Interactive monoaminergic basis of drug dependence

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11.1. Introduction

The cover of the October 3, 1997 issue of *Science* showed Picasso's *The Absinthe Drinker*. The cover caption described absinthe as a narcotic made from a mixture of distilled spirits and plant extracts. Absinthe was a popular drink in Parisian cafes in the nineteenth century and was a favourite of artists such as Toulouse-Latrec and Modigliani, for example. Its widespread use led to interdiction in France early in the twentieth century. This pattern of escalating drug use followed by restrictive legislation has been repeated many times in many countries during the last centuries.

This cover of *Science* introduced a special issue reporting on various aspects of drug addiction including its basic biological mechanisms and approaches to therapy. One aspect of particular importance in this special issue was a discussion about how new findings about the biology of drug addiction should influence political policy decisions concerning the treatment of people who abuse drugs. This discussion underscores the broad social importance of basic scientific investigations of the mechanisms of drug addiction. As Dr. Floyd Bloom (1998) pointed out in his Editorial introducing the special issue of *Science* on drug abuse, "...the daily misfortunes and calamities associated with recreational use and abuse of and dependence on legal and illegal drugs reveal a problem with global dimensions and highly complex legal, moral, economic and health ramifications, both public and personal." These comments highlight the value of the chapters presented in this section. The following chapters collectively represent a broadening of the basis of understanding the mechanisms of drug dependence by taking those mechanisms beyond the critical role of dopamine to incorporate numerous interactions with other neurotransmitter systems contributing to the interactive monoaminergic basis of behaviour.

This chapter will review briefly the role of dopamine in drug dependence an how dopamine-mediated incentive learning can produce repeated use of drugs c abuse. It then will provide an overview of the following seven chapters showin the contribution of cholinergic, opiate, glutamatergic and cannabinoid systems t the underlying mechanism of drug abuse. Findings continue to expand knowledg of the complex interactions among neurotransmitter systems in the control o behaviour.

11.2. Incentive learning, dopamine and drug dependence

Since the beginning of the twentieth century, behavioural scientists and neuroscientists have developed and tested hypotheses concerning the environmental circumstances and biological mechanisms underlying the effects of rewarding or reinforcing stimuli on behaviour. It was clear to Thorndike (1911), for example, in his classic statement of the law of effect, that rewarding stimuli (satisfiers) lead to an increase in the likelihood that responses preciding them will recur in the future when the same environmental stimuli are present. This somewhat rigid stimulus-response connectionist view of the effects of reward on behaviour has yielded over the years to incentive conditioning views (Bindra, 1978; Bolles, 1972). These more modern theories of reward provide a basis for understanding the mechanisms of drug dependence.

Incentive learning occurs when a rewarding stimulus is encountered by an animal and is defined as the acquisition by neutral stimuli of the ability to elicit approach and other responses in the future (Bindra, 1978; Bolles, 1972). When an animal learns to press a lever for food, for example, the lever itself and lever-related stimuli (*e.g.*, the location of the lever on the wall, a cue light just above the lever, *etc.*) acquire the ability to elicit approach and other responses (depressing the lever in this case) through their close temporal contiguity with the presentation of the rewarding food stimulus. When the animal encounters the lever or lever-related stimuli after incentive learning has taken place, those stimuli elicit approach and pressing responses. Thus, incentive learning has occurred, previously neutral stimuli acquiring the ability to elicit approach and other responses.

In recent years, many experimental findings have pointed to a critical role for dopamine in incentive learning (Beninger, 1983). The now classic study of Wise *et al.*, (1978) provides a good example. They showed that lever pressing and running responses of rats rewarded with food declined gradually when the rats were treated with the dopamine receptor blocker pimozide. This effect occurred in spite of the fact that the animals continued to receive food for lever pressing and that they were observed to continue to consume the food. The pattern of decline resembled the well-known extinction effect seen when food no longer is presented following conditioned operant responses. From an incentive learning point of view, the ability of reward-related stimuli to elicit approach and other responses was lost gradually when the animals were treated with pimozide (even though they continued to receive food rewards which they consumed). This and many other related obser-

tions (Miller *et al.*, 1990; Wise and Rompre, 1989) suggested that dopamine ayed a critical role in the acquisition and maintenance of incentive learning eninger, 1983).

When dopamine levels in the nucleus accumbens were measured directly following the presentation of food reward, they were found to be elevated; this observation was made in *in vivo* microdialysis and voltammetry studies (Kiyatkin, 1995; as *et al.*, 1995; Phillips *et al.*, 1989; Westerink, 1995). Similarly in electrophysiological recording studies, dopaminergic neurons have been found to be activated y natural rewarding stimuli such as food (Schultz *et al.*, 1997; Schultz, 1997). Results re consistent with findings from behavioural pharmacological studies implicating opamine in the neural mechanisms of reward.

It is no coincidence that it turned out that drugs of abuse including psychomotor stimulants such as amphetamine and cocaine produce their rewarding effects by activating dopaminergic neurotransmission (Koob and Bloom, 1988; Wise and Rompre, 1989). Because these drugs activate dopaminergic neurons in a manner similar to that produced by natural rewards such as food, they would be expected to produce incentive learning. In self-administration studies, for example, animals learn to press a lever to activate a pump that injects a small volume of a psychomotor stimulant directly into their blood stream via a chronic indwelling catheter (Katz, 1989). The subsequent increase in synaptic concentrations of dopamine would serve to produce incentive learning, increasing the ability of stimuli signalling reward, for example, the lever and related stimuli, to elicit approach and other responses in the future. These conditioned stimuli would serve to maintain drug seeking and drug taking by the animal. The self-administered drug could be seen as highjacking the natural incentive learning mechanism to create dependence in the user. In recent years, incentive theory has been applied directly to the understanding of drug craving and dependence (Di Chiara, 1995; Robinson and Berridge, 1993).

An important question that follows from the observation that dopamine plays a critical role in incentive learning and that incentive learning contributes to drug dependence, concerns the mechanism by which dopamine mediates the effects of rewarding stimuli on behaviour. One step in identifying this mechanism is to evaluate the contribution of dopamine receptor subtypes to reward-related incentive learning. Dopamine receptors have been found to exist in at least five different subtypes, termed D_1 through D_5. Based on their ability either to stimulate or inhibit the enzyme adenylate cyclase, these receptors have been classified into two groups, D_1-like, including D_1 and D_5 and D_2-like, including D_2, D_3 and D_4, respectively (Civelli *et al.*, 1993; Niznik and Van Tol, 1992; Sibley *et al.*, 1993). As reviewed in Chapter 30 of this volume, there now is strong evidence that D_1-like receptors mediate incentive learning. As this subtype of dopamine receptors activates the second messenger cyclic adenosine 3'5'-monophosphate (cAMP) that in turn activates cAMP-dependent protein kinase, it follows that this second messenger pathway may play a role in incentive learning. Possible mechanisms for the involvement of the cAMP pathway in reward-related learning are discussed in Chapter 30 and elsewhere (Beninger and Miller, 1998; Nestler and Aghajanian, 1997).

Two of the chapters in this section deal directly with dopamine: Chapters and 18. Chapter 14 by Oglesby presents a carefully argued case for the develo ment of tolerance to the subjective effects of psychomotor stimulants such amphetamine and cocaine as a basis of understanding drug dependence. The su jective effects of a drug can be evaluated experimentally in rats using the drug di crimination and self-administration paradigms. Oglesby reviews studies that sho that following chronic exposure to cocaine or amphetamine, the dose-effect cur for drug discrimination or self-administration is shifted to the right, indicating th development of tolerance. He assessed the monoaminergic mechanisms of this to erance with an apomorphine challenge test. This ingenious approach revealed th the basis of tolerance to cocaine was postsynaptic. However, microdialysis studi also implicated presynaptic mechanisms. Finally, Oglesby discusses the possibil ty that tolerance to cocaine is mediated by changes in the dynorphin system in th striatum. This chapter is a good example of the continuing exploration of the ro of dopamine in drug dependence and the identification of interactions with othe neurotransmitter or neuromodulator systems in this phenomenon.

Chapter 18 by Malberg and Seiden is unique to this volume in its exploratior of the mechanisms of neurotoxicity of amphetamine and related compounds. These amine release-enhancing drugs that are self-administered by humans and experimental animals have been shown to be toxic to serotonergic and dopaminergic nerve terminals in the central nervous system. In keeping with the study of the interactive nature of the monoamines in this volume, Malberg and Seiden discuss findings showing that dopamine is necessary for the amphetamine-related compounds to have their neurotoxic action on serotonergic terminals. They then review many of the agents that have been found to be neuroprotective when co-administered with the toxic substituted amphetamines. The diverse pharmacological actions of these agents (shown in Malberg and Seiden's Table 1) begin to come under a single critical variable when their actions on core body temperature are considered. It appears that agents that produce hyperthermia are neurotoxic and that neuroprotective agents reverse this hyperthermic response. Furthermore, amphetamine may actually impair the animals' ability to thermoregulate by interfering with hypothalamic thermoregulatory circuits. There is a continuing need to further investigate and identify the role of several variables in amphetamine toxicity including core temperature and ambient temperature. This chapter underscores the complexity of neurotransmitter interactions and interactions with other variables that underlie normal brain function and that contribute to drug dependence.

11.3. Acetylcholine and drug dependence: nicotine and ethanol

Two of the most widely abused drugs in the world are nicotine and ethanol. In recent years, both of these agents have been found to involve dopamine in producing their rewarding properties. Thus, dialysis studies have shown that nucleus accumbens dopamine is increased following injections of nicotine (Di Chiara, 1995)

ethanol (Di Chiara and Imperato, 1988). Furthermore, nicotine has been report- to produce a place preference that is blocked by a dopamine receptor antago- (Acquas *et al.*, 1989) and 6-hydroxydopamine lesions of the nucleus accum- ns have been reported to decrease ethanol intake in rats (Rassnick *et al.*, 1993). us, there is good evidence that the rewarding properties of nicotine and ethanol volve dopamine (Di Chiara, 1995). The mechanisms underlying the actions of ese agents on dopaminergic neurotransmission differ (Koob and Le Moal, 1997). owever, both may involve the cholinergic system.

By way of introduction to the harsh realities of nicotine addiction and its world- ide impact on health and the global economy, Chapter 12 by Henningfield and nt provides an in-depth look at the epidemiology and pathophysiological basis f tobacco dependence. The enormity of the situation is driven home by the pro- ction that *500 million* people worldwide who are presently smokers will die as a sult of their use of tobacco. This chapter reviews nicotine tolerance, dependen- y and reward. In the end it focuses on the delivery system (the cigarette) and the roblems that it poses for the development of effective pharmacotherapies for obacco addiction. Overall, this chapter provides a wealth of information con- cerning the health and policy implications of nicotine addiction and how decisions will be guided by findings from basic research.

Chapter 13 by Engel *et al.*, is especially interesting and appropriate for this volume because it focuses on the interactions of ethanol and nicotine. The authors begin by reviewing the evidence from animal and human studies that implicates dopamine in the rewarding effects of ethanol; some of that evidence was mentioned above. They then review evidence linking the effects of ethanol to an increase in responsiveness of the nicotinic cholinergic receptor; this action of ethanol leads to increased activation of the mesolimbic dopaminergic system which has nicotinic cholinergic receptors on its cell bodies in the ventral tegmental area (VTA). Evidence includes the finding that nicotinic receptor antagonists decrease ethanol intake (Blomqvist *et al.*, 1996). As mentioned above, there is good evidence from microdialysis studies that ethanol increased dopamine release in the nucleus accumbens; this effect also is blocked by nicotinic receptor antagonists (Blomqvist *et al.*, 1993). Data provide strong evidence that ethanol produces its rewarding effects by activating the mesolimbic dopamine system and that it does so via the activation of nicotinic cholinergic receptors.

In the latter part of Chapter 13, Engel *et al.*, present evidence that the locus of action of ethanol in modifying nicotinic receptor effectiveness and thereby changing the activity of dopaminergic neurons is the VTA, not the nucleus accumbens. Thus, intra-VTA but not intra-accumbens injections of the nicotinic antagonist mecamylamine decreased ethanol intake and also decreased ethanol-induced dopamine outflow in the nucleus accumbens in microdialysis studies. Further studies evaluate cross sensitization between nicotine and ethanol. The results summarized in this chapter provide valuable insights into the interactions of ethanol and nicotine with each other and with the dopamine system that begin to provide a basis for understanding the excessive dependence seen for these agents.

11.4. Glutamate and drug dependence

There may be a glutamatergic link in drug dependence that can be underst with reference to the theoretical neurotransmitter interactions that underlie in tive learning. Thus, it has been suggested that dopamine produces incentive le ing by altering the effectiveness of glutamatergic synapses in the striatum inc ing the nucleus accumbens (Wickens, 1990). The basic idea is that as diffe environmental stimuli are encountered by an animal, different subsets of cc costriatal glutamatergic synapses are activated. When a rewarding stimulu encountered there is a burst of activity in dopaminergic neurons (Schultz *et* 1997; Schultz, 1997). It has been suggested that the momentary increase in syn tic concentrations of dopamine produced by the burst leads to a modificatior the effectiveness of those glutamatergic synapses that were most recently act (Miller *et al.*, 1990; Wickens, 1990). As a result, the stimuli that were present j before reward occurred become incentive stimuli, having strengthened conn tions to striatal efferents that lead to motor output including approach and otl responses (Beninger, 1993). Thus, glutamate may be involved in incentive lea ing; to the extent that incentive learning is involved in drug dependence, as di cussed above, glutamate also may be involved in drug dependence.

It is noteworthy that glutamatergic projections are massive in the brain ar include many targets other than the striatum (Nieuwenhuys, 1985). Thus, althou glutamatergic agents may lead to reward and drug dependence, it would not b possible to attribute their effects to an action in the striatum following system administration. It will be the job of future studies to determine the precise loci of action in the brain of abused glutamatergic agents with the use of local injec tion and/or microdialysis experiments.

Chapter 15 by Balster reviews the involvement of N-methyl-D-aspartat (NMDA) glutamate receptors in the actions of drugs of abuse. NMDA receptor are one of several subtypes of glutamate receptors. This chapter begins with a lis of some of the disease states that possibly involve NMDA receptor dysfunction Balster then reviews some of the evidence that NMDA receptors contribute tc neural and behavioural plasticity. For example, some data show that NMDA recep tors participate in morphological development of neurons during ontogeny of the nervous system (Brewer and Cotman, 1989). Other studies implicate NMDA recep tors in learning and memory. Thus, long term potentiation, a model of activity dependent neuroplasticity, seems to require intact function at NMDA receptors (Izquierdo and Medina, 1995) and a number of studies show that learning in the water maze, for example, is impaired by NMDA antagonists (Morris, 1989; Mor ris *et al.*, 1986). Thus, NMDA receptors seem to play an important role in neuro plasticity.

Balster suggests that adaptive changes such as sensitization, tolerance and dependence to the effects of drugs of abuse [changes which have been implicated in the development of dependence (see Chapter 14)] can be viewed as examples of neuroplasticity involving learning. All of these processes are influenced by NMDA antagonists, further implicating NMDA glutamatergic receptors in the

learning that underlies drug dependence. Thus, NMDA antagonists reduce the development of sensitization to cocaine, amphetamine, morphine and nicotine. Further studies point to the striatum as a possible site of interaction between glutamate and dopamine mediating these plastic changes (see Chapter 27). These findings are consistent with the model of Wickens (1990) suggesting that dopamine subserves changes in glutamatergic synaptic effectiveness in the striatum when some forms of learning occur.

Chapter 15 then describes the variety of sites on the NMDA receptor where antagonists can act, and reviews the behavioural effects of a number of agents known to act relatively selectively at one of these sites or to influence glutamatergic neurotransmission through another mechanism. Of particular relevance to the drug dependence section of this book is the observation that phencyclidine (PCP), an NMDA channel blocker, and other similarly acting agents are drugs of abuse. Thus, PCP, for example, is self-administered by monkeys (Beardsley *et al.*, 1990). On the other hand, competitive NMDA antagonists generally do not have the same properties as the channel blockers. Balster concludes with the suggestion that it may be possible to develop effective pharmacotherapeutics for the treatment of drug abuse using NMDA antagonists that block the development of sensitization, tolerance and dependence but at the same time do not have abuse potential of their own. This chapter provides another example of the important interactions between various neurotransmitter systems underlying drug dependence.

11.5. Opiates and drug dependence

Neuropharmacological studies have revealed both a dopamine-dependent and a dopamine-independent process of reward produced by opiates (Koob and Le Moal, 1997). The data supporting this conclusion are reviewed in detail by Wise and Rompre (1989). Supporting a role for dopamine in opiate reward, intra-VTA injections of morphine increase the rewarding effects of electrical brain stimulation (Broekkamp *et al.*, 1976), are self-administered (Bozarth and Wise, 1981), produce a place preference (Phillips and LePaine, 1980) and, in microdialysis studies, increase nucleus accumbens dopamine release (Wise and Bozarth, 1987). Furthermore, heroin self-administration showed a compensatory increase following injections of a D_1-like dopamine receptor antagonist (Wise and Rompre, 1989). All of these findings support a role for the mesolimbic dopamine system in opiate reward.

Additional findings show that opiates also can produce rewarding effects when injected into sites other than the VTA. Thus, opiate self-administration directly into the nucleus accumbens has been reported (Goeders *et al.*, 1984; Olds, 1982) and intra-accumbens injections of morphine produce a conditioned place preference (van der Kooy *et al.*, 1982). Intra-accumbens injections of an opiate antagonist increased heroin self-administration rates, suggesting that the rewarding effects of the heroin were attenuated (Vaccarino *et al.*, 1985). The further observation that selective lesions of nucleus accumbens or VTA dopaminergic neurons

had little effect on heroin self-administration while blocking cocaine self-administration (Pettit *et al.*, 1984) provides strong evidence for a rewarding effect of opiates independent of the dopamine system. These findings suggest that opiates in the accumbens act on the reward circuitry that is downstream from the effects of dopamine.

Chapter 16 by Jiménez-Arriero *et al.*, reports the results of an ongoing clinical trial of the opiate receptor antagonist naltrexone for the treatment of ethanol dependence. The underlying rational for this work is as follows. As reviewed above, there is good evidence that activation of the mesolimbic dopamine system is important in the rewarding effects of ethanol; Chapter 16 also reviews some of this evidence. Chapter 16 then goes on to point out that the ability of ethanol to increase levels of dopamine in the nucleus accumbens requires endogenous opiate activity (Benjamin *et al.*, 1993; Widdowson and Holman, 1992) and that ethanol self-administration in rats and monkeys is reduced by opiate antagonists (Altshuler *et al.*, 1980). Furthermore, ethanol has been shown to stimulate the release of opiates in the brain (Patel and Pochorechy, 1989). Thus, endogenous opiates appear to mediate the effects of ethanol on dopamine and, therefore, on reward.

It should be possible to reconcile the mediating effects of opiates on dopamine release and reward produced by ethanol with the mediating effects of nicotinic cholinergic receptors on dopamine release and reward produced by ethanol. The role of nicotinic receptors is discussed in the above section on "Acetylcholine and drug dependence: nicotine and ethanol" and in detail in Chapter 13. Jiménez-Arriero *et al.* may provide a means to reconcile these different mechanisms. Thus, opiates liberated by ethanol act in the VTA to increase the synthesis and release of dopamine from mesolimbic dopaminergic neurons. Additionally, opiates released in the nucleus accumbens by ethanol act in a synergistic manner with dopamine on the target cells for dopamine in that nucleus. Thus, both nicotinic and opiate receptors in the VTA appear to participate in ethanol-induced dopamine release in the accumbens. The dual action of opiates in the VTA and the accumbens also is consistent with the dopamine-dependent and dopamine-independent mechanisms of opiate reward discussed above.

In Chapter 16, Jiménez-Arriero *et al.* describe the results of a clinical trial with naltrexone or placebo in 194 alcoholics who came to a clinic for treatment. They report that a significantly greater proportion of alcoholic patients treated with naltrexone had a positive outcome, defined as total or near total abstinence, during the first three months and upon follow-up at 12 months. These findings provide some encouraging evidence that it may be possible to bridge successfully from the findings of basic science to the development of effective treatments for disorders known to involve complex neural systems.

11.6. Cannabinoids and drug dependence

One of the most exciting discoveries in neuroscience in recent years has been the identification of endogenous ligands for the cannabinoid receptor. Thus, anan-

damide (Devane *et al.*, 1992) and 2- arachydonyl glycerol (Mechoulam *et al.*, 1995) have been found in the brain and/or gut and are able to displace binding of cannabinoids to synaptosomal membranes and to mimic the effects of known psychotropic cannabinoids on electrically-evoked contractions in a mouse muscle preparation. Recent studies have shown that anandamide can produce impairments in memory like those seen with exogenous cannabinoid agents such as Δ^9-tetrahydrocannabinol, the active ingredient of marijuana (Mallet and Beninger, 1996); the memory-impairing effects of anandamide are reversed by the cannabinoid antagonist SR 141716A (Mallet and Beninger, in press). As cannabis is widely abused, it will be of great interest to learn about the relationship between endogenous cannabinoids and other neurotransmitter and neuromodulator systems, especially the dopamine system that has been implicated in the mechanisms of many drugs of abuse.

Chapter 17 by Navaro *et al.* begins to address this issue by examining the interactions of dopaminergic agents with cannabinoid agents using behavioural, neurochemical and endocrine dependent measures. As might be expected from what we have seen of other drugs of abuse, cannabinoids can activate dopaminergic neurons. In this case it appears that cannabinoids act by modulating the activity of GABAergic neurons which, in turn, influence dopamine neuron activity. Thus, systemic cannabinoids produced a small increase in the release of dopamine in the striatum probably by inhibiting GABA release from afferents to the dopaminergic cells (Ng Cheong Ton *et al.*, 1988). Similarly, systemic cannabinoids increased dopamine release in the nucleus accumbens (See Table 17.1). Navaro *et al.*, discuss the possibility that the mechanism of this effect is through the release of glucocorticoids induced by cannabinoids and the subsequent action of glucocorticoids on VTA dopaminergic neurons. There is some indirect evidence to support this hypothesis but further work is needed.

Navaro *et al.*, present the results of studies evaluating the effects of chronic stimulation or subchronic blockade of dopamine receptors on acute sensitivity to cannabinoids. They report a variety of effects suggesting regional differences in the interactions of dopaminergic and cannabinoid systems. More studies will be needed to unravel the complex interactions between these two systems.

It is noteworthy that at present there are no good animal models of cannabinoid reward. Thus, cannabinoids do not produce a place preference; in fact they produce an aversion (Mallet and Beninger, 1998). There are no reports of cannabinoid self-administration in animals (see Mansbach *et al.*, 1994) and examinations of the possible enhancement of responding for brain stimulation reward by cannabinoids have produced equivocal results (see Mallet and Beninger, 1998). These findings are puzzling when they are considered along with the results reviewed above that cannabinoids, like other drugs of abuse, produce an increase in dopamine release in the nucleus accumbens. It will be the task of future research to identify the mechanisms underlying cannabinoid reward and to validate findings by demonstrating the circumstances under which animals will self-administer this widely abused agent.

11.7. Summary

Activation of the meso-accumbens dopaminergic projection has emerged as a common feature of a wide range of drugs of abuse including psychomotor stimulants, nicotine, ethanol, opiates and cannabinoids. The release of dopamine produces reward leading to incentive learning, increasing the ability of stimuli associated with reward to elicit approach and other responses in the future. This learning effect would be produced by drugs of abuse and may contribute to craving and the development of dependence. Thus, drugs of abuse act directly on brain circuits normally activated by natural rewards such as food and sex, bypassing the fulfilment of biological needs but still producing the pleasurable experiences normally felt upon fulfilling those needs.

The following seven chapters provide many details of the mechanisms underlying the action of drugs of abuse on the brain. These include possible neurotoxicity produced by amphetamine-like compounds (Chapter 18) and a detailed consideration of the development of tolerance as a basis for the development of drug dependence (Chapter 14). Chapter 12 provides a sobering look at the epidemiology and pathophysiology of nicotine abuse and then Chapter 13 discusses in detail a mechanism for ethanol abuse that involves the activation of nicotinic cholinergic receptors on dopaminergic neurons in the VTA. Chapter 15 reviews the role of NMDA glutamatergic receptors in learning and memory and discusses the finding that agents acting at one of the sites on this receptor are also drugs of abuse. Chapter 16 begins by discussing the common theme of this section, the underlying role for dopamine in ethanol reward but then reviews data suggesting a role for opiates in this action of ethanol on dopamine; this is followed by findings from a clinical trial with the opiate antagonist naltrexone used for the treatment of alcoholism. Finally, Chapter 17 rounds off this section on the interactive monoaminergic basis of drug dependence by reviewing cannabinoid-dopamine interactions. The reader is treated to many interesting findings that at once impress with their level of specific details and their generality in bringing neuroscience closer to a new synthesis of findings into a general theory of the mechanisms of drug dependence.

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