Drugs of abuse: anatomy, pharmacology and function of reward pathways

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Drugs of abuse are very powerful reinforcers, and even in conditions of limited access (where the organism is not dependent) these drugs will motivate high rates of operant responding. This presumed hedonic property and the drugs' neuropharmacological specificity provide a means of studying the neuropharmacology and neuroanatomy of brain reward. Three major brain systems appear to be involved in drug reward—dopamine, opioid and GABA. Evidence suggests a midbrain–forebrain–extrapyramidal circuit with its focus in the nucleus accumbens. Data implicating dopamine and opioid systems in indirect sympathomimetic and opiate reward include critical elements in both the nucleus accumbens and ventral tegmental areas. Ethanol reward appears to depend on an interaction with the GABA subcomplex but may also involve common elements such as dopamine and opioid peptides in this midbrain–forebrain–extrapyramidal circuit. These results suggest that brain reward systems have a multidetermined neuropharmacological basis that may involve some common neuroanatomical elements.

The concepts of reward, motivation and reinforcement are difficult to study from a neurobiological perspective primarily because quantitative measurement is difficult even if these terms are defined operationally. A reinforcer can be defined operationally as any event that increases the probability of a response. Reward is often defined similarly but with some positive affective coloring, such as pleasure. This review adopts the latter definition of reward; measurement will largely be restricted to reward associated with any event (drug) for which an animal will perform an operant response.

Animals will readily self-administer drugs either intravenously or orally, and drugs that are self-administered by animals correspond well with those of high abuse potential in humans. Drug self-administration behavior follows many of the same rules as behavior reinforced by conventional reinforcers such as food, water and sex. In the nondependent state (usually a condition of limited access), the drug generates a motivational state much as other incentives with low drive, such as saccharine. Psychomotor stimulant drugs, such as cocaine, are very powerful reinforcers. Even in a limited-access, nondependent condition, rats will press up to 150 times for one injection of 0.75 mg/kg of cocaine. In the dependent state, additional motivational power is exerted by negative reinforcement where the drug blocks or reduces the presumably aversive state of withdrawal.

These properties and the neuropharmacological specificity of drugs make them ideal for studies of the neurochemistry of reward. Three important neurochemical systems—dopamine, opioid peptides and GABA—are explored here for their role in drug reward. The insights derived from these studies are used to propose a reward circuit of possible heuristic value for future work in drug dependence and psychopathology.

Reward: neuroanatomical distribution

Two major dopamine systems originate in the ventral midbrain: the nigrostriatal dopamine system and the mesocorticolimbic dopamine system. The mesocorticolimbic dopamine system has been implicated in drug reinforcement. The cell bodies of this system originate in the ventral tegmental area (VTA), originally described as the A10 group of catecholamine neurons, and project to the forebrain, largely the nucleus accumbens, olfactory tubercle, frontal cortex, amygdala and septal area (see Fig. 1). There is a reverse topographic distribution, with ventral dopamine neurons in the VTA projecting to dorsal regions and the dorsal VTA neurons projecting to ventral regions.

Mesocorticolimbic dopamine

As an interface between the midbrain and forebrain, the mesocorticolimbic dopamine system may be one of the more anterior components of the complex isodendritic core of the reticular formation. It has been hypothesized to modulate the activity of the ventral striatum, a brain region thought to be involved in converting emotion into motivated action and movement (for review see Ref. 6). Selective destruction of the dopamine projection to the ventral striatum causes decreases in locomotor activity induced by new environments, in motor activity produced by food presentation, and inactivation produced by scheduled food delivery (schedule-induced polydipsia) (for reviews see Refs 5 and 7).

Similar lesions have also produced a syndrome of perseveration with reduced distraction caused by irrelevant information, and a decrease in behavioral switching and flexibility. In learning tasks, animals with similar 6-hydroxydopamine lesions show impaired spontaneous alternation, disturbed acquisition of spatial habits and difficulty in reversing previously learned habits.

The effects of direct injection of dopamine and amphetamine antagonists have implicated the mesocorticolimbic dopamine system in locomotor activation and the psychostimulant actions associated with indirect sympathomimetics. Dopamine and amphetamine injected into the nucleus accumbens stimulate locomotor activity, and injection of haloperidol into the nucleus accumbens blocks the locomotor activation produced by D-amphetamine. A similar blockade of amphetamine-, cocaine- and methylphenidate-induced locomotor activation has been observed following 6-hydroxydopamine lesions of the region of the nucleus accumbens. (For review, see Ref. 5.)
In the absence of drug administration, the mesocorticolimbic dopamine system appears to act as a modulator or a filtering and gating mechanism for signals from the limbic regions, signals mediating basic biological drives and motivational variables. These signals are thought ultimately to be translated into motor acts via the output of the extrapyramidal motor system (see Refs 5, 6 and 8 for more details and review). It is still not clear why activation of this system is reinforcing but substantial evidence suggests that the rewarding actions of psychomotor stimulants are mediated by the mesocorticolimbic dopamine projection (see below). One hypothesis is that the mesocorticolimbic dopamine system has a critical role in the species-typical motor arousal associated with anticipation of reward. Another view is that all addictive drugs have a psychostimulant action that contributes to the reward.

Dopamine in acute rewarding effects of psychomotor stimulants

Neuropharmacological studies have established an important role for central dopamine in the acute reinforcing effects of cocaine (see Woolverton and Johnson, this issue). Low doses of dopamine receptor antagonists, when injected systemically, reliably increase self-administration of amphetamine and cocaine in the rat. This increased self-administration has been interpreted as a partial blockade of the rewarding actions of cocaine because rats will compensate for decreases in the magnitude of reinforcement with an increase in cocaine self-administration (or a decrease in the interval between injections). This increase is similar to the increase observed after lowering the dose of cocaine in the self-administration session (see Stolerman, this issue). Adrenoceptor antagonists, such as phenoxybenzamine, phenol-
amine and propranolol, have no effect on stimulant (amphetamine) self-administration.

Recent work using systemic injections of selective dopamine receptor antagonists has shown that both D1 and D2 receptors may be important for the reinforcing actions of cocaine in animals (see Woolverton and Johnson, this issue).

A role for dopamine in the reinforcing properties of cocaine was strengthened by the observation that 6-hydroxydopamine lesions of the nucleus accumbens produce extinction-like responding in cocaine and amphetamine self-administration, as reflected in a significant and long-lasting reduction in responding over days. Decreases in the reinforcing effects of cocaine have also been observed following 6-hydroxydopamine lesions of the nucleus accumbens using a progressive ratio schedule. Similar 6-hydroxydopamine lesions of the frontal cortex and caudate nucleus fail to significantly alter established cocaine self-administration.

Neurochemical studies using in vivo microdialysis confirm that dopamine release is increased in the nucleus accumbens during i.v. self-administration of cocaine. I.v. self-administration of cocaine in experienced, trained animals produces a gradual increase in dopamine levels in the nucleus accumbens that reflects the pattern of self-administration, although an exact relationship with the interval between injections and the self-administered dose has yet to be demonstrated.

When saline is replaced by cocaine, rats rapidly stop responding and dopamine levels in the nucleus accumbens rapidly decline.

Dopamine in acute rewarding effects of ethanol

Several studies have suggested that brain dopamine systems may also be involved in the reinforcing properties of low doses of ethanol. Dopamine receptor antagonists reduce lever pressing for ethanol in nondeprived rats and also reduce home-cage ethanol drinking. Dopamine receptors in the nucleus accumbens may have an important role in ethanol self-administration, since dopamine receptor antagonists injected into the nucleus accumbens decrease oral ethanol self-administration in male Wistar rats that have not been deprived of food or water and have been trained in a two-lever, free-choice self-administration task. In this task, within the dose range of 5-10% ethanol, decreases in dose produce decreases in responses for ethanol and in the amount of ethanol consumed. The difference between the dose-response function of ethanol (ascending) and cocaine (descending) probably reflects the difference in the route of administration - oral for ethanol and i.v. for cocaine.

Low doses of ethanol stimulate locomotor activity in certain strains of rats and produce marked increases in extracellular dopamine levels in the nucleus accumbens of rats. Extracellular dopamine levels have also been shown to increase in nondependent rats orally self-administering low doses of ethanol. Extracellular dopamine levels in the nucleus accumbens appeared to be directly related to the amount of ethanol consumed and were much higher in the genetic strain of alcohol-preferring P rats. Thus, there is also neurochemical evidence that dopamine systems may be involved in the low-dose reinforcing actions of ethanol. These data suggest that dopamine receptors in the nucleus accumbens may be involved in ethanol reinforcement in the nondependent rat. However, there is some evidence for dopamine-independent ethanol reward in free-choice, home-cage drinking (24-hour access) for review see Ref. 27, and Samson and Harris, this issue).

Opioid peptides

Opioid peptides are distributed throughout the brain and form three major functional systems defined by their precursor molecules: β-endorphin from pro-opiomelanocortin, enkephalins from proenkephalin, and dynorphin from prodynorphin. These peptides are involved in three major functions: modulation of the nociceptive response to painful stimuli and stressors, reward, and homeostatic adaptive functions such as food, water and temperature regulation (for reviews see Refs 29 and 30 and Di Chiara and North, this issue).

When injected intracerebrally, opioid peptides, like opiate drugs, raise nociceptive thresholds without altering basic sensory processing (touch, temperature and proprioception). Endogenous opioid peptides are thought to modulate brain nociceptive processing at many different levels of the neuraxis from the spinothalamic tract in the dorsal horn of the spinal cord to the periaqueductal gray to the medial thalamus. Stressors can induce analgesia that is reversed by opioid antagonists, suggesting a role for endogenous opioid systems in stress-induced analgesia.

Opiate drugs and opioid peptides alter consummatory behavior in animals. When injected intracerebrally, opioid peptides can induce feeding and drinking in rats while opioid antagonists reduce these behaviors.

Opioid peptides, like opiate drugs, have rewarding properties (see Di Chiara and North, this issue). Injection of opioid peptides into the VTA or nucleus accumbens facilitates intracranial self-stimulation. Rats will intracranially self-administer β-endorphin and β-endorphin injected i.c.v. produces place preferences. Rats will self-administer opioids into the VTA and the nucleus accumbens. Opioid peptides injected into these two regions stimulate locomotor activity and produce place preferences (see Di Chiara and North, this issue). Other regions supporting rewarding effects for opioids are the hippocampus and hypothalamus. Consistent with these results, opioid receptor antagonists produce robust place aversions in nondependent animals and reverse the lowering of intracranial self-stimulation thresholds produced by psychomotor stimulants.

Acute reinforcing effects of opiates

Opiate drugs such as heroin, like psychostimulants, are readily self-administered i.v. by animals. If there is limited access, rats and primates will maintain stable levels of opiate intake on a daily basis without any major signs of physical dependence. As with cocaine, decreases in the dose of heroin available i.v. to a nondependent animal will change
Fig. 2. Sagittal rat brain section illustrating opioid peptide-containing neurons (green), some of which may mediate opiate reward. These opioid peptide systems include the local enkephalin circuits (short segments) and the hypothalamic midbrain beta-endorphin circuit (long segment). These opioid peptide systems are superimposed on the neural reward circuit shown in Fig. 1. FC, frontal cortex; VTA, ventral tegmental area; VP, ventral pallidum; LH, lateral hypothalamus; SNr, substantia nigra pars reticulata; DMT, dorsomedial thalamus; PAG, periaqueductal gray; OT, olfactory tract; AC, anterior commissure; LC, locus coeruleus; AMG, amygdala; Hippo, hippocampus; Cer, cerebellum; C-P, caudate-putamen; IF, inferior colliculus; SC, superior colliculus; ARC, arcuate nucleus. Left: effect of different paradigms on opiate reward in rat.

Opiate reward

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<td>Intracranial electrical self-stimulation Lateral hypothalamus</td>
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<tr>
<td>Intracranial self-administration</td>
<td>Nucleus accumbens ↓</td>
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<td>Lateral hypothalamus ↑</td>
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<td>Ventral tegmental area ↑</td>
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<td>Intravenous self-administration</td>
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<td>Dopamine receptor antagonists -</td>
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<td>Dopamine denervation (6-hydroxydopamine) ↓</td>
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<td></td>
<td>Nucleus accumbens -</td>
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↑, facilitation; ↓, inhibition; -, no change; -↓, mixed results.

The pattern of self-administration such that the interval between injections decreases and the number of injections increases. Similar increases in the number of injections have been observed after systemic and central administration of competitive opioid receptor antagonists. This suggests that the animals attempt to compensate for opioid antagonism by increasing the amount of drug injected, and that there is a competitive interaction between antagonist and agonist at the receptor.

The μ-opioid receptor subtype appears to be important for the reinforcing actions of opiates. μ-Receptor agonists produce dose-dependently increase heroin self-administration (Negus, S. S. et al., unpublished). However, δ-opioid receptors appear to have an important role in the opioid motor stimulation that is dopamine (D1 receptor) dependent.

To determine the location of central opioid receptors important for the reinforcing properties of heroin, a series of studies was initiated using intracerebral injection of quaternary derivatives of opioid antagonists. These quaternary derivatives are charged, hydrophilic compounds that do not readily spread from the injection sites.

L.c.v. administration of methylnaloxonium dose-dependently increased heroin self-administration in nondependent rats. Small doses and small volumes of quaternary nalorphine, a mixed agonist/antagonist, increased heroin self-administration when injected into the VTA but not the nucleus accumbens.

By contrast, using larger injection volumes than in the study with quaternary nalorphine, a subsequent study with methylnaloxonium showed the region of the nucleus accumbens to be particularly sensitive to the effects of methylnaloxonium on heroin self-administration. Methylnaloxonium injected into the nucleus accumbens dose-dependently increased heroin self-administration at doses significantly lower than those required by the intracerebroventricular
route. However, injections of methylnaloxonium into the VTA increased heroin self-administration only at doses similar to those required by the intracerebroventricular route.

Rats will also self-administer opioid peptides directly into the region of the nucleus accumbens. In addition, opioid peptides injected into either nucleus accumbens or the VTA produce a dose-related increase in locomotor activity. These results suggest that neural elements in the region of the nucleus accumbens are responsible for the reinforcing properties of both opiates and cocaine.

Opiates, like other drugs of abuse, can increase dopamine release in the nucleus accumbens as measured by in vivo microdialysis in awake, freely moving animals. However, there is evidence to suggest that the reinforcing effect of opiates in the nucleus accumbens can be independent of dopamine release. Rats trained to self-administer cocaine and heroin on alternate days and receiving 6-hydroxydopamine lesions of the nucleus accumbens showed a time-dependent decrease or extinction of cocaine self-administration, whereas heroin self-administration returned to near-normal levels. A similar dopamine-independent effect for both heroin self-administration and heroin-induced place preference has been obtained using chronic dopamine receptor blockade. Nevertheless, opioids are self-administered directly into the region containing the cell bodies of origin of the mesocorticolimbic dopamine system, the VTA. Furthermore, microinjections of opioids into the VTA lower the reward thresholds for brain stimulation and produce robust place preferences (see Di Chiara and North, this issue).

Others have shown that the place preferences produced by opioids appear to have a major dopaminergic component. Thus, the reinforcing actions of opiates may involve both a dopamine-dependent (VTA) and a dopamine-independent (nucleus accumbens) mechanism (Fig. 2).

**GABA**

GABA is the most widely distributed inhibitory transmitter in the CNS. Its receptor is a macromolecular complex through which not only benzodiazepines but also barbiturates and alcohol may act (see Samson and Harris, this issue). At the molecular level GABA increases Cl⁻ ion flux in synaptic neurosomal prepar-
ations. This increase in ion flux is potentiated by benzodiazepines, barbiturates and ethanol at the electrophysiological level GABA produces postsynaptic inhibition. Benzodiazepines, barbiturates and ethanol have been shown to potentiate this inhibition, but the phenomenon has been relatively difficult to demonstrate for ethanol except in certain brain areas.

Ethanol, barbiturates and benzodiazepines all have classic sedative/hypnotic actions as measured in pharmacological studies, which include euphoria, disinhibition, anxiety reduction, sedation and hypnosis. These effects correlate well with the ability of sedative/hypnotics to modulate GABA-induced Cl⁻ fluxes. All of these drugs produce a release of punished responding in conflict situations, which correlates well with their ability to act as anxioytics in the clinic. This anxiolytic or tension-reducing property of sedative/hypnotics may be a major component of their reinforcing actions. Therefore, the neurobiological basis of their anxiolytic properties may provide clues to their reinforcing properties and their abuse potential.

GABA receptor mechanisms have been hypothesized to be involved in the anxiolytic actions of sedative/hypnotics as a result of studies showing that GABAₐ receptor antagonists block their anti-conflict effects and GABAₐ agonists potentiate these effects. Further, benzodiazepine inverse agonists and GABAₐ receptor antagonists have stress-inducing or anxiogenic properties in many animal models and in humans. These results suggest that the status of the GABAₐ receptor complex may determine endogenous stress levels. It follows then that GABA function in some limbic and extra-pyramidal regions such as the amygdala, ventral forebrain, olfactory tubercle and globus pallidus could easily influence and contribute to drug reward (see Fig. 3).

Role of GABAₐ receptor complex

Studies of the functional significance of GABA mechanisms in drug reward have focused on ethanol. While direct i.v. self-administration of drugs has been an effective tool for the study of the neuropharmacology of the reinforcing actions of drugs such as cocaine and opiates (see above), i.v. self-administration of ethanol (and most sedative/hypnotics) is not readily obtained in rats. The alternative model, oral ethanol self-administration in the rat, has been fraught with problems of confounding taste and consummatory behavior and the lack of reliable blood alcohol determinations.

Nevertheless, several recent studies using taste adulteration methods (sucrose or saccharine substitution) have provided reliable procedures for initiation and maintenance of alcohol intake. Reliable, sustained operant responding for 10% ethanol can be obtained in free-feeding and free-drinking rats (nondeprived), even after complete removal of sweetener, provided that the sweetener is withdrawn slowly.

GABA has long been hypothesized to have a role in the intoxicating effects of ethanol, since GABAₐ receptor antagonists reverse many of the behavioral effects of ethanol. GABAₐ antagonists decrease the ability of ethanol to produce ataxia, anesthesia and a release of punished responding (anti-conflict effects). At a biochemical level, ethanol in the range 10-50 mM potentiates stimulation by GABA of Cl⁻ uptake in synaptosomes from the cerebral cortex and cerebellum.

Further support for a role of brain GABA is provided by the observation that the partial inverse benzodiazepine agonist Ro154513, which has been shown to reverse some of the behavioral effects of ethanol, produces, in nondeprived rats, a dose-dependent reduction of oral ethanol (10%) in an operant self-administration procedure and in an operant free-choice situation. GABA-mimetic drugs also potentiate the effects of ethanol in many behavioral situations.

Both barbiturates and benzodiazepines, particularly the short-acting compounds such as methohexital and midazolam, are intravenously self-administered by rats. While one would expect some interaction of these drugs with the GABAₐ receptor complex to contribute to the self-administration of these drugs, there seem to be no systematic studies to date.

Another potential connection between GABA function and drug reward involves the functional output of the nucleus accumbens. The substantia innominata—ventral pallidum has been established as an important connection in the expression of behavioral stimulation produced by activation of the nucleus accumbens (for reviews see Refs 6 and 74). Furthermore, there are established efferent connections from the nucleus accumbens to the substantia innominata ventral pallidum that are thought to use GABA (see Fig. 3).

To test the hypothesis that the processing of the reinforcing properties of cocaine and heroin may also involve the substantia innominata—ventral pallidum, rats trained to self-administer cocaine intravenously received bilateral ibotenic acid lesions of the region of the substantia innominata—ventral pallidum. The lesions significantly decreased baseline cocaine and heroin self-administration, and when the rats were subjected to a progressive ratio procedure they showed a significant decrease in the highest ratio obtained for both drugs.

These results suggest that the substantia innominata—ventral pallidum may be an important site for processing the reinforcing effects of cocaine and heroin. Thus a GABA-mediated pathway may be a common output for drug reward.

Neurobiological circuit for drug reward

Based on studies of psycho-motor stimulants, opiates and ethanol, a reward circuit appears to involve several common elements. The circuitry connecting the ventral midbrain to the ventral forebrain forms a starting point for such a drug reward circuit. Classically known as the medial forebrain bundle, this pathway is composed of largely myelinated fibers connecting the olfactory tubercle, diagonal band of Broca, septum and nucleus accumbens with the hypothalamus and the VTA. It forms a major afferent and efferent conduction system of the hypothalamus. In addition,
there are the well-documented ascending monoamine pathways in the medial forebrain bundle such as the mesocorticolimbic dopamine system (see above).

The medial forebrain bundle has been extensively studied as a substrate for intracranial self-stimulation behavior (for review see Refs 77 and 78). There is evidence that this pathway supports the most robust self-stimulation with the least amount of current compared with all other brain reward sites. In addition, lesions of the medial forebrain bundle severely disrupt, but fail to eliminate, intracranial self-stimulation. While dopamine is thought to be an important component of the circuit supporting intracranial electrical self-stimulation, many other neuronal systems play a role. Numerous physiological studies have established that activity within the medial forebrain bundle that supports intracranial self-stimulation involves a descending myelinated component that is not dopaminergic (for review see Ref. 79).

These same brain structures connected by the medial forebrain bundle may be critical for drug reward (see Figs 1, 2 and 3), and the study of drug reward may provide some insight into the neurochemical components of this system. Dopamine appears to be critical in the rewarding properties of indirect sympathomimetics such as cocaine and amphetamine. In addition, both the VTA and the nucleus accumbens appear to be important for opiate reward. These same regions and other limbic connections to them, such as the amygdala, may be involved in sedative/hypnotic reward.

However, a critical role for dopamine in both opiate and sedative/hypnotic reward is not as compelling as for the indirect sympathomimetics. There is evidence for dopamine-independent opiate and ethanol reward (see above). Thus, while dopamine may contribute to the reinforcing properties of these drugs, it may not be essential. The alternate view favored by Wise and colleagues suggests that dopamine forms a critical link for all reward, including opiates and sedative/hypnotics. While open to multiple neurotransmitter inputs and outputs, this view still holds a centrist position for dopamine in all reward. An emphasis on multiple independent neurochemical elements, as opposed to a critical role for dopamine, effectively places the focus on the nucleus accumbens and its circuitry as an important, perhaps critical, substrate for drug reward.

The nucleus accumbens is anatomically situated such as to receive important limbic information that may then be converted to motivational action via its connections with the extra-pyramidal motor system. These limbic structures, such as the amygdala, frontal cortex and hippocampus, may also be important in drug reward via modulation of nucleus accumbens activity. New data suggest that the nucleus accumbens is not a simple homogeneous structure, and the shell portion (medial and ventral) may be more part of an extended amygdala system while the core resembles more the corpus striatum. If these anatomical distinctions reflect functional differences, this would give new impetus to the old hypotheses regarding a role for the amygdala in reward-related function.

This review has focused on the neurobiology of the acute rewarding effects of drugs. Information about such actions contributes to understanding of the neuropharmacology of endogenous systems involved in responses to naturally hedonic stimuli. In addition, these studies can provide a basis for investigating the neurochemistry of drug dependence.

Most models of drug dependence recognize that, as the organism reacts to the effects of a drug, adaptive processes are initiated to counter these effects. These processes persist after the drug has been cleared from the body and result in the withdrawal syndrome characteristic of drug dependence. An adaptation opposite to the acute effects of the drug itself can also have motivational consequences.

Opponent process theory proposes that reinforcers activate positive affective and hedonic processes, which for drugs are hypothesized to be simple, stable and occur soon after administration. As an adaptation to the presence of the drug, these positive affective processes are followed by negative affective and hedonic processes, which are slow to build up strength and slow to decay. The circuitry and neurochemical systems outlined in studies of the acute rewarding effects of drugs could also be important for the motivational effects of drug withdrawal. Identification of the cellular and molecular components of these adaptations may help in understanding not only drug addiction but also the function and dysfunction of the reward system in normal and abnormal behavior.

Acknowledgements

This work was supported in part by NIDA grants DA04043 and DA04398 and the National Institute of Alcohol Abuse and Alcoholism grants AA08459 and AA06420. The author is grateful to the Molecular and Experimental Medicine Word Processing Center for manuscript preparation, to colleagues and collaborators (past and present) for their contribution to the hypotheses expressed herein, and in particular to Friedbert Weiss, Athina Markou, Gery Schulteis, Barak Caine and Rocio Carrera for help in correcting the manuscript.

References

13 Roberts, D. C. S., Koob, G. F., Klonoff,
Note on drug nomenclature

The longhand chemical structure for SCH23390 has been cited incorrectly in TIPS. We are advised by Schering-Plough that the correct structure is as follows:

![Chemical structure of SCH23390](image)

We apologize for this error.