the liquid diet is adjusted to meet the primate's needs. Thus, the ethanol content of the baboon liquid diet is significantly higher than that in the rat

because of a lesser aversion to ethanol in the former species (Lieber and DeCarli 1989).

Advantages of Liquid Diet Techniques

The liquid diet technique is a relevant model for alcohol consumption in humans. It provides high daily alcohol intake and sufficient blood-alcohol concentrations. It does not cause severe body weight loss. Even body weight increases have been reported in rats consuming ethanol-containing liquid diet (Lieber and DeCarli 1989; Uzbay and Erden 2003).

One of the major advantages of this technique is the facilitation of the pair-feeding process. Usually, the alcohol-fed animals are allowed dietary consumption *ad libitum*, with amounts consumed being self-limited. Their dietary intake is monitored by determining the amount of liquid consumed (Lieber and DeCarli 1989).

The liquid diet technique has also the advantage of allowing for an accurate recording of the nutrients consumed and for an easy change of the nutritional components according to specific experimental needs. This technique has been useful in characterizing the metabolism of alcohol, in assessing the interactions between ethanol and nutrition, other drugs that are also hepatotoxic agents and carcinogens, and in elucidating the mechanisms of alcoholic liver injury, endocrine abnormalities, withdrawal states, developmental problems, and other central nervous system changes, including some degenerative and harmful complications (Lieber and DeCarli 1989).

Another use for the liquid diet technique is the investigation of prenatal exposure to alcohol in animals. When prenatal exposure to alcohol is required, pregnant rats should receive a liquid diet as their sole source of nutrition, and thus, a proportion of their caloric intake will consist of ethanol or an isocaloric carbohydrate such as sucrose. A commercially available liquid diet with high protein content meets the requirements during pregnancy and lactation. This technique facilitates comparisons with controls by simplifying pair-feeding procedures (Lieber and DeCarli 1989); this method also avoids effects due to inadequate maternal diets that can exacerbate the effects of ethanol (Lieber 1991).

In contrast to administering ethanol by gastric intubation, not allowing the development of physical dependence to alcohol in rats within a short time may be the main disadvantage of the liquid diet technique. More exposure time is necessary for a satisfactory model of physical dependence in animals.

Cross-References

- ▶ Abuse
- ▶ Alcohol
- ▶ Alcohol Abuse and Dependence
- ▶ Animal Model
- ▶ Physical Dependence
- ▶ Prenatal Exposure to Alcohol
- ▶ Tolerance
- ▶ Withdrawal Syndromes

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Lisdexamfetamine

Definition

Lisdexamfetamine (L-lysine-D-amphetamine) belongs to the phenethylamine and ► [amphetamine](#) chemical classes and is a drug specifically developed as an alternative to D-amphetamine for the treatment of ADHD. Lisdexamfetamine has been tailored to have a more prolonged effect than D-amphetamine, yet with a reduced abuse potential. Despite these advantages, the use of lisdexamfetamine has been associated with several side effects including dry mouth, decreased appetite, insomnia, and heart attack or stroke in individuals with preexisting cardiovascular disorders.

Cross-References

- [Adolescence and Responses to Drugs](#)
- [Amphetamine](#)
- [Attention-Deficit/Hyperactivity Disorder](#)
- [Hyperactivity](#)
- [Impulsivity](#)

Listening Span Test

Definition

In this test, subjects listen to sets of two to seven sentences and complete a written factual verification question for the content of each sentence. After the last sentence of each set, subjects recall the final word of each sentence in the order in which they were presented. The span (working memory capacity) represents the maximum number of sentences performed correctly on at least two out of three trials.

Lithium

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Synonyms

Lithium salts

Definition

Lithium is an alkali metal. Its salts, lithium salts, are used as a psychopharmacological drug for recurrence prevention of manic-depressive illness, in the treatment of acute mania, in augmenting the effects of antidepressants, and in cluster headache. The pharmacologically active compound is the lithium ion (Li^+).

Pharmacological Properties

History

Lithium was first used in psychiatric patients in 1871, based on a wrong pathophysiological hypothesis, and abandoned shortly afterwards. In 1949, the Australian psychiatrist John Cade first demonstrated the antimanic effects of lithium in psychotic patients. Starting an intensive program of research in the 1950s, his Danish colleagues Mogens Schou and Poul Christian Baastrup proved the efficacy of lithium in the treatment of acute mania and in the prevention of affective episodes in controlled studies.

Mechanism of Action

The initial direct target of Li^+ is the competition with Mg^{2+} at circumscribed metal ion-binding sites of proteins that need the binding of this ion as a cofactor in order to function. The enzymes

thus inhibited by Li^+ comprise quite a heterogeneous group of enzymes such as inositolmonophosphatase (IMPase), phosphoglucomutase (FGM), biphosphate-3'-nucleotidase (BNP1), adenylyl cyclase (AC), and glycogen synthase kinase 3 (GSK-3). AC, IMPase, and GSK-3 play a critical role in cellular signal transduction mechanisms, which are believed to be the main targets in the mechanism of action of Li^+ ions. Signal transduction mechanisms transmit the information impinging at receptors on the surface of the cell into the interior of the cell. Particularly important components are the "G-proteins," a family of heterotrimeric proteins located at the inner plasma membrane consisting of an α -subunit and the tightly associated $\beta\gamma$ -subunits. The α -subunit binds guanyl nucleotides. Interaction with an activated receptor induces exchange of the bound GDP with GTP and dissociation into free α - and $\beta\gamma$ -subunits which can activate various effector proteins. Activation is terminated by hydrolysis of GTP to GDP by the intrinsic GTPase activity of the α -subunit and reassociation of the heterotrimeric $\alpha\beta\gamma$ -complex. Effector proteins encompass enzymes like AC and phospholipases (C, D, A_2), which synthesize second-messenger molecules such as cyclic AMP, inositol trisphosphate (IP_3), or diacylglycerol (DAG). "Second messengers" often act via activation of protein kinases, which phosphorylate various target proteins such as ion channels or transcription factors. Given the crucial role of signal transduction in cellular regulation, it is not surprising that these systems in the brain are also critically involved in neural plasticity and resilience and are therefore candidates as potential targets in the mechanism of action of mood stabilizers such as lithium. Effects of lithium ions on signal transduction mechanisms have therefore been a major focus of research during the last two decades (for review, see Bauer et al. 2006).

Effects of Lithium on the Adenylyl Cyclase System

The inhibition by Li^+ ions of AC has been known for 30 years. It appears to be due to a competition with Mg^{2+} ions at the catalytic unit of AC.

In contrast, the chronic inhibitory effects of lithium on AC are not influenced by Mg^{2+} ions, but reversed by GTP, and therefore believed to be due to actions of lithium on G-proteins (discussed below). More recent research has also confirmed an inhibitory effect of lithium on the inhibitory interaction of receptors with AC and revealed its mediation by an action of lithium on the G_i -protein. In summary, lithium ions appear to balance signal transduction via the AC system. This could dampen the excessive pathological fluctuations of signaling that might be causative with regard to the mood swings in bipolar disorder.

Effects of Lithium on Phosphatidylinositol (PI) Signaling

Phosphatidylinositolphosphates (PIP), minor components of the lipids in the cell membrane, play an important role in the process of receptor-activated signal transduction. Hormones and neurotransmitters stimulate via activation of particular receptor subtypes the hydrolysis of PIP_3 to two second-messenger molecules, DAG and IP_3 , which activate, respectively, protein kinase C (PKC) and the intracellular release of Ca^{2+} -ions. IP_3 is metabolized to myo-inositol, which is used together with DAG for the resynthesis of PIs. The last step in the metabolism of IP_3 , the hydrolysis of inositolmonophosphate to myo-inositol by IMPase, is inhibited by lithium ions in the therapeutic concentration range ($K_i = 0.8 \text{ mM}$). The "inositol depletion hypothesis" postulates that the lithium-induced inhibition of IMPase leads to a depletion of the brain of myo-inositol and, subsequently, due to a compromised synthesis of PIs to a reduction of receptor-stimulated formation of PI-dependent second-messenger molecules. It is, however, now clear that even a 90 % reduction of myo-inositol content in the brain as observed in mice with targeted deletion of the Na^+ /myo-inositol-cotransporter (SMIT, discussed in detail below) does not result in functionally relevant reduction of PI synthesis although these mice show behavioral abnormalities reminiscent of mice treated with lithium salts. Thus, while myo-inositol appears to play a role in the

behavioral effects of lithium, effects beyond PI-formation seem to be responsible.

Measurements of the effects of lithium treatment on myo-inositol levels in the human brain are partly consistent with the inositol depletion hypothesis. Proton magnetic resonance spectroscopy (MRS) scans of bipolar patients show a significant reduction of myo-inositol content in the frontal cortex already after 5 days of lithium administration, at a time when the patient's clinical state was completely unchanged. Thus, while lithium indeed lowers the myo-inositol in the brain, this action alone cannot explain the therapeutic effect but may be the initial trigger for a cascade of subsequent alterations that ultimately account for the therapeutic effect.

In addition to hydrolysis of PIs, brain cells also acquire myo-inositol from the extracellular space by virtue of the sodium/myo-inositol cotransporter (SMIT), a high-affinity myo-inositol transport system that transports myo-inositol into the cells against a steep concentration gradient. Both the activity of SMIT and the expression of its mRNA in astrocytes are downregulated after chronic treatment with therapeutic concentrations of lithium salts. Two other mood stabilizers, valproate and carbamazepine, elicit the same effect, indicating that it might represent a common mechanism of action of mood stabilizers.

Similar to rat astrocytes, downregulation of SMIT mRNA expression also occurs in vivo in bipolar patients chronically treated with lithium or valproate as measured in neutrophils (Willmroth et al. 2007). SMIT expression in neutrophils was increased in bipolar-I patients. On the one hand, IP₃ and Ca²⁺ signaling were found to be compromised in peripheral blood cells of patients chronically treated with lithium salts. On the other hand, peripheral blood cells of depressive or manic patients showed an increased sensitivity of the PI system when compared with controls. These results provide evidence for an increased sensitivity of the PI system in peripheral cells of manic-depressive patients that is compensated or even overcompensated by treatment with lithium and, perhaps, other mood

stabilizers (see Bauer et al. 2006; van Calker and Belmaker 2000 for review).

Effects of Lithium on the Arachidonic Acid Cascade in the Brain

Membrane phospholipids can serve as a substrate for phospholipase A₂ (PLA₂), which is also activated by receptor/G-protein coupling. The released arachidonic acid (AA) and its bioactive eicosanoid metabolites can influence many physiological processes, including membrane excitability, gene transcription, apoptosis, sleep, and behavior. All three mood stabilizers, lithium, carbamazepine, and valproate, downregulate the gene expression, protein level, and activity of the AA-specific PLA₂ and also reduce the protein level and activity of cyclooxygenase 2 (COX-2) and prostaglandin E₂. Thus, AA metabolism might be another common target of mood stabilizers (see Rao et al. 2008 for review).

Effects of Lithium on Glycogensynthase-Kinase-3 (GSK-3)

GSK-3 is recognized as an important regulator of many vital cellular functions such as apoptosis, synaptic plasticity, cytoskeletal rearrangement, and circadian rhythm. Lithium inhibits GSK-3 directly by virtue of competition with Mg²⁺-ions and indirectly by virtue of Akt-mediated phosphorylation on the n-terminal serine (for review see Beaulieu et al. 2009). The inhibition by lithium of GSK-3 likely contributes to its antiapoptotic and neuroprotective effects.

Effects of Lithium on Protein Kinase Activities and Protein Phosphorylation

As discussed above, lithium ions modulate the basal and agonist-stimulated concentrations of the second-messenger molecules cyclic AMP, IP₃, Ca²⁺, and DAG and should therefore also influence the activity of the protein kinases A, C, and others that are regulated by these second messengers. Several studies have reported that lithium can modulate protein kinase A-mediated protein phosphorylation. Alterations of PKC activity by lithium have been conjectured earlier after the formulation of the inositol depletion hypothesis, since a depletion of inositol should

result in a decreased consumption for PI resynthesis and, thus increased accumulation of DAG, the activator of PKC. PKC regulates many pre- and postsynaptic aspects of neurotransmission including long-term alterations in gene expression and neuronal plasticity. Persistent activation of PKC is often followed by its rapid proteolytic degradation and downregulation of enzyme activity. This could explain why lithium after acute or subchronic treatment induces an increase, while chronic treatment results in a decrease of PKC or PKC-mediated processes. The alterations in gene expression observed after chronic lithium treatment (see below) could at least in part be mediated by effects on PKC.

Effects of Lithium on G-Proteins

As discussed above, the effects of lithium on AC and its actions on PI signaling suggest the involvement of mechanisms beyond alterations of the catalytic subunit of AC or depletion of myo-inositol, respectively. One additional mechanism by which lithium could modify the activity of these signal transduction systems is the alteration of activity of G-proteins. An influence of lithium on G-protein function can be assessed by cholera toxin and pertussis toxin, which via ADP-ribosylation directly activate or inhibit, respectively, the G_s -protein, which stimulates and the G_i -protein, which inhibits adenylyl cyclase. Using this approach, it was shown by *in vivo* experiments with microdialysis technique that chronic lithium treatment inhibits the function of G_i thereby increasing the basal level of cyclic AMP in the brain of rats. On the other hand, chronic lithium treatment apparently also inhibits the function of G_s , since the inhibition by chronic lithium of the receptor-mediated activation of adenylyl cyclase is counteracted by GTP. The inhibition of G_i may be due to a lithium-induced stabilization of the undissociated, inactive heterotrimeric $\alpha\beta\gamma$ state of the G_i -protein. Only this form is subject to ADP-ribosylation (for review, see Manji and Lenox 2000).

Effects of Lithium on Gene Expression

As already mentioned the activation by second messengers of protein kinases can lead to

phosphorylation of nuclear transcription factors that regulate gene expression. Accordingly, treatment with Li^+ ions affects the expression of a number of genes, most likely at least in part secondary to modulation of PKC and/or GSK-3 (for review, see Bauer et al. 2006). Of particular interest are the actions of lithium on so-called “immediate early genes,” members of the c-fos and c-jun families, which encode proteins that form the constituents of a family of transcription factors called AP-1 (activator protein 1). These genes are of pivotal importance for long-term changes in neuronal function. Genes regulated by AP-1 include neurotrophins, neuropeptides, neurotransmitter synthesizing enzymes, and other transcription factors. It is now well established that lithium regulates AP-1-binding activity and function. The regulation by lithium of transcription factors is obviously not restricted to AP-1, since it also modulates two other such factors, cyclic AMP-responsive element-binding protein (CREB) and nuclear factor κB (NF- κB).

Effects of Lithium on Cellular Resilience

The neuroprotective effects of lithium were only recently fully appreciated. They are at least partly explained by the finding that lithium upregulates the neuroprotective and antiapoptotic protein Bcl-2. Very recently, it has been shown that mood stabilizer also increases BAG-1, an antiapoptotic, glucocorticoid receptor co-chaperone protein. Many of these effects may be in part mediated via inhibition of GSK-3 β . That neuroprotection could also be an important mechanism *in vivo* is suggested by the findings that lithium induces neurogenesis in adult rodent brain and increases the total gray matter in human brain. These results are particularly important in view of the recent evidence from brain imaging and postmortem studies that mood disorders are associated with morphometric changes suggestive of cell loss and/or atrophy (see Machado-Vieira et al. 2009 for review).

Pharmacokinetics

After oral application lithium salts are almost completely resorbed from the intestine. Maximal plasma concentrations are reached after 1–3 h.

Elimination occurs exclusively through the kidneys. Steady-state concentrations are achieved after 4–5 days of treatment.

Dosage

The dosage of lithium should be slowly escalated if possible to minimize initially more pronounced adverse effects. At steady state, i.e., 5 days after the last dose escalation, plasma levels should be determined (12 h after last intake). When determining the dose of lithium, it is important to consider that different lithium salts have quite different molecular weights. Lithium tablets must therefore be dosed according to their content of Li^+ given in mmol. When switching from one lithium salt to another, this must be accounted for to avoid, for example, severe intoxication. Thus, for example, while lithium aspartate tablets of 500 mg contain 3.2 mmol Li^+ , lithium carbonate tablets of 450 mg contain 12.2 mmol Li^+ . When changing 1:1 from lithium aspartate to lithium carbonate, this would slightly reduce the dose measured in milligrams but, in fact, increase the dose of the active compound (Li^+) by a factor of almost 4, given the narrow therapeutic range of Li^+ – perhaps, already a toxic dose! While ordinary daily doses amount to 20–30 mmol, older patients with reduced lithium clearance often need much smaller doses.

Efficacy

Lithium salts have been proven efficacious as a monotherapy of acute mania of the euphoric type. Lithium is only a second-line treatment in dysphoric mania and mania with mixed features where valproate, atypical antipsychotics, and carbamazepine are considered first-line choices (Grunze et al. 2013).

The second indication for lithium is the treatment of acute depression in bipolar disorder. Lithium can be used as monotherapy as well as in combination with an antidepressant agent. The latter strategy of primarily combining lithium with an AD should not be mistaken as lithium augmentation (see below). The combination of lithium and the antidepressant should prevent the patient from switching into mania.

There is convincing evidence that lithium is the drug of first choice in the long-term treatment and prophylaxis of bipolar disorder. However, with the expansion of the bipolar spectrum, data on the effectiveness of lithium in routine care have been controversial.

Current guidelines specify that long-term lithium treatment is indicated in patients

1. who experienced at least one single-manic episode of disruptive severity and have a positive family history;
2. who experienced two episodes, one of them manic, and have a positive family history;
3. who experienced three episodes.

In addition, lithium has the greatest evidence supporting an antisuicidal and mortality-reducing effect in bipolar disorder. Clinicians should thus strongly consider initiating lithium treatment in patients with mood disorders accompanied by a high risk of suicide (Cipriani et al. 2013).

Lithium augmentation of an antidepressant has been recommended as the strategy of first choice in patients with therapy-resistant major depressive disorder in many of the current guidelines. The addition of lithium to a preceding antidepressant has a net enhancing effect on serotonin function.

Lithium may also be used for the long-term treatment of recurrent major depressive disorder, first of all as the antisuicidal effect has been proven for this diagnostic group too but in addition due to lithium's episode-preventing effect. However, evidence is not as solid as for bipolar illness.

Other indications for lithium treatment are:

- Conduct disorder and intermittent explosive disorder including severe aggression and explosive affect in children and mentally retarded patients, based on lithium's serotonin-enhancing effects
- Cluster headache, with a minor role of lithium behind various first-choice drugs
- Prophylaxis of herpes virus infections, based on lithium's antiviral activity

Recent research covers the immunoregulatory effects of lithium, possibly relevant in AIDS and

cancer as well as neuroprotective effects that are potentially useful in the prevention of dementia and neurological diseases (Machado-Vieira et al. 2009).

Safety/Tolerability

Long-term side effects of lithium are infrequent and serious side effects are rare, if the patients and the dosage are properly selected and monitored. Because lithium ions influence a large number of important biochemical processes (see above), lithium has a potential to induce a relatively wide spectrum of adverse reactions in a variety of organ systems. With regard to safety and tolerability, acute and prophylactic lithium therapies follow similar basic principles. When considering side effects, it is important to distinguish between acute and long-term changes, the relatively common symptoms that can appear during the normal course of lithium prophylaxis, and the rare, intense symptoms indicative of lithium intoxication.

Table 1 shows the relative and absolute contraindications to lithium therapy.

Table 2 shows adverse effects of lithium therapy and comments on frequency and therapeutic options.

The most important laboratory tests before starting long-term lithium treatment are:

- Serum creatinine and creatinine clearance (estimate using the Cockcroft equation)
- T3, T4, TSH levels
- Complete blood count
- ECG
- Fasting glucose levels

The serum lithium level should be measured 12 ± 1 h after the last dose has been taken. The dose requirement can then be estimated proportionally. Following the initiation of lithium prophylaxis, serum lithium levels must be checked on a weekly basis. Later, monitoring should be performed approximately once per month during the first year of treatment and, subsequently, every 6–12 weeks.

In general, for most patients, a serum lithium level in the range of 0.6–0.8 mmol/l is recommended for lithium prophylaxis. In older

Lithium, Table 1 (Absolute and relative) Contraindications to lithium

| | Absolute | Relative | Special caution with |
|----------------|-----------------------------|--|--|
| Renal | Acute renal failure | Disorders with decreased glomerular filtration rate, tubular disorders | |
| Cardiovascular | Acute myocardial infarction | Cardiac rhythm disorders (“sick sinus” syndrome) | Arterial hypertension |
| Neurological | | Cerebellar disorders myasthenia gravis | Cerebral sclerosis Dementia; epilepsy Parkinson’s disease |
| Dermatological | | Psoriasis | |
| Endocrine | | Hypothyroidism Addison’s disease | |
| Gynecological | | Pregnancy, 1st trimester | Pregnancy, 2nd and 3rd trimesters; childbirth; breastfeeding |
| Hematological | | Myeloid leukemia | |
| General | | Low sodium diet Anesthesia/surgery | Diarrhea, vomiting, fever |
| Medication | | Diuretics | Antiphlogistics Muscle relaxants; anesthesia Anticonvulsants Tetracyclines; spectinomycin ACE inhibitors Methyldopa; neuroleptics |

**Lithium, Table 2** Adverse effects of lithium salts

| Organ system | Symptoms | Remarks/therapy |
|---|---|---|
| Neurological/ Psychiatric | Fine tremor of the fingers | Frequent side effect. Therapeutic options: dose reduction, change of dose regimen, beta-receptor blockers |
| | Muscle weakness | More likely at start of therapy |
| | Memory impairment | |
| Gastrointestinal | Nausea | Often at start of therapy |
| | Vomiting | Diarrhea and vomiting can be signs of lithium intoxication! |
| | Abdominal pain | |
| | Diarrhea | |
| Cardiovascular | Changes in ECG; flattening/ inversion of T wave | Reversible. Nonspecific changes are not dangerous |
| | Arrhythmias | Very rare. Result from initiation or conduction defects |
| | First-degree atrioventricular block | Regular ECG monitoring |
| | Sick-sinus syndrome, ventricular extrasystoles | Discontinuation of lithium |
| | Second- and third-degree AV block, bundle-branch block | |
| Renal | Polyuria, polydipsia, reduced concentration capacity | Reversible on discontinuation. Management options: dose reduction, amiloride |
| | Reduced glomerular filtration rate | Rare, prevent or avoid transient lithium subintoxications |
| | Nephrotic syndrome | Rare, reversible on discontinuation |
| Metabolism, electrolytes, and water balance | Weight gain | Frequent. Consider low caloric diet with normal sodium intake |
| | Edema | Rare. Caution when administering diuretics |
| Endocrine | Euthyroid goiter | Common. Suppressive therapy with l-thyroxin |
| | Rise of TSH, hypothyroidism | Common in long-term treatment, substitution necessary |
| | Hyperparathyroidism with hypocalcemia | Infrequent. Check serum calcium |
| Hematological | Moderate leukocytosis | Common. Reversible |
| Dermatological | Acne | Treat as usual |
| | Hair loss | Rare (check for hypothyroidism) |
| | Psoriasis | Can be exacerbated; maybe a relative contraindication |

patients, in most women, and in patients who are particularly sensitive to side effects, it may be advisable to reduce lithium levels to 0.6 mmol/l.

Serum creatinine should be monitored at least every 6–12 months. Serum calcium should be monitored every 6–12 months due to the risk of hyperparathyroidism during lithium treatment. The patient's thyroid hormone status should be checked by measuring serum T3, T4, and basal TSH once a year. Regular ultrasound examination of the thyroid is also recommended.

A complete blood count (or at least a leukocyte count) should be performed every 6–12 months.

Medical diseases occurring during lithium treatment should be carefully monitored. Serum lithium should be assessed more frequently and the dosage adjusted so that serum lithium levels remain as low as possible.

In patients with arterial hypertension, low-salt diets should not be used, and diuretics should only be administered cautiously. Furthermore, in renal hypertension and diabetes mellitus, the

late renal sequelae of each disease must be taken into account.

In cases of cerebral sclerosis, dementia, and other psychoorganic disorders, lithium – even at therapeutic levels – can lead to disorientation and other neurotoxic symptoms.

Pregnancy, Breastfeeding

The risk of abnormal fetal development under lithium therapy has been overestimated for a long time. Based on case-control studies, the risk can be estimated as only slightly higher than normal during lithium therapy in pregnant women (at standard serum lithium concentrations). If the course of affective illness does not allow for interrupting long-term treatment, a continuation of lithium treatment during the first 3 months of pregnancy may be considered (Cohen et al. 1994). The side effects of lithium therapy apply both to the pregnant mother and the fetus. However, the toxicity threshold for the fetus is lower. A mother may nurse her child when on lithium therapy. However, the child's development must be properly monitored and the advantages of breastfeeding over formula-feeding need to be weighed against the risks.

Cross-References

- ▶ [Bipolar Disorder](#)
- ▶ [Depression](#)
- ▶ [Gene Expression](#)
- ▶ [Gene Transcription](#)
- ▶ [Mania](#)
- ▶ [Mood Stabilizers](#)
- ▶ [Neuroprotection](#)

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Local Field Potentials

Synonyms

Field potentials

Definition

The electrophysiological recorded local field potential (LFP) is thought to represent the synchronized input (sum of somato-dendritic potentials) into a neuronal ensemble, as opposed to output neuronal spiking activity. This signal is typically recorded using a low impedance

extracellular microelectrode that is subsequently band-pass filtered to remove slower (<10 Hz) and faster (>300 Hz) signal fluctuations, indicative of sleep-related slow oscillations and neuronal spiking (action potential) activity, respectively.

Cross-References

- ▶ [Magnetic Resonance Imaging \(Functional\)](#)

Lofepamine

Synonyms

Gamanil

Definition

Lofepamine is a tricyclic antidepressant with a tertiary amine chemical structure. It acts by inhibiting the reuptake of norepinephrine and serotonin. Its primary use is in the treatment of depression, but it is also occasionally used in treating anxiety disorders. It is metabolized to desipramine, a tricyclic associated with relatively selective norepinephrine reuptake inhibition, which is itself marketed as an antidepressant. Usage of lofepramine has declined in recent years in conjunction with the general decline in the use of tricyclics. Lofepamine has a side effect profile similar to that of other tricyclics, including drowsiness and anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention), although such side effects appear to be mild. Lofepamine appears to have fewer cardiovascular effects than other tricyclics, with a correspondingly lower potential for lethality in overdose.

Cross-References

- ▶ [Antidepressants](#)
- ▶ [Tricyclic Antidepressants](#)

Lofexidine

Synonyms

(*RS*)-2-[1-(2,6-dichlorophenoxy)ethyl]-4,5-dihydro-1*H*-imidazole

Definition

Lofexidine is an agonist at α_2 adrenoceptors that was originally used for treating hypertension. It acts presynaptically to decrease adrenergic neurotransmission in the central nervous system, notably activity of the locus coeruleus. Through this mechanism it decreases many of the autonomic symptoms of opioid withdrawal in humans and in animal models. It is under investigation for managing withdrawal from heroin and ▶ [methadone](#) and has been found more effective than placebo. Its efficacy appears similar to that of clonidine, another α_2 agonist, but it has lesser adverse effects.

Cross-References

- ▶ [Opioid Use Disorder and Its Treatment](#)

Long QT Syndrome

Synonyms

LQTS

Definition

A cardiac arrhythmia where the QT interval on the ECG is prolonged; it can be inherited or acquired. The acquired form is due to disturbances in blood electrolytes or to various drugs. It is a condition with delayed repolarization following depolarization (excitation) of the heart, associated with syncope (fainting) due to ventricular arrhythmias, which can deteriorate into ventricular fibrillation and ultimately sudden death.

Cross-References

- ▶ [Opioid Use Disorder and Its Treatment](#)
- ▶ [Sex Differences in Drug Effects](#)

Long-Delay Learning

Definition

Long-delay learning refers to the phenomenon whereby an association of two temporally related stimuli can be made when there is an extended period of time between their presentations. Traditional learning theory suggests that as the temporal delay between the presentations of two stimuli increases, there is a graded reduction in the strength of the association between the two. When long-delay learning occurs, the association of the two stimuli occurs over longer intervals than seen under traditional learning conditions. Such learning is usually suggested to be evolutionarily important.

Cross-References

- ▶ [Conditioned Taste Aversions](#)

Long-Term Depression and Memory

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Definition

Memory

Memory describes the storage of information acquired during learning in a form that can be

accessed and retrieved. It encompasses the conscious memory of factual information as well as the unconscious use of procedural information.

The acquisition, storage, and retrieval of information are arguably the most complex and fascinating functions of the nervous system and undoubtedly involve many brain regions. Following pioneering studies in the twentieth century, a convenient working model of learning and memory emerged whereby different brain regions are deemed responsible for storing different types of learned information (Table 1). The famous case of patient H.M. who suffered specific memory deficits following bilateral removal of the medial temporal lobe (reviewed by Squire and Zola-Morgan 1988) was pivotal in highlighting the separation of brain systems concerned with declarative memory (conscious recollection of episodic or semantic information) versus nondeclarative memory (unconscious use of learned information). Whether or not the different forms of memory stored in different brain regions involve common mechanisms, such as alterations in synaptic strength (e.g., long-term depression), remains controversial.

Long-Term Depression

Long-term depression (LTD) is the weakening of neuronal synaptic connections, typically following a specific pattern of neuronal activity. The reduction in synaptic strength (a form of synaptic plasticity) lasts from hours to days. It can be homosynaptic (specific to the synapses that are subject to the inducing pattern of activity) or heterosynaptic (spreading to nonstimulated synapses).

LTD is widely expressed throughout the central nervous system (CNS) and is elicited at excitatory and inhibitory synapses via a diverse number of mechanisms (Table 2). Evidence suggests that the mechanisms of LTD contribute to experience-dependent development and forms of learning and memory as well as being implicated in neurological disorders, including mental retardation, Alzheimer's disease, and drug addiction. For the purpose of simplicity, we have chosen to focus on LTD at excitatory synapses in two brain regions: the hippocampal CA1 area, where the



Long-Term Depression and Memory, Table 1 Classification of memory (Reviewed by Squire and Zola-Morgan 1988)

| | Declarative | Nondeclarative |
|---------------|---|---|
| Synonyms | Explicit | Implicit |
| Definition | Conscious recollection of specific information | Unconscious use of learned information |
| Brain regions | Hippocampus | Basal ganglia |
| | Perirhinal cortex | Amygdala |
| | Prefrontal cortex | Cerebellum |
| Examples | Episodic memory – the features of an event, e.g., <i>what, where, who</i> | Procedural learning of skills and habits |
| | Semantic memory of factual information | Operant conditioning |
| | Recognition memory | Classical Pavlovian conditioning, e.g., emotional conditioning; motor conditioning (e.g., eyeblink) |
| | Working (short-term) memory | |

classical form of LTD is expressed, best understood mechanistically, and a potential target site for cognition-enhancing drugs, and the ventral tegmental area (VTA) of the midbrain, where LTD is targeted by drugs of abuse and is therefore of particular psychopharmacological interest.

LTD and Memory in the Hippocampal CA1 Region

The hippocampus forms part of the temporal lobe learning and memory system concerned with declarative memory of episodic and semantic information (Table 1). Three forms of glutamate receptor-dependent LTD have been described in the hippocampal CA1 region (reviewed by Malenka and Bear 2004); each form is summarized in Table 3. The first description of LTD in the hippocampus was homosynaptic NMDAR-dependent LTD at Schaffer collateral synapses onto pyramidal cell dendrites in the CA1 region of hippocampal slices (Fig. 1). Postsynaptic NMDA glutamate receptors permit Ca²⁺ entry into the neuron, and it is generally well accepted that this Ca²⁺ influx triggers activation of postsynaptic proteins including the protein phosphatases, calcineurin, and protein phosphatase 1 (PP1). The expression of NMDA receptor-dependent LTD depends on the modification of AMPA glutamate receptor phosphorylation states in addition to physical loss of AMPA receptors from the synapse (“► [Receptor Trafficking](#)”). Protein synthesis and degradation of postsynaptic

density-95 (PSD-95) are required for the expression of this form of LTD.

Hippocampal mGluR-dependent LTD was first described in the CA1 region of hippocampal slices (reviewed by Malenka and Bear 2004) and requires mGluR5 receptor activation for its induction. This form of LTD can be induced chemically, via application of the selective group I mGluR agonists, or electrically via synaptic stimulation (Table 3). mGluR-dependent LTD, like NMDA receptor-dependent LTD, is expressed via mechanisms involving protein synthesis and the loss of postsynaptic AMPARs.

A distinct form of mGluR-dependent LTD exists in young rats that is induced by the group I mGluR agonist, DHPG, and synaptic stimulation but is expressed presynaptically. A retrograde messenger released from the postsynaptic cell is required, and likely candidates include endocannabinoids and 12-lipoxygenase metabolites of arachidonic acid, including 12(S)-HpETE, recently shown to be the endogenous mediator of mGluR-dependent LTD at excitatory synapses onto CA1 stratum radiatum interneurons (Gibson et al. 2008). This heterosynaptic form of LTD (*TRPV1-dependent LTD*) occurs in response to high-frequency stimulation and release of endocannabinoid-like molecules known as endovanilloids that act on presynaptic TRPV1 (transient receptor potential vanilloid 1) receptors.



Long-Term Depression and Memory, Table 2 Examples of LTD in different brain regions

| Brain region | LTD expressing synapses | Drugs affecting LTD | Implications in memory |
|------------------------|--|--|---|
| Hippocampus | SC-CA1 pyramidal neurons | NMDAR and Ca ²⁺ channel antagonists | Declarative learning and memory |
| | SC and A/C input to CA1 and CA3 pyramidal neurons | mGluR antagonists | e.g., semantic and spatial memory, novelty and learned recognition of environment, stress-induced memory recall |
| | PP to dentate gyrus interneurons | mGluR antagonists | |
| | SC-CA1 interneurons | Rimonabant (SR141716A), CB1 and TRPV1 receptor antagonists, mGluR antagonists | Clinical relevance: amnesia and cognitive impairment |
| | Interneuron to CA1 pyramidal neurons | Δ ⁹ -THC | |
| Ventral tegmental area | EPSCs onto dopamine neurons, IPSCs onto dopamine neurons | Amphetamine, D2 receptor agonists, opioids | Nondeclarative forms of learning and memory |
| Caudate/putamen | Cortical inputs to medium spiny neurons | NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and CB1 receptor antagonists | Adaptive learning of motivated actions in response to salient stimuli; development of habits |
| Nucleus accumbens | Cortical inputs to medium spiny neurons | Δ ⁹ -THC, CB1 and TRPV1 receptor antagonists, mGluR antagonists | Clinical relevance: development of “unhealthy” habits, e.g., drug addiction |
| Perirhinal cortex | Cortical inputs from entorhinal cortex to layer II/III pyramidal neurons | Quinpirole, NMDA, and kainate receptor antagonists | Recognition memory |
| Prefrontal cortex | Layer II/III fibers to layer V/VI pyramidal neurons | 5-HT _{2A/C} antagonists, group I mGluR antagonists, CB1R antagonists, MAPK inhibitors | Executive memory functions, e.g., working memory, organization of voluntary movements, emotion |
| Visual cortex | Thalamocortical input to layer V pyramidal neurons | Group II mGluR antagonists, NMDAR antagonists, cocaine | Development of visual circuitry |
| | White matter to layer II–IV neurons | mGluR antagonists | |
| Cerebellum | Parallel fiber input to Purkinje neurons | NOS and soluble guanylyl cyclase inhibitors, mGluR, D2 and CB1 receptor antagonists | Procedural (motor) learning |

CB1 cannabinoid type 1 receptor, EPSCs excitatory postsynaptic currents, 5-HT serotonin, IPSCs inhibitory postsynaptic currents, MAPK mitogen-activated protein kinase, mGluR metabotropic glutamate receptor, NMDAR N-methyl-D-aspartate receptor, NOS nitric oxide synthase, Δ⁹-THC delta 9-tetrahydrocannabinol, TRPV1 transient receptor potential vanilloid 1, SC Schaffer collateral, A/C associational/commissural, PP perforant path

The question of whether or not experimental models and mechanisms of LTD in the hippocampus underlie memory (reviewed by Massey and Bashir 2007) remains controversial. In principle, one would determine whether or not LTD is induced in the hippocampus coincidentally with

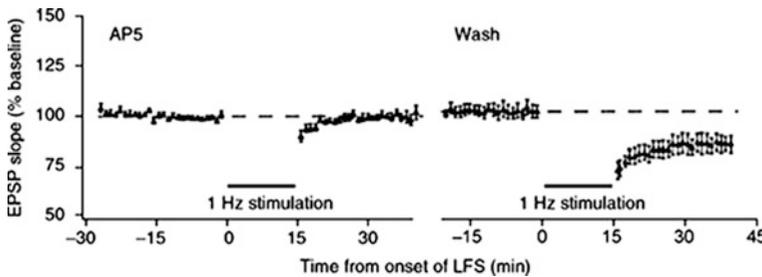
learning and memory and then blocks LTD, producing correlating impairments in memory acquisition and storage. In practice, the difficulties of “measuring” learning and memory make definitive, conclusive experiments of this kind challenging. CA1-restricted NMDAR1 gene



Long-Term Depression and Memory, Table 3 Different forms of LTD in the hippocampal CA1 region

| | NMDAR-dependent LTD | mGluR-dependent LTD | Endocannabinoid/ endovanilloid-mediated LTD |
|-------------------------|---|--|--|
| Synapses expressing | <i>SC-CA1</i> pyramidal neuron | <i>SC-CA1</i> pyramidal neuron, <i>SC-CA1</i> stratum radiatum interneuron | <i>SC-CA1</i> pyramidal neuron, <i>SC-CA1</i> stratum radiatum interneuron |
| Induction protocol | Low-frequency stimulation (<i>LFS</i>), 0.5–3.0 Hz, typically 1 Hz for 15 min | Paired-pulse low-frequency stimulation (<i>PP-LFS</i>), typically 1 Hz for 15 min; application of <i>DHPG</i> | <i>PP-LFS</i> , typically 1 Hz for 15 mins; application of <i>DHPG</i> ; high-frequency stimulation (<i>HFS</i>); e.g., 100 Hz (×2, 20 s inter-train interval) |
| Mechanism of induction | <i>Postsynaptic</i> : NMDAR activation; Ca ²⁺ influx and release from intracellular stores | <i>Postsynaptic</i> : Group I mGluR activation; Ca ²⁺ influx | <i>Postsynaptic</i> : Group I mGluR activation; Ca ²⁺ influx; phosphoinositide hydrolysis; release of retrograde messengers |
| Mechanism of expression | <i>Postsynaptic</i> : Activation of protein phosphatase, calcineurin, <i>PPI</i> ; <i>PSD-95</i> degradation; modification and internalization of <i>AMPARs</i> ; protein synthesis | <i>Postsynaptic</i> : Activation of protein tyrosine phosphatase, p38 mitogen-activated protein kinase cascade, <i>PI3K</i> and Ras-activated <i>ERK</i> ; <i>AMPAR</i> internalization; protein synthesis | <i>Presynaptic</i> : Activation of presynaptic receptors, e.g., <i>CBI</i> and <i>TRPV1</i> by retrograde messengers; decreased presynaptic neurotransmitter release |

AMPAR α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor, *CBI* cannabinoid type 1 receptor, *DHPG* dihydroxyphenylglycine, *HFS* high-frequency stimulation, *Hz* hertz, *mGluR* metabotropic glutamate receptor, *NMDAR* N-methyl-D-aspartate receptor, *PI3K* phosphoinositide-3 kinase, *PPI* protein phosphatase 1, *PP-LFS* paired-pulse low-frequency stimulation, *PSD-95* postsynaptic density-95, *TRPV1* transient receptor potential vanilloid 1, *SC* Schaffer collateral



Long-Term Depression and Memory, Fig. 1 Original experimental data of Dudek and Bear (1992) showing NMDA receptor-dependent LTD in the hippocampus. In the presence of the NMDA receptor antagonist AP5, low-frequency synaptic stimulation (1 Hz for 15 min) produces no change in the synaptic response. When AP5 is washed off, the same low-frequency synaptic stimulation

now produces a decrease in synaptic responses: LTD (Reproduced from Dudek S, Bear M (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 89: 4363–4367 with permission)

knockout mice lack NMDA receptor-dependent LTD at CA1 synapses and exhibit impaired spatial memory during a hippocampal-dependent task, while learned recognition of a novel environment in rats correlates well with the facilitation of homosynaptic NMDAR-dependent CA1

LTD. Hippocampal LTD is also enhanced by stress, which may be significant in stress-induced cognitive impairment. Overall, evidence suggests that LTD in the hippocampus is associated with at least certain forms of learning and memory (Massey and Bashir 2007).

LTD in the Ventral Tegmental Area (VTA)

The VTA is a midbrain nucleus containing dopaminergic neurons that project to the ventral striatum and the prefrontal cortex, along with nondopaminergic projection and local circuit neurons, some of which are GABAergic. Ascending mesocorticolimbic dopaminergic pathways along with nigrostriatal pathways play a role in internally generated movements, motivation and reward processing, learning, and cognitive functions, including nondeclarative forms of learning and memory. From a psychopharmacological perspective, these pathways are interesting because they are targets for drugs of abuse and are likely target sites for antipsychotic drugs.

A substantial body of literature suggests that glutamatergic synaptic plasticity in dopaminergic pathways may contribute to reward-related learning and the neuronal plasticity mechanisms underlying drug addiction (reviewed by Kauer and Malenka 2007; Wolf et al. 2004). Persistent forms of synaptic plasticity have been described in dopaminergic pathways (reviewed by Kauer 2004; Kauer and Malenka 2007; Wolf et al. 2004). A form of LTD at glutamatergic synapses was first described in VTA dopaminergic neurons in 2000. This form of VTA LTD was not dependent on either NMDARs or mGluRs, but did require an increase in intracellular Ca^{2+} , most likely via influx through voltage-gated Ca^{2+} channels, subsequent activation of a novel signaling mechanism utilizing protein kinase A, and downregulation of AMPARs. A second form of mGluR-dependent LTD is also expressed in VTA (Bellone and Lüscher 2006).

VTA LTD has been proposed as a potential “brake” on dopaminergic neuron excitability (Kauer 2004), as weakening excitatory synaptic strength would limit the tonic and phasic excitatory drive to these neurons from cortical and brainstem regions, potentially minimizing opportunities for synaptic strengthening such as long-term potentiation. Removal of this “braking” mechanism is a plausible route for psychoactive drugs to manipulate synaptic plasticity in

dopaminergic pathways and drive forms of learning that may be dysfunctional, such as habit learning in drug addiction.

Impact of Psychoactive Drugs

Hippocampal LTD, Cognitive Dysfunction, and Cognition-Enhancing Drugs

Evidence supports the idea that LTD may contribute to cognitive dysfunction. For example, soluble amyloid-beta protein ($A\beta$) extracted from the brains of Alzheimer’s disease patients enhances hippocampal mGluR-dependent LTD and disrupts the memory of learned behavior in rats (Shankar et al. 2008). Mouse models of Huntington’s disease, a neurological disorder involving cognitive dysfunction, exhibit impairments in hippocampal CA1 LTD as well as behavioral deficits in hippocampal spatial learning tasks (e.g., Murphy et al. 2000). NMDAR-dependent hippocampal LTD is both necessary and sufficient to cause an acute stress-induced impairment of spatial memory retrieval and may be involved in mediating some of the cognitive deficits that occur in disorders whose symptoms are aggravated by stress (reviewed by Massey and Bashir 2007). Taken together, these data suggest an underlying role for the mechanisms of hippocampal LTD in some aspects of cognitive dysfunction associated with specific neurological disorders.

Mechanisms underlying hippocampal LTD serve as possible drug targets for the treatment of cognitive dysfunction. For example, 17 β -estradiol ameliorates cognitive and memory dysfunction in postmenopausal women in addition to minimally suppressing hippocampal LTD in adult rats, suggesting that estrogen may act to improve memory by suppressing forgetfulness via a synaptic mechanism such as LTD (Vouimba et al. 2000). The NMDAR co-agonist D-serine enhances NR2B-dependent hippocampal LTD and reversal learning in the Morris water maze, supporting a role for NMDAR-dependent LTD in spatial learning and



highlighting molecular components of the LTD mechanism as targets for cognition-enhancing drugs.

VTA LTD and Psychoactive Drugs

VTA LTD is blocked by dopamine D2 (but not D1) receptor agonists (reviewed by Wolf et al. 2004) and therefore may be targeted by drugs of abuse that cause an increase in extracellular dopamine levels in the VTA. This has been shown for amphetamine, which blocks and reverses the somatodendritic dopamine transporter, thus causing the release of dopamine within the VTA. One might expect that D2 receptor antagonists, such as many of the antipsychotic drugs used to treat schizophrenia, could potentially enhance VTA LTD. However, comprehensive testing of the antipsychotic drugs used in clinical practice against VTA LTD has not been carried out.

If VTA LTD acts as a “brake” on the excitability of dopaminergic neurons (Kauer 2004), inhibiting LTD may provide a window of opportunity for synaptic strengthening. This synaptic plasticity would be associated with the salient event that caused elevated levels of extracellular dopamine in the VTA – for example, the acquisition of novel reward information or the presence of a drug of abuse. Such associations may contribute to the learning of procedural information with respect to drug-seeking and drug-taking behaviors that are, one might argue, maladaptive forms of memory. Conversely, induction of VTA mGluR-LTD reverses the cocaine-induced strengthening of glutamatergic synapses in dopaminergic neurons and is a putative mechanism for reversing the neuronal plasticity induced by cocaine (Bellone and Lüscher 2006).

Cross-References

- ▶ [Antipsychotic Drugs](#)
- ▶ [Cannabinoids and Endocannabinoids](#)
- ▶ [Classical \(Pavlovian\) Conditioning](#)
- ▶ [Cocaine](#)

- ▶ [Declarative and Nondeclarative Memory](#)
- ▶ [Excitatory Amino Acids and their Antagonists](#)
- ▶ [Long-Term Potentiation and Memory](#)
- ▶ [Short-Term and Working Memory in Animals](#)
- ▶ [Short-Term and Working Memory in Humans](#)
- ▶ [Spatial Memory](#)
- ▶ [Stress](#)
- ▶ [Synaptic Plasticity](#)

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Long-Term Potentiation and Memory

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Definition

Memory is central to our understanding about ourselves with a personal history, and consequently, memory loss has a devastating impact on both the individual concerned and their carers. Thus, one of the major goals in neuroscience is to understand the neural mechanisms that underlie the formation of memory within different brain regions. Long-term potentiation (LTP), which is the long-lasting increase in synaptic strength produced by trains of stimuli, has been proposed to provide a suitable cellular model of information storage in the brain. This argument is based on the defining characteristics of LTP (i.e., specificity, associativity, and persistence) and the demonstration that psychoactive drugs that block LTP have been shown to impair memory. This entry presents the evidence that the mechanisms that underlie LTP may be the same as those that are responsible for the formation of memory, with a focus on the impact of specific pharmacological manipulations. Memory formation clearly relies on fast, long-lasting changes in the connections between neurons; however, whether LTP, per current studies, underlies learning and memory is still unproven and consequently a matter for ongoing debate.

Impact of Psychoactive Drugs

Any neural mechanism underlying learning and memory must involve processes that enable rapid but lasting changes in the efficacy of synaptic connections in the brain. Hebb (1949) famously proposed that memories may be stored in the brain through changes in the strength of communication between neurons. He postulated that

“When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A’s efficiency, as one of the cells firing B, is increased.” In 1973, Bliss and Lømo showed that the repeated application of high-frequency stimulation (a tetanus) to the perforant pathway in the hippocampus produced a long-lasting increase in the synaptic response to a subsequent single-pulse stimulus. This long-lasting increase in synaptic strength is termed long-term potentiation (LTP).

The Induction of LTP

LTP has been most extensively studied in the CA1 region of the hippocampus, a region significant because damage here results in severe memory impairments in both humans (specifically, impairments in episodic memory) and in animals (spatial and associative memory). At excitatory synapses in this region, there are two subtypes of ionotropic glutamate receptor, the AMPA and NMDA receptors. LTP is known to depend on the activation of NMDA receptors, which are not involved in normal synaptic transmission owing to the presence of magnesium in the ion channel pore of the receptor. However, sustained release of glutamate, which occurs during high-frequency stimulation, causes the postsynaptic cell to depolarize, which removes the magnesium ions from the pore of the NMDA receptor, thus enabling the NMDA receptor to become activated. The NMDA receptor is therefore in a position to detect the coactivation of the presynaptic and postsynaptic cells and can act as what has been described as a “coincidence detector” (Collingridge 2004). Following the activation of the NMDA receptor, there is an influx of calcium into the postsynaptic cell, which triggers a range of intracellular second messenger systems, the effect of which is to produce an increase in synaptic strength (LTP). Thus, in most synapses that show LTP, the increase in calcium and thus the induction of LTP depend on the activation of NMDA receptors, but note that there are other forms of LTP, for example, in the mossy fiber-CA3 synapses, that do not depend on

NMDA receptors (described as NMDA receptor-independent LTP).

LTP, A Cellular Basis for Memory

It has been argued that LTP displays properties that are consistent with the premise that it is a cellular mechanism underlying memory storage (see Collingridge 2004). These properties include the demonstration that LTP is (1) input-specific, (2) associative or cooperative, and (3) persistent. Input specificity refers to the demonstration that only the afferents that have received stimulation show potentiation. Associativity or cooperative refers to the demonstration that if stimulation of one pathway is insufficient for the induction of LTP, simultaneous strong stimulation of another pathway will induce LTP at both pathways. If LTP is to be considered as a model mechanism for the storage of information, it needs to fulfill other criteria; for example, it must be relatively long lasting, although how long it is required to last is still unclear. Further, LTP must be demonstrated in regions of the brain other than the hippocampus, and indeed, there is now accumulated evidence that LTP may be induced in brain areas associated with memory including the cortex, striatum, thalamus, cerebellum, and amygdala (see Lynch 2004).

One strategy to investigate the link between memory and LTP has been to investigate whether learning produces LTP-like changes. A number of studies have reported that exposure to stimulus-enriched environment or training on learning tasks such as eyeblink conditioning or radial arm maze can result in increases in synaptic strength within the hippocampal formation (see Martin and Morris 2002). In addition, there is increasing interest in the relationship between LTP in the amygdala and a specific form of learning and memory process known as fear conditioning. Fear conditioning is a simple Pavlovian conditioning paradigm, which involves pairing a neutral stimulus, for example, a tone (the conditioned stimulus, CS), with an aversive stimulus, for example, a mild footshock (the unconditioned stimulus, US). This form of memory is rapidly acquired, the memory is long-lasting, and the paradigm presents an attractive model for

investigation of the neural basis of memory as it is relatively simple when compared with the memory paradigms associated with the hippocampus.

There are several lines of evidence to suggest that LTP in the amygdala underlies the formation of fear conditioning memory. For example, first, LTP may be induced in the same sensory afferents to the amygdala, which show enhanced synaptic transmission during fear conditioning, and second, pharmacological and molecular manipulations that block LTP have also been shown to block the acquisition of fear conditioning (see below). It has also been demonstrated that both LTP and fear conditioning are dependent on the reliability of the CS to predict the US (known as CS-US contingency). Thus, in fear conditioning paradigms, it is well reported that if the CS does not accurately predict the US, or if there is a better predictor, for example, other environmental cues, then the memory will be weaker. Similarly, in electrophysiological experiments, it has been shown that when a train of high-frequency stimuli applied to the afferents of the amygdala were paired with a series of depolarizing current pulses to the postsynaptic cell in the lateral amygdala, robust LTP was produced. However, if a further, unpaired, depolarization was added 10 s after the pairing, no LTP occurred (see Martin and Morris 2002).

Different Forms of LTP May Subserve Different Memory Processes

Further evidence to support the link between LTP and memory is provided by the demonstration that neither LTP nor indeed the formation of a memory is a single process. Different forms of LTP have been described, depending on how long the increase in synaptic efficacy lasts and the degree to which each form of LTP is sensitive to receptor antagonism, dependent on protein synthesis and/or gene transcription. Broadly, LTP has been divided into two subcategories: early LTP (E-LTP) and late LTP (L-LTP), where L-LTP lasts for hours *in vitro* and weeks *in vivo*. E-LTP (also described as LTP1) decays rapidly, is insensitive to protein synthesis inhibitors, and therefore does not depend on the

formation of new proteins in the cell. L-LTP has been further subdivided into LTP2 and LTP3. LTP2 lasts for an intermediate length of time and depends on new protein synthesis, but not on gene transcription, while LTP3 is the long-lasting and most stable component of LTP, which depends on both new protein synthesis and gene transcription (Raymond 2007).

In light of this dissociation between different forms of LTP, mediated by distinct cellular processes, it has been suggested that each may subserve different mnemonic processes. Thus, LTP1 may underlie short-term memory; LTP2 intermediate memory, i.e., memory that lasts up to 3 h; and LTP3 may underlie long-term memory, i.e., memory retained for longer than 3 h (see Blockland and Boess 2008).

The Effects of Pharmacological Agents on LTP and Memory

There is now a vast body of experimental evidence, which has identified pharmacological agents that block both LTP and memory or indeed enhance LTP and memory; hence, a comprehensive review of all such treatments is beyond the scope of this entry and the reader is referred to the references provided.

Glutamate

NMDA Receptors

One of the first pieces of evidence to suggest that LTP might be required for memory formation *in vivo* was provided by the demonstration that blockade of NMDA receptors, by the NMDA receptor antagonist AP5, in the hippocampus, blocks both the induction of LTP and produces an impairment in spatial learning but not in visual discrimination learning in the rat (see Martin and Morris 2002). Since that initial demonstration, NMDA receptor blockade has been shown to impair a range of hippocampal-dependent memory tasks including T-maze alternation, contextual fear conditioning, and non-hippocampal-dependent tasks such as fear conditioning. Interestingly, while blockade of NMDAR has been shown to impair both the encoding and early consolidation of memory information and the

induction of LTP, blockade of these receptors has been shown to have no effect on memory retrieval or on preestablished LTP (Collingridge 2004; Martin and Morris 2002).

Metabotropic Glutamate Receptors

There has been disagreement over the role that metabotropic glutamate receptors (mGluRs) play in LTP. LY341495, an mGluR antagonist, which at certain concentrations antagonizes all known mGlu receptors, has been shown to have no effect on LTP at hippocampal CA1 synapses. In contrast, antagonism of group 1 mGlu receptors has been shown in some studies to block the induction of LTP, and blockade of group 1 mGluRs has also been shown to impair a range of behaviors including spatial learning, contextual fear conditioning, and inhibitory avoidance learning (see Lynch 2004).

AMPA Receptors

Ampakines are a class of compounds, which bind to AMPA receptors but do not show either agonist or antagonist effects. These compounds act to keep the channel open once glutamate has bound, thus prolonging current flow through the receptor. Ampakines have been shown to lower the threshold for the induction of LTP and increase the magnitude of LTP. Behavioral studies have revealed that these compounds improve retention in the radial arm maze and improve short-term memory (Lynch and Gall 2006).

Acetylcholine

Muscarinic Receptors

Muscarinic acetylcholine receptors (mAChRs) are G protein-coupled receptors of which there are five subtypes (M₁–M₅). mAChRs have long been implicated in a variety of memory functions, for example, scopolamine a nonselective mAChR antagonist has been shown to produce significant behavioral impairments in tasks including the water maze, fear conditioning, and object recognition. Consequently, the roles of the mAChRs in LTP at many areas of the central nervous system have been extensively studied. Activation of mAChRs has been shown to facilitate the induction of LTP, and the application of

the muscarinic agonist carbachol has been shown to enhance LTP and to improve memory performance (see Blockland and Boess 2008; Shinoue et al. 2005). However, in contrast to such reports, administration of the nonselective mAChR antagonist atropine was found to have no effect on the induction of LTP, although it did significantly reduce the magnitude of the LTP, and scopolamine has been shown to have no effect on the induction of LTP in the perirhinal cortex.

Nicotinic Receptors

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels comprising either α subunits or a combination of α and β subunits, with $\alpha 7$ and $\alpha 4\beta 2$ being the two main subtypes in the central nervous system. Studies have shown that the application of nicotine can both induce LTP and enhance LTP produced by subthreshold levels of stimulation, an effect dependent on both $\alpha 7$ and non- $\alpha 7$ nAChRs. In memory tasks, acute intrahippocampal administration of nicotine after training has been shown to enhance hippocampal-dependent memory, and chronic administration of nicotine has been shown to improve spatial working memory in the radial arm maze; however, other studies using different doses, dosing methods, and regimes have found conflicting results (see Kenney and Gould 2008).

Dopamine and Noradrenaline

The neuromodulators dopamine and noradrenaline have been implicated in both LTP and memory. Thus, pharmacological blockade of dopamine D1/D5 receptors has been shown to impair L-LTP in the CA1 region of the hippocampus and to impair long-term but not short-term spatial memory in the water maze while blockade of beta-adrenergic receptors modulates E-LTP (see Martin and Clark 2007). LTP has been produced in the mesolimbic dopamine system, which comprises the ventral tegmental area and nucleus accumbens, and in view of the key role this neural system plays in the behavioral effects of drugs of abuse, there is increasing research into the role of LTP and other forms of synaptic plasticity in the development of addiction (see Saal and Malenka 2005).

Conclusions

There is now a huge body of research attempting to evaluate the hypothesis that LTP is a cellular substrate for learning and memory, and clearly, much of this evidence has been obtained from pharmacological studies like those described above. However, such evidence is correlative, and although both LTP and memory may be disrupted by the same interventions, this does not prove that both processes are mediated by the same underlying mechanisms. For example, it has been argued by some investigators that the observed impairments in the water maze following NMDA or muscarinic receptor blockade might be accounted for by impairments in sensorimotor processes or that LTP might play a role in cognitive processes other than memory, for example, attention, that contribute to performance in behavioral tasks (see Martin and Morris 2002). Further, LTP is often studied *in vitro*, using highly artificial stimulation protocols; so, while the processes that produce LTP in the laboratory may provide valuable insights into synaptic physiology, it must be remembered that they do not represent the actual mechanism for the storage of information *in vivo*.

Thus, while the acquisition and consolidation of memory must require quick and long-lasting changes in neural circuitry, a definitive link between LTP and the engram has not yet been provided.

Cross-References

- ▶ [Excitatory Amino Acids and Their Antagonists](#)
- ▶ [Nicotinic Agonists and Antagonists](#)
- ▶ [Spatial Learning in Animals](#)
- ▶ [Synaptic Plasticity](#)

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Loprazolam

Definition

Loprazolam is a high-potency medium-acting benzodiazepine medication used in the treatment of sleep disorders. It has some antispasmodic and anticonvulsant effects. It is not an antidepressant. Unwanted effects include sedation, headaches, paradoxical excitement, confusion, cognitive and psychomotor impairment, and confusion in the elderly. Long-term use may induce dependence with withdrawal reactions. Recreational use and abuse can occur: loprazolam is a scheduled substance.

Cross-References

- ▶ [Benzodiazepines](#)
- ▶ [Insomnias](#)
- ▶ [Minor Tranquilizer](#)

Lorazepam

Definition

Lorazepam is a ▶ [benzodiazepine](#) that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., its ▶ [elimination half-life](#) is 10–18 h), and it does not have active (i.e., benzodiazepine) metabolites. Lorazepam is used primarily to treat anxiety, including panic. Like most similar compounds, it is subject to tolerance, dependence, and abuse.

Cross-References

- ▶ [Anxiolytics](#)
- ▶ [Benzodiazepines](#)

Lormetazepam

Synonyms

Methyl-lorazepam

Definition

Lormetazepam is a benzodiazepine medication that has anxiolytic, sedative, and anticonvulsant properties. Its duration of action is of intermediate length relative to other benzodiazepines (i.e., ▶ [elimination half-life](#) 10–12 h), and it does not have active (i.e., benzodiazepine) metabolites. It has been used clinically as a hypnotic. Like most similar compounds, lormetazepam is subject to tolerance, dependence, and abuse.

Cross-References

- ▶ [Anxiolytics](#)
- ▶ [Benzodiazepines](#)
- ▶ [Hypnotics](#)