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FEATURE ARTICLE

Glutamatergic mechanisms in addiction

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Traditionally, addiction research in neuroscience has focused on mechanisms involving dopamine and endogenous opioids. More recently, it has been realized that glutamate also plays a central role in processes underlying the development and maintenance of addiction. These processes include reinforcement, sensitization, habit learning and reinforcement learning, context conditioning, craving and relapse. In the past few years, some major advances have been made in the understanding of how glutamate acts and interacts with other transmitters (in particular, dopamine) in the context of processes underlying addiction. It appears that while many actions of glutamate derive their importance from a stimulatory interaction with the dopaminergic system, there are some glutamatergic mechanisms that contribute to addiction independent of dopaminergic systems. Among those, context-specific aspects of behavioral determinants (ie control over behavior by conditioned stimuli) appear to depend heavily on glutamatergic transmission. A better understanding of the underlying mechanisms might open new avenues to the treatment of addiction, in particular regarding relapse prevention.
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Introduction

Addictive drugs are characterized by their ability to induce tolerance, somatic dependence and psychological dependence. However, the extent to which addictive drugs produce tolerance and somatic dependence varies considerably; while opioids produce strong somatic dependence, some drugs, for example, cocaine, cannabinoids and LSD, produce only weak or no somatic dependence. Common to all addictive drugs, however, is their ability to induce psychological dependence that manifests itself as compulsive drug-seeking behavior, drug-taking and loss of control over apparently voluntary acts. For reasons of readability 'psychological dependence' will be labelled 'addiction' in this paper.

Drug addiction is a complex neuro-behavioral disorder. Determinants of addictive behavior include factors such as primary (unconditioned) reward, secondary (conditioned) reward, sensitization processes, reinforcement learning, withdrawal, and reinstatement and relapse after periods of abstinence. It is increasingly recognized that contextual (conditioned) factors are of particular importance in addiction, mainly because through context conditioning neutral stimuli can gain control over behavior and produce relapse, which constitutes the biggest and most treatment-resistant problem in current addiction therapeutics.

Until a few years ago, most attention was focused on dopaminergic and opioidergic mechanisms of addiction. More recently, it has become increasingly evident that glutamate is also involved in addiction, and glutamatergic mechanisms may be responsible for plastic changes in the brain that lead to addictive behavior and relapse.

Anatomical and functional relationship between dopamine and glutamate

It is clear that neither dopamine nor glutamate alone mediate processes underlying the development and maintenance of addiction. While the consideration of other potentially important transmitters such as the endogenous opioids, GABA, acetylcholine, noradrenaline, cholecystokinin, or neurotensin are beyond the scope of this review, it is worth to briefly consider the interactions between dopamine and glutamate in the context of reward and addiction (see Figure 1).

The dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAS) is considered to represent a crucial part of the reward system.[1,2] It has been hypothesized that virtually all addictive drugs enhance dopaminergic neurotransmission in this pathway. The dopaminergic projection from the VTA to the prefrontal cortex (PFC) is also involved in the mediation of reward.[2,3]

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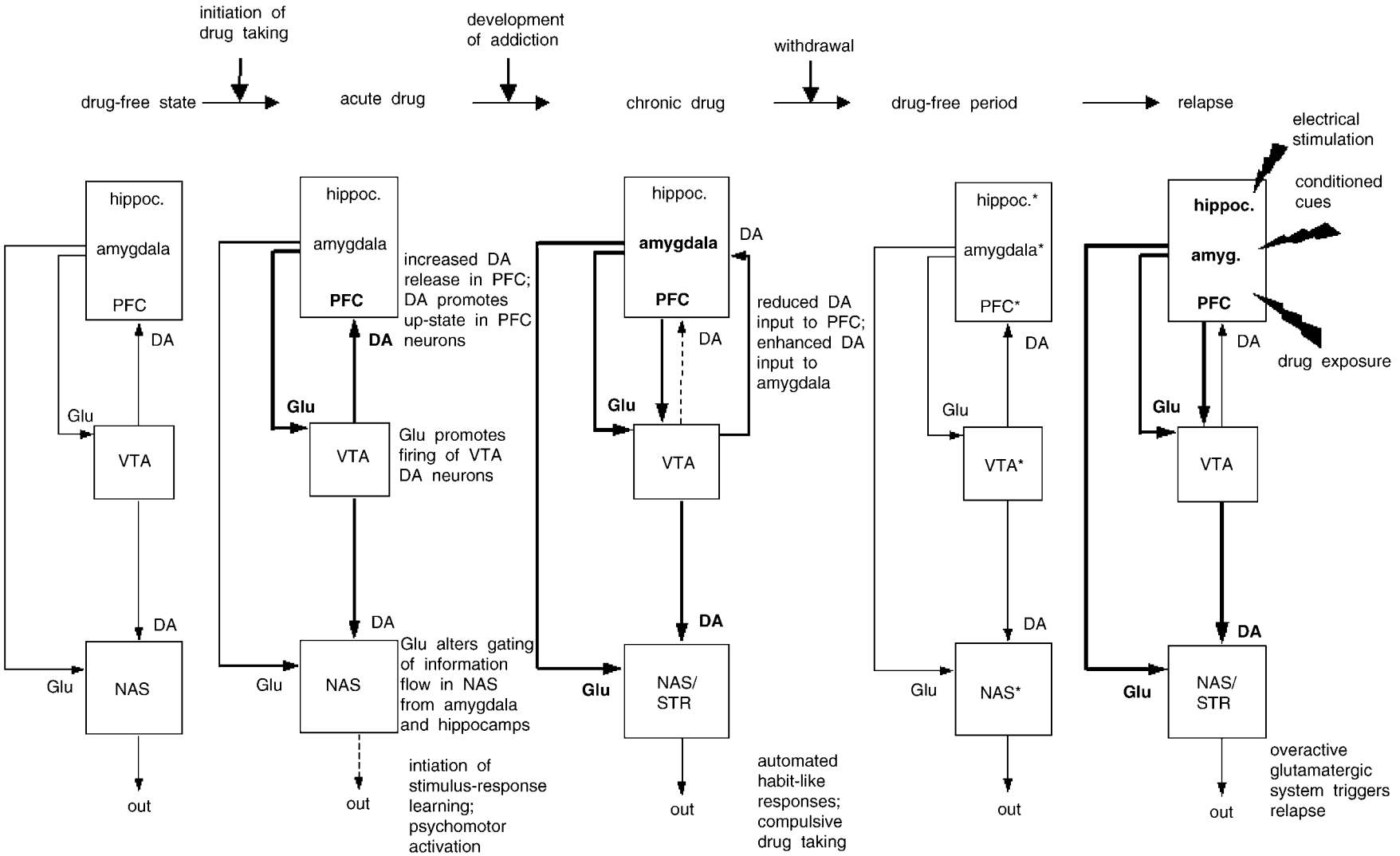

Figure 1 Summary of the main points elaborated in the text. When drug-taking is initiated, dopaminergic and glutamatergic neurotransmission in the mesocorticolimbic system is activated. Dopamine and glutamate interact in a complex way in the NAS. The net result of these interactions may be a reduction of medium spiny neuron activity and a decrease of GABAergic output from the NAS (see Nestler[111] and Wise. In the addicted state, different dopaminergic projections may be altered differentially, resulting in an altered dopamine–glutamate interaction that ultimately lead to aberrant control over behavior by the drug and to compulsive drug-taking behavior. The shift from controlled to compulsive drug intake may also involve a shift from the NAS to the striatum (STR) as the structure controlling behavioral output. During withdrawal and drug-free period, dopaminergic and glutamatergic activity within the mesocorticolimbic system normalizes but remains in a hypersensitive state (indicated by asterisks). Exposure to drug, stress, conditioned cues, or appropriate electrical stimulation can trigger a full-blown relapse.

There is good evidence that a major part of the role of glutamate in addiction is related directly or indirectly to the modification of the activity of the dopaminergic system. The mesocorticolimbic dopamine system is intricately connected with glutamatergic structures or their efferents. Both the cell body region in the VTA and the terminal region in the NAS receive massive glutamatergic input from several corticolimbic structures such as PFC, amygdala and hippocampus,[4–7] structures that have been implicated in aspects of reward evaluation, conditioning and learning.[8,9] The interaction between glutamate and dopamine in VTA and NAS is rather complex, but in simplified terms, glutamatergic input to the VTA increases the activity of dopaminergic cells and enhances dopamine release in the NAS.[10,11] At the level of the NAS, glutamate also facilitates dopaminergic transmission, presumably by presynaptically influencing dopamine release.[12,13] The dopamine-releasing effect of glutamate in the NAS may be predominantly mediated by AMPA (rather than NMDA) receptors.[14] It is tempting to speculate that this is the reason why relapse to drug-seeking behavior can be produced selectively by intra-NAS infusion of an AMPA (but not of an NMDA) receptor agonist, or why cocaine-induced relapse to drug-seeking behavior can be blocked by intra-NAS infusion of an AMPA (but not of an NMDA) receptor antagonist[15,16] (see below). There is, however, an alternative potential explanation for the different effects of AMPA *vs* NMDA receptor ligands with respect to relapse that deserves mentioning. Medium spiny neurons in the NAS have relatively hyperpolarized resting potentials and only little spontaneous activity, in contrast to dopaminergic cells in the VTA.[17] Therefore, an AMPA receptor antagonist may be expected to effectively turn off the NAS while NMDA antagonists would have less effect, since NMDA receptors are not active at hyperpolarized resting potentials. Thus, if the activity of (at least a subpopulation of) NAS projection neurons is required for reinstatement to occur, AMPA receptor antagonists may be expected to have a stronger effect than NMDA receptor antagonists, not because of a preferential involvement of AMPA receptors *per se*, but because of the electrophysiological properties of the medium spiny neurons in the NAS.

Dopamine also affects glutamatergic transmission. For example, dopamine modulates glutamatergic signals in the NAS originating from the amygdala and hippocampus in a manner consistent with the concept of a gating mechanism or input selection.[18] Glutamatergic pyramidal projection neurons in the PFC show membrane potential fluctuations between relatively hyperpolarized 'down' states and relatively depolarized 'up' states, and action potentials can more easily be triggered by excitatory input when the cells are in the 'up' state.[19] Although dopamine released from the mesocortical projection does not directly induce firing in pyramidal neurons, it promotes the 'up' state in these cells, thus increasing the probability that these cells fire action potentials.[20] This mechanism might even be enhanced after repeated psychostimulant treatment, since repeated cocaine administration results in increased glutamate releasability in the NAS.[21,22] The fact that this increase in glutamatergic activity in the NAS is related to the PFC is suggested by the finding that it is partly prevented by lesions of the PFC.[23]

As mentioned above, activation of the projection from the PFC to the VTA causes dopamine release in the NAS, and this seems to be a key process in the mediation of cocaine and morphine reward. Destruction of this pathway by quinolinic acid-induced lesions of the PFC can weaken cocaine and morphine reward.[24] Also, the rewarding effects of NMDA receptor antagonists, when infused into the PFC, may be mediated by the projection from the PFC to the VTA, since a lesion of the PFC blocks reward produced by systemic administration of an NMDA receptor antagonist.[24] The behavioral arousal and activity that is produced by the infusion of an NMDA receptor antagonist into the PFC is accompanied by an increase in extracellular levels of dopamine. However, this behavioral activation is not blocked by co-infusion of dopamine antagonists but is completely inhibited by co-infusion of an AMPA receptor antagonist, suggesting that the behavioral activation is not causally related to the observed increase in dopamine, but is rather mediated by an increased glutamatergic transmission at AMPA receptors within the PFC.[25]

The prefronto-accumbal glutamatergic pathway may also contribute to the mediation of reward; however, it is not clear in which way. It has been proposed that inhibition of the medium spiny output neurons of the NAS represents a final pathway for reward mediation.[26] Taking this hypothesis as a basis, one would assume that reward is mediated by a decrease of prefronto-accumbens activity and by an increase in prefronto-VTA activity (leading to enhanced dopamine activity in the NAS, which in turn inhibits medium spiny neurons through D2 receptors). Although there is good evidence in favor of inhibition of medium spiny neurons as the 'endpath' for reward mediation, one has to keep in mind that these neurons are not a homogenous population, and that subsets of these cells may react to reinforcers with excitation rather than with inhibition.[27,28] Furthermore, only a subset of these neurons is inhibited by D2 receptor agonists, and the induction of ΔFosB, a protein that may be an important step in the development of persistent neuronal changes leading to addiction, by chronic drug administration appears to be restricted to the dynorphin-containing subset of medium spiny neurons.[29,30] Taken together, because the NAS is a complex of functionally distinct neuronal ensembles,[31] inhibition of one subset of NAS medium spiny neurons may indeed be an important mechanism in the mediation of reward, yet other mechanisms (of excitatory nature) in other subpopulations may also play a role (see Figure 1).

At least some glutamatergic mechanisms appear to be independent of dopaminergic mechanisms. Recently, it has been demonstrated that in mice lacking the metabotropic glutamate receptor-subtype mGluR5, cocaine does not produce locomotor-stimulant effects and lacks rewarding effects, as evidenced by an absence of cocaine self-administration behavior.[32] These deficits were selective for cocaine self-administration, since lever-pressing for food was unaltered in the mutant animals, and they were mimicked by the mGluR5 antagonist MPEP. These findings are particularly intriguing in light of the observation that these deficits occurred despite normal dopamine function in the mGluR5 null mutants (basal dopamine levels, cocaine-stimulated dopamine release, and dopamine receptor and transporter expression were not different from wild-type animals). This suggests that the deficits in the mutant mice were not secondary to changes in the dopaminergic system but were solely due to (dopamine-independent) changes in glutamatergic signalling. mGluR5 is highly expressed in the NAS,[33] and mGluR5 mRNA levels in the NAS (shell) are increased by repeated systemic administration of cocaine.[34] Taken together, these findings suggest that mGluR5 receptors are involved in neuronal changes underlying the addictive properties of cocaine. The interaction between dopamine and glutamate (via mGluR5 receptors) in the NAS may take place at the level of the medium spiny neurons. These cells express both dopamine and mGluR5 receptors.[33,35] If the dopamine receptor-mediated effect in these cells is dependent on the activation of mGluR5 receptors, this arrangement would explain the lack of effect of a dopaminergic drug (cocaine) despite normal dopaminergic activity.[32]

Role of glutamate in sensitization

Behavioral sensitization refers to the intensification of a behavior upon repeated exposure to a stimulus. In the context of addiction research, this stimulus is usually the repeated intermittent administration of a drug. The possible link between sensitization and addiction has been elaborated by Robinson and Berridge,[36] who hypothesized that by way of sensitization drug-associated stimuli are endowed with increasing incentive salience, up to the point at which the urge to take the drug becomes so powerful that it gains control over and suppresses voluntary behavior. The view that sensitization is associated with addiction is further supported by the following findings: (1) Sensitization includes functional alterations which are very stable. In the rat, sensitized locomotor activity can persist for several months after the end of drug administration.[37] (2) The degree of sensitization determines the vulnerability for relapse; that is, strongly sensitized animals relapse more easily than weakly sensitized animals.[38] (3) Sensitization facilitates subsequent drug-taking, for example, amphetamine or cocaine pretreatment facilitates the acquisition of cocaine self-administration.[39] (4) There is considerable inter-individual variation in the degree of sensitization that develops under a given drug treatment schedule, just as there are large inter-individual differences in the vulnerability to develop addiction.[40]

Sensitization is not a unitary phenomenon. It is increasingly recognized that at least two forms of sensitization have to be distinguished, a context-independent, non-associative and a context-dependent, associative form of sensitization.[41,42] Furthermore, development of sensitization and expression of established sensitization are mediated by different neurochemical mechanisms and brain structures. During development, that is, the incremental increase of the behavioral response with repeated drug administration appears to be mediated primarily at the level of the VTA, the expression of sensitization is mediated primarily at the level of the NAS.[43–45]

While non-associative sensitization can account for some of the enduring adaptations in the central nervous system, it cannot account for the specificity of drug-associated cues to provoke relapse (see below). The latter involves associative, that is, context-dependent sensitization mechanisms. Context-dependent sensitization refers to the dependence of the augmentation of behavioral responses on repeated pairings between drug effect and context, and this form of sensitization can only be fully expressed in the drug-paired context.[41] The relationship between conditioned activity and context-dependent (conditioned) sensitization is not entirely clear.[42,46,47] Contextual contingencies can have a complex influence on both the development and expression of sensitization, and both components of sensitization can be enhanced or attenuated by varying the contingencies of drug administration and behavioral testing (see the series of elegant studies by Robinson and colleagues[47–49] for details. The conditioned response is not necessarily dependent on a complex contextual stimulus. Discrete stimuli, such as a tone or a light, are sufficient to produce conditioned activity when paired repeatedly with a drug.[50,51]

Context-dependent sensitization can be considered as a special form of habit learning, which refers to the learning of consistent relationships between stimuli and responses.[52,53] There is some evidence that through habit learning the controlled intake of drugs, which is an evaluative and flexible behavior, shifts to an automated stimulus–response habit.[52–54]

A number of changes in glutamatergic neurotransmission have been observed after sensitizing treatment schedules with drugs of abuse. For example, repeated cocaine or amphetamine administration enhances the responsiveness to glutamatergic stimulation of mesolimbic dopamine neurons and reduces the responsiveness to glutamatergic stimulation of NAS neurons,[55,56] alters the expression of glutamate receptor subunits/splice variants, in particular, in the mesolimbic system,[34,57,58] and results in increased

glutamate releasability in the NAS.[21,22] Furthermore, even a single systemic administration of cocaine can produce NMDA receptor-dependent long-term potentiation of AMPA receptor-mediated currents at excitatory synapses on dopaminergic cells in the VTA that lasts for at least 5 days,[59] and a behaviorally sensitizing treatment regimen of cocaine produces long-term depression at excitatory synapses between afferents from the PFC and medium spiny neurons in the NAS shell that lasts for at least 2 weeks.[60] These functional findings fit very nicely to the presumed transient role of the VTA in the initiation of sensitization and a more permanent role of the NAS in the expression of sensitization (see above).

Expression of context-dependent sensitization seems to depend on augmentation in glutamatergic activity in the projection from the PFC to the NAS.[61] A specific role for glutamate-mediated mechanisms in context-dependent sensitization is suggested by the findings of Bell and Kalivas,[62] who reported on a context-specific cross-sensitization between systemic cocaine and intra-NAS AMPA infusions: animals that had received repeated cocaine injections in the test cage showed much higher locomotor response to an intra-NAS injection of AMPA than animals that had received cocaine injections in their home cage or saline injections in the test cage. On the other hand, the NMDA receptor agonist *cis*-ACDA produced sensitized locomotion in both cocaine groups (home cage and test cage treatment). Furthermore, the sensitized motor stimulant response to cocaine was reduced by intra-NAS infusion of the AMPA receptor antagonist CNQX only in those animals that had received daily cocaine injections in the test environment on previous days while having no effect in animals that had received cocaine in their home cages; in this study intra-NAS infusion of the NMDA receptor antagonist CPP did not affect locomotor response to cocaine in either treatment group.[63] This suggests that while AMPA receptors may selectively mediate the context-dependent component of behavioral sensitization to cocaine, NMDA receptors may be involved in the mediation of the context-independent component of sensitization.

A specific role for AMPA receptors was also found by Giorgetti *et al*,[64] who reported that in amphetamine-pretreated rats intra-VTA infusion of AMPA resulted in a greater increase in extracellular levels of dopamine and glutamate in the VTA and the NAS than in saline-pretreated rats. On the contrary, intra-NAS infusion of NMDA produced a similar increase in extracellular dopamine in VTA and NAS, and did not affect extracellular levels of glutamate. The enhanced responsiveness of dopamine levels to intra-NAS AMPA was a transient effect in that it was no longer evident 10–14 days after amphetamine withdrawal. These results indicate that an early step in the cascade leading to the establishment of drug-induced alterations involves increased glutamate signalling at AMPA receptors in the VTA. This effect may involve an increase in glutamate release in the VTA induced by repeated drug administration.[65] However, it does not seem to involve changes in expression of AMPA receptor subunits[66] or glutamate transporters.[67]

Role of glutamate in reinforcement learning

Addictive behavior does not result from repeated drug exposure *per se*, but is a result of learning. Although experimenter-administered drugs can clearly produce rewarding effects, for example, in conditioned place preference or intracranial self-stimulation, self-administered drugs can have quantitatively and qualitatively different effects. Animals that are forced to take drugs do not become addicted, and they show a greater vulnerability to toxic side effects and somatic dependence.[68,69] Thus drug-taking in a free choice situation is a prerequisite for addiction learning which implies that drugs are addictive only if the organism is in a certain anticipatory state.

Glutamatergic mechanisms in the NAS core are involved in response-reinforcement learning in the acquisition of a lever-press task to obtain food reward.[70] Injection of the NMDA receptor antagonist AP-5 into the NAS core impaired the acquisition (but not the performance) of this task, while leaving feeding and locomotor responses and the formation of stimulus–reward associations intact. Co-infusion of low doses of the D1 receptor antagonist SCH23390 and AP-5 strongly potentiated the impairment in the acquisition of intrumental learning that each drug produced when administered alone, suggesting that a glutamate–dopamine interaction (co-activation of NMDA and D1 receptors) is a key mechanism in the acquisition of appetitive instrumental learning.[71]

The role of reinforcement learning has also been conceptualized in more formal terms. As opposed to the temporal difference (TD) learning model which views the mesocorticolimbic dopamine system as the central error-coding unit (comparing predicted/expected reward to the actual reward obtained),[72] the glutamate hypothesis of reinforcement learning 'assumes that subsets of neurons in the amygdala, prefrontal and cingulate cortex participate in the formation of stimulus–reward associations and relay this associative information to sensorimotor structures by way of glutamatergic fibers forming discrete boutons on postsynaptic membranes. Glutamatergic fibers assume the reward-signalling role that is fulfilled by dopaminergic fibers in neurobiological versions of TD Learning.' (Pennartz *et al*,[73] p 236; see the same for references and in-depth discussion of the topic).

Role of glutamate in drug-craving, reinstatement and relapse

Relapse to drug-taking behavior can occur even after prolonged periods of abstinence. Since relapse rates are usually very high in drug addicts having

undergone detoxification, relapse poses the biggest challenge in the treatment of addiction. Relapse in humans is commonly preceded by intense craving for the abused drug, and this eventually leads to the reinitiation of compulsive drug-taking behavior. This craving can be induced by the administration of the drug itself or by the exposure to cues associated with drug-taking or the drug effect. Such stimuli activate an 'addiction memory' that has developed during the period of active drug-taking and that is very stable, perhaps permanent. Possibly, this memory is built up by a process of sensitization (see the preceding section).

Recent imaging studies in human addicts have shown that the presentation or mental representation of drug-related cues can trigger craving and is associated with increased activity in the amygdala and prefrontal and orbitofrontal cortical areas.[74–80] The increased activity in these areas could result in increased glutamatergic transmission in the NAS, which nicely fits the emerging picture on the role of NAS glutamate in reinstatement of drug-seeking behavior derived from animal studies.

In rats, evidence for the involvement of structures that use glutamate as their primary efferent transmitter comes from the observation that inactivation of the amygdala prevents cue-induced reinstatement of cocaine self-administration,[81–83] and the PFC has been implicated in cocaine-induced reinstatement of cocaine self-administration.[84] Cornish and Kalivas[15] reported that glutamate, not dopamine, is the primary mediator of cocaine-induced reinstatement of drug-seeking behavior. In animals trained to self-administer cocaine and having undergone extinction reinstatement was induced by systemic cocaine injection or microinjection of dopamine or AMPA into the NAS. The predominant role of glutamate in cocaine-induced reinstatement was demonstrated by the finding that the microinjection of a dopamine receptor antagonist into the NAS only blocked reinstatement by intra-NAS dopamine while injection of an AMPA receptor antagonist blocked reinstatement by all agents, including systemic cocaine. This is complemented by the observations that AMPA receptor antagonism in the NAS also blocks reinstatement produced by intra-PFC cocaine infusion (which also further implicates the prefronto-accumbal glutamatergic projection in these mechanisms),[85] and that infusion of AMPA into the NAS reinstates cocaine-seeking behavior.[16] It is noteworthy that in the study of Park *et al*[85] infusion of the NMDA receptor antagonist AP-5 into the NAS produced reinstatement of cocaine-seeking behavior in at least a subset of animals, suggesting that AMPA and NMDA receptors in the NAS may have opposite roles with respect to reinstatement and relapse. This, in turn, reinforces the view that the NAS is composed of functionally diverse subpopulations of neurons, as discussed before. As mentioned previously, it is tempting to speculate that the ability of AMPA to reinstate drug-seeking behavior is related to its local dopamine-releasing effects within the NAS.[14] However, this speculation is obviously at odds with the observation that a dopamine antagonist injected into the NAS does not block AMPA-induced reinstatement.[15] This does not mean to say that dopamine does not play a role in cocaine-induced reinstatement. As mentioned above, cocaine-seeking behavior is reinstated by intra-NAS dopamine infusions; thus dopamine transmission in the NAS is sufficient but not necessary for reinstatement. Dopaminergic projections to the amygdala[86] appear to be important for the reinstatement of cocaine-seeking behavior (but not for primary cocaine reward).[87–89] Given the excitatory amino acid projections from the amygdala to the NAS,[4] an increased dopamine release in the amygdala produced by systemic cocaine might in turn increase glutamate release in the NAS by increasing the activity of amygdalar efferents,[90–92] closing the circuitry involved in cocaine-induced reinstatement. As the work of Rosenkranz and Grace demonstrates, dopamine in the (basolateral) amygdala acts to reduce prefrontal cortical suppression of sensory inputs from other cortical areas. Given that dopamine release in the amygdala sensitizes in response to repeated amphetamine treatment,[93] this suggests the intriguing possibility that with repeated drug treatment, cognitive–evaluative information relayed from the PFC is increasingly inhibited while sensory information relayed from entorhinal and perirhinal cortices is increasingly disinhibited. Thus, sensory input would gain increasing influence over behavioral output. This could be the mechanism by which drug-associated stimuli, which would enter the information-processing circuit via sensory channels, gain increasing control over behavior, up to the point of compulsive 'automatic' drug-taking behavior. If this increased control is maintained beyond withdrawal, this may also account for cue-induced relapse to drug-seeking and drug-taking behaviors (see Figure 1).

Another line of evidence showing a (dopamine-dependent) role of glutamatergic transmission in reinstatement of drug-seeking behavior comes from the work of Hayes *et al*[94] and Vorel *et al*.[95] These authors showed that electrical stimulation with physiologically relevant parameters of the amygdala or the ventral subiculum of the hippocampal formation potently reinstates cocaine-seeking behavior. In the case of ventral subiculum stimulation, it was furthermore shown that comparable reinstatement effects could be obtained by intra-VTA infusion of NMDA, and that stimulation-induced reinstatement is completely blocked by microinfusion of kynurenic acid into the VTA.[95] Stimulation of the ventral subiculum enhances firing of dopamine neurons in the VTA and increases dopamine release in the NAS[12,96] that similarly can be blocked by intra-VTA infusion of kynurenic acid. Since dopamine can also produce reinstatement when injected into the NAS,[15] these findings, taken together, would suggest that stimulation of the ventral subiculum activates glutamatergic projections to the VTA which in turn activates the dopaminergic projection to the NAS,

increasing dopamine release which would then trigger relapse. In this case, dopamine in the NAS would play a pivotal role in producing relapse. This is different from the situation outlined above where, in the case of reinstatement induced by systemic cocaine, it was concluded that dopamine in the NAS does not play a necessary role.[15] Clearly, reinstatement produced by a systemic drug injection and that by electrical stimulation of a discrete brain region are likely to involve different neural mechanisms. A systemic drug injection could activate a multitude of different mechanisms compared to electrical stimulation, and this could also result in a relative independence of reinstatement from NAS dopamine. It should be noted here, however, that Vorel *et al*[95] have argued, based on their finding that electrical stimulation of the medial forebrain bundle that was highly reinforcing did not produce reinstatement of drug-seeking behavior, that separate neural systems may subserve positive reinforcing stimulation on the one hand, and incentive stimulation on the other. Both systems, however, may ultimately involve activation of mesolimbic dopamine transmission,[12,96,97] although with different temporal contingencies.[95]

These findings from self-administration reinstatement studies are supported by data from studies on cocaine-conditioned hyperactivity. Locomotion produced by a cocaine-associated environment was blocked selectively by pharmacological inactivation of the NAS and the medial PFC.[98] Conditioned locomotion in a cocaine-paired environment was not associated with increased levels of extracellular dopamine in the NAS[99] (but see, eg Ito *et al*[100]), but exposure to discrete contextual stimuli repeatedly paired with cocaine significantly increased extracellular levels of glutamate in the NAS.[50] In view of the above discussion, this cue-induced glutamate release in the NAS might be a trigger for relapse. It should be noted, however, that significant increases in glutamate levels occurred only more than 1 h after the onset of exposure to the conditioned cue, while conditioned locomotor activity in this study (and reinstatement of lever-pressing behavior in self-administration studies) occurred immediately after exposure to the conditioned cue; thus, there does not seem to be a good temporal relationship between increases in glutamate transmission and behavioral activity, although inadequacies in the sensitivity or resolution of the microdialysis technique employed might also account for these discrepancies. Microdialysis measures only nonsynaptic 'spill-over' of neurotransmitters, and, in particular, in the case of glutamate the contribution from nonneuronal pools can be substantial. Thus, it may be inherently difficult to directly relate fast glutamatergic synaptic transmission to behavior.

Clinical implications

Despite the well-established role of dopamine in mechanisms underlying addiction, dopaminergic medications have thus far failed to make valuable contributions to the treatment of drug addiction. The evidence reviewed in this paper clearly suggests that glutamatergic agents, in principle, should be effective as drugs that, for example, block the establishment of compulsive drug-taking behaviors, reduce physical dependence/withdrawal, or prevent relapse. First results from trials in man appear to be promising. For example, it has been shown that the low-affinity NMDA receptor channel blockers memantine and dextromethorphan reduce the severity of physical withdrawal in opiate addicts[101,102] and that memantine reduces the alcohol deprivation effect in rats (an animal model of drug-craving).[103] Furthermore, acamprosate, which can reduce relapse rates in alcoholics, also acts as an NMDA receptor antagonist (although it is not clear to what extent this particular mechanism contributes to the clinical efficacy of acamprosate since its NMDA-antagonistic potency is only weak and it has numerous other pharmacological effects).[104] Until now, the major stumbling blocks in the therapeutic use of NMDA receptor antagonists were their psychotomimetic and potentially neurotoxic effects. Furthermore, the high-affinity NMDA receptor channel blocker dizocilpine (MK-801) was shown to induce relapse to cocaine-seeking by itself,[105] suggesting that only antagonists with low-to-moderate potency may yield the desired therapeutic effect in the absence of untolerable side effects. More recently, the focus has shifted towards subtype-selective compounds, in particular for receptors containing the NR2B subtype, and on compounds that modulate NMDA receptor function via modulatory binding sites (eg glycine-B receptors). Thus far, drugs acting at these receptors appear to produce less severe side effects while retaining their therapeutic efficacy (see, eg Parsons[106] and Chizh *et al*[107]).

However, these drugs have not yet been evaluated in the context of addiction. AMPA receptor antagonists might also hold therapeutic potential since these drugs appear to be more effective than NMDA receptor antagonists in animal studies in inhibiting the expression of addiction-related behaviors such as conditioned or sensitized locomotion, conditioned place preference, and drug-seeking behavior.[108–110] Based on the ubiquitous distribution of AMPA receptors in the central nervous system and their involvement in basic neurophysiological functions, a critical side-effect profile might also be expected. Currently, we know of one AMPA receptor antagonist in clinical development for ischemic stroke (YM-872, see Pharmaprojects #26645). Whether such compounds would be useful in the treatment of addiction remains to be seen. Another class of drugs that might hold therapeutic potential are metabotropic glutamate receptor ligands, in particular, mGluR5 antagonists (see Chiamulera *et al*[32]). Indeed, a number of mGluR ligands are already in preclinical development (eg NS-3763 [Pharmaprojects #34018], PRE-703 [Pharmaprojects #33499]) but again, with the exception of MPEP, they have not yet been evaluated in the context

of addiction. As in other disease states such as stroke or pain, the challenge for the future will be to develop drugs that are both therapeutically effective *and* devoid of use-limiting side effects, a problem of particular urgency for glutamatergic drugs).

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