# The glutamate homeostasis hypothesis of addiction

*Peter W. Kalivas*

Abstract | Addiction is associated with neuroplasticity in the corticostriatal brain circuitry that is important for guiding adaptive behaviour. The hierarchy of corticostriatal information processing that normally permits the prefrontal cortex to regulate reinforcement-seeking behaviours is impaired by chronic drug use. A failure of the prefrontal cortex to control drug-seeking behaviours can be linked to an enduring imbalance between synaptic and non-synaptic glutamate, termed glutamate homeostasis. The imbalance in glutamate homeostasis engenders changes in neuroplasticity that impair communication between the prefrontal cortex and the nucleus accumbens. Some of these pathological changes are amenable to new glutamate- and neuroplasticity-based pharmacotherapies for treating addiction.

Dopaminergic mechanisms are a traditional focus in the field of addiction because the acute rewarding effects of addictive drugs are mediated by enhancing dopamine transmission, and dopamine release reinforces reward learning[1,2]. Accordingly, the release of dopamine by addictive drugs is important for progressively shaping drug use into drug-seeking behaviours that are difficult to control[2–5]. The act of engaging in drug seeking is termed relapse, and a particularly insidious aspect of drug addiction is that the vulnerability to relapse endures for many years in the absence of repeated drug use. In contrast to the acute stimulation of dopamine transmission produced by drug use, the enduring vulnerability to relapse arises from pervasive, long-lasting neuroadaptations in the corticostriatal circuitry in which the dopamine axon terminals are embedded. The past decade has seen increasing strides towards understanding the corticostriatal glutamatergic mechanisms of relapse and how these could be used in developing medications for addiction.

Corticostriatal projections are responsible not only for generating learnt, well-established behaviours such as in drug taking, but also for changing behaviours in response to a variable environment, and thereby generating new adaptive behaviours[2,6,7]. In this context, the behavioural pathology of addiction can be viewed as an impaired ability to inhibit drug seeking in response to environmental contingencies that designate this behaviour as maladaptive. In other words, addicts have difficulty modulating drug-seeking behaviours with information that should suppress the behaviour. This impairment could arise from two general pathologies in corticostriatal circuitry: addicts could have pathologically strengthened drug-seeking behaviours[1], or they could have pathological impairments in the capacity to control drug-seeking behaviours. These two possibilities are not mutually exclusive, and in this Review I explore the physiological mechanisms residing in prefrontal projections into the ventral striatum (nucleus accumbens (NAc) that could constitute the pathological impairments in the ability to control drug-seeking behaviour.

## A corticostriatal circuitry of addiction

A common perspective on addiction is that, with repeated drug use, drug-seeking behaviours become more habitual and less amenable to regulation by environmental contingencies, a viewpoint developed in recent reviews[8–10]. The argument relies on the topography of both corticostriatal glutamatergic and mesencephalic-striatal dopaminergic projections that mediate the processing of sensory information into adaptive behaviours[11]. The anatomical and functional hierarchy of projections from the cortex to the basal ganglia is well characterized[7,12,13], and permits both serial and parallel processing of information (BOX 1). FIGURE 1a distils the topographical hierarchy of the corticostriatal circuitry into two subcircuits: the limbic subcircuit, which comprises limbic brain regions such as the prefrontal cortex, the amygdala, the NAc and the ventral tegmental area; and the motor subcircuit, which contains the motor cortex, the dorsal striatum and the substantia nigra.

*173 Ashley Avenue, BSB 410, Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina 29425, USA.*
*e-mail: kalivasp@musc.edu*
doi:10.1038/nrn2515
Published online 1 July 2009



© 2009 Macmillan Publishers Limited. All rights reserved

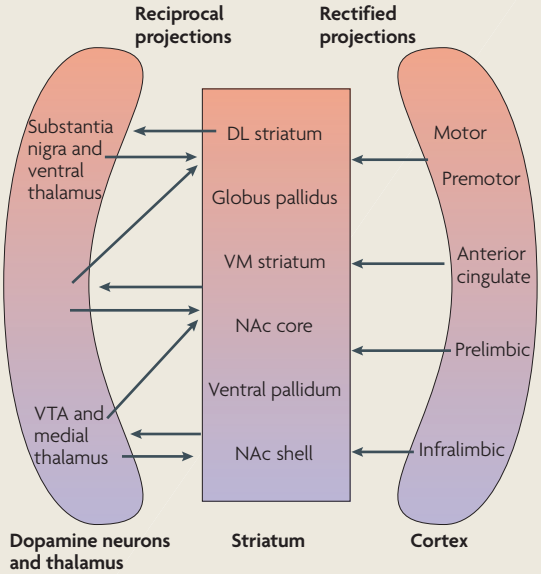
Operant task
A behavioural act with a consequence. In the context of addiction, this is most often a lever press to deliver an addictive drug.

In this simplified corticostriatal circuit, the NAc serves as a gateway through which information that has been processed in the limbic subcircuit gains access to the motor subcircuit[7,14]. When a novel stimulus capable of motivating an adaptive behavioural response (for example, food) is encountered, the limbic subcircuit is engaged to attend to and process new and previously learnt information that is relevant to the stimulus. In this way, an animal can determine the adaptive value of implementing a previously learnt behaviour and/or forming new behavioural strategies. If an established behaviour continues to yield the desired outcome (for example, if pressing a lever successfully provides food), the influence of the limbic subcircuit progressively diminishes, and neuronal activity in the motor subcircuit becomes more organized around task performance[6,7]. However, if the behaviour fails to yield the adaptive outcome (for example, if a lever press no longer delivers food), then the limbic subcircuit is strongly engaged by the altered environmental contingencies and activity in the motor subcircuit becomes more disorganized, which in turn allows modification of the established behaviour and maximizes the likelihood of an adaptive outcome[6,15]. Once a behaviour has been updated to a new environmental contingency (for example, if pressing a different lever provides food), over the course of repeated successful outcomes the limbic subcircuit progressively exerts less of an influence as the updated behaviour becomes the preferred behavioural response.

Owing to how the limbic and motor subcircuits interface to generate adaptive behaviours, it has been proposed that relapse to compulsive drug seeking arises from an impaired ability of the limbic subcircuit to effectively process and/or use the negative environmental contingencies associated with relapse. The result is that behaviour is dominated by the previously learnt, well-established drug-seeking strategies. BOX 2 briefly outlines the animal models that are most widely used to investigate the role of corticostriatal circuitry in drug-seeking behaviour in relapse. Different models have revealed a role for the limbic subcircuit. These include those in which drug seeking is evaluated during training in an operant task to self-administer a drug (contingent administration), and those that evaluate drug seeking following a period of withdrawal, after which drug seeking is reinstated by the drug-associated context, the presentation of a conditioned cue, stress or a non-contingent drug injection[16]. Consistent with a crucial involvement of the motor subcircuit during relapse, pharmacological inactivation of the dorsolateral striatum prevents drug seeking using a second-order schedule or reinstatement paradigm (BOX 2), with or without extinction training[17–20]. The imposition of environmental contingencies on the success of drug seeking by extinction training (BOX 2) promotes involvement of the prefrontal cortex, and its projections to the NAc, to differentially regulate drug seeking. For example, as illustrated in FIG. 1b, inactivation of the prelimbic cortex prevents reinstatement[21–26], whereas inactivation of the infralimbic cortex reinstates drug seeking[27] (although inactivation of the infralimbic cortex was found to inhibit drug seeking in animals undergoing extended withdrawal without extinction training)[28]. Thus, extinction training decreases the adaptive value of drug-seeking behaviours that no longer deliver the drug, and this causes progressive recruitment of the limbic subcircuit to regulate the execution of drug-seeking behaviour.

Importantly, involvement of the motor versus the limbic subcircuit is progressively augmented in the absence of training to countermand drug seeking (for example, extinction training). Thus, animals with more extensive self-administration training show greater evidence of prepotent involvement of the motor subcircuit. For example, neuroimaging of primates that were trained to self-administer cocaine revealed activation of the entire striatal complex during the early self-administration period, but after weeks of training activation in the dorsal striatum was augmented[29]. Similarly, when drugs are self-administered by responding to cues using a second-order schedule of reinforcement (BOX 2), extended training augments cue-associated dopamine release in the dorsal striatum[30,31] and makes drug-seeking behaviour susceptible to dopamine receptor blockade in the

Box 1 | **Hierarchy of information processing through corticostriatal circuits**




The processing of motivationally relevant information into adaptive behavioural responses occurs through serial and parallel processing in the cortico-striato-thalamic projections[12,14]. Although greatly simplified, the figure illustrates how reciprocal and rectified projections, combined with topographic organization, facilitate a flow of information from limbic regions (bottom of the figure) to motor regions of the circuit. For example, cortical input to the striatum is topographically discrete, as are striatal projections made directly or indirectly to the thalamus and to dopamine neurons in the ventral mesencephalon. However, indirect projections from the thalamus and direct projections from the ventral mesencephalon to the striatum are more permissive, allowing information to move through the circuit (from the bottom to the top of the figure). Information encoded as neuronal firing in the motor circuit becomes more focused as a behaviour is learnt and becomes well-established[6], and some evidence shows that this process moves from limbic into motor regions as a task is learnt[7,138]. Moreover, extinction of a learnt, well-established behaviour might in part reverse this process, as it disrupts the task-synchronized firing of neurons in the dorsal striatum[6]. Importantly, although the anatomical organization of the circuit might bias information flow from limbic to motor regions, simultaneous parallel processing of information permits not only limbic regions to influence learnt motor behaviours, but also motor regions to influence the processing of new information by the limbic circuitry[7,139,140]. This Review proposes that the drug-induced impairments in glutamate transmission between the prelimbic cortex and the nucleus accumbens (NAc) core disrupt information processing in the cortico-striato-thalamic circuit, decreasing the ability of addicts to regulate drug-seeking behaviours and increasing their vulnerability to relapse. DL striatum, dorsolateral striatum; VM striatum, ventromedial striatum; VTA, ventral tegmental area.



© 2009 Macmillan Publishers Limited. All rights reserved

dorsal striatum[20]. Finally, more extended periods of self-administration training make animals less responsive to environmental stimuli that disrupt drug seeking, such as associating drug administration with an aversive stimulus[32,33]. Taken together, these data support the view that repeated engagement of drug-seeking behaviours causes progressively greater reliance on the motor subcircuit, and less receptivity to environmental contingencies that are processed in the limbic subcircuit. Next, I explore data supporting the hypothesis that the reduced influence of the limbic subcircuit arises from an enduring imbalance in glutamate homeostasis in the NAc.

## Impaired glutamate homeostasis

Glutamate homeostasis involves the regulation of extracellular glutamate levels in the synaptic and perisynaptic extracellular environment. It affects synaptic activity and plasticity by controlling glutamate access to ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors (FIG. 2a). A crucial factor in maintaining glutamate homeostasis is the balance between glial and synaptic glutamate release and elimination.

Below I evaluate the evidence for alterations in glutamate homeostasis in the NAc in animal models of nicotine, heroin and cocaine addiction. Next I describe the effects of these drug-induced alterations in glutamate homeostasis on dendritic spine morphology, on the postsynaptic proteins that regulate dendritic spine morphology and glutamate signalling, and on metaplasticity in glutamate synaptic physiology. Finally, all aspects of glutamate homeostasis are considered together in a model of impaired communication between the prefrontal cortex and the NAc that could explain why addicts cannot effectively regulate drug-seeking behaviour.

***The regulation of glutamate homeostasis by presynaptic and glial glutamate release and elimination.*** Glutamate transmission is traditionally measured using *in vitro* recording of glutamate-dependent electrophysiological responses. These studies underpin the classic description of glutamate action: presynaptic release, binding to postsynaptic glutamate receptors and subsequent elimination by high-affinity $Na^+$-dependent glutamate transporters[34,35]. In this scheme, synaptic glutamate transmission is confined to individual synapses and does not typically communicate between synapses[36]. In the 1990s, *in vivo* microdialysis measurements began to reveal that synaptic release of glutamate as described *in vitro* is embedded in a more complex regulatory environment in which extracellular, non-synaptic glutamate can strongly shape excitatory synaptic transmission and plasticity. Microdialysis experiments revealed that extracellular glutamate measured *in vivo* is largely unaffected by blocking synaptic transmission with voltage-dependent $Na^+$ or $Ca^{2+}$ channel antagonists[37]. The fact that extracellular, non-synaptic glutamate is measured at concentrations between 1 and 5 μM revealed three important physiological influences on excitatory transmission: first, extracellular glutamate

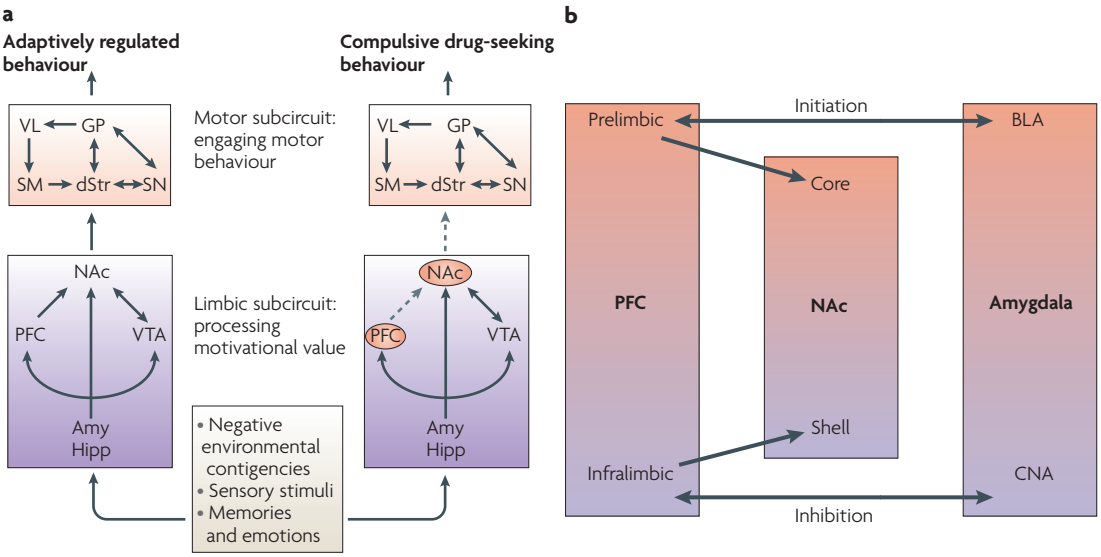



Figure 1 | **Corticostriatal circuits in addiction. a** | Simplified corticostriatal circuits, highlighting the role of the nucleus accumbens (NAc) as a gateway between a limbic subcircuit, which is responsible for integrating environmental contingencies, and the motor subcircuit, which guides ongoing behaviour. It is proposed that in drug seeking (right-hand side), drug-induced cellular changes in the prefrontal cortical input to the NAc decrease the capacity of information integrated in the limbic subcircuit to regulate drug-seeking behaviours (dotted arrows). **b** | Differential roles for increased activity in the prelimbic and infralimbic cortices in the prefrontal cortex (PFC) in initiating or inhibiting the reinstatement of drug-seeking behaviour. Also incorporated into the figure are topographically organized cortical projections to the amygdala subnuclei and subcompartments of the NAc (core and shell) that also can contribute to the inhibition and initiation of drug seeking. Double-headed arrows indicate reciprocal projections between nuclei. BLA, basolateral amygdala; CNA, central nucleus of the amygdala; dStr, dorsolateral striatum; GP, globus pallidus; hipp, hippocampus; SM, sensorimotor cortex; SN, substantia nigra; VL, ventrolateral thalamus; VP, ventral pallidum; VTA, ventral tegmental area.



© 2009 Macmillan Publishers Limited. All rights reserved

is derived primarily from non-synaptic, glial sources; second, extrasynaptic mGluRs are regulated by non-synaptically released glutamate; and third, glutamate uptake protects iGluRs in the synaptic cleft from exposure to non-synaptically released glutamate (conversely, uptake reduces the influence of synaptically released glutamate on perisynaptic mGluRs)[36,38,39] (FIG. 2a). Data exist showing that all three of these processes are altered by chronic treatment with cocaine, and to some extent by chronic treatment with heroin and nicotine.

In the NAc core, ~60% of the basal extracellular glutamate is derived from constitutive cystine–glutamate exchange[40] (FIG. 2). This exchange is a rate-limiting step in glutathione synthesis and occurs more in glia than in neurons; cystine uptake is linked to the release of cytoplasmic glutamate in 1/1 stoichiometry[41]. The exchanger is functionally expressed as a heterodimer, and cocaine and nicotine self-administration reduce membrane levels of the catalytic subunit, xCT (also known as SLC7A11), in the NAc[51,42–44]. Consequently, the basal levels of extracellular glutamate are reduced by ~50% in the NAc core of animals treated with repeated contingent and non-contingent cocaine[23,45–52]. In addition to being regulated by cystine–glutamate exchange, extracellular glutamate levels are strongly governed by glutamate transporters[53], the most influential of which is the primarily glial transporter GLT1 (also known as SLC1A2). GLT1 is concentrated in the vicinity of the synaptic cleft and serves in part to buffer glutamate released through cystine–glutamate exchange and from synaptic vesicles[42] (FIG. 2a). This organization maintains synaptic glutamate transmission at iGluRs, which are concentrated in the synaptic cleft, as a primarily phasic, time-limited event. Conversely, as basal activity of cystine–glutamate exchange maintains an extrasynaptic concentration of glutamate in the low-micromolar range, mGluRs that have a dissociation constant for glutamate in the high-nanomolar range are subjected to tonic stimulation[54–57].

Although further study is necessary to clarify the relationship between cystine–glutamate exchange and mGluR activation, it has been shown *in vitro* that activation of cystine–glutamate exchange in the NAc by physiological levels of cystine stimulates mGluR2 (also known as GRM2) and mGluR3 (also known as GRM3) (mGluR2/3), decreasing the synaptic glutamate release probability[55]. This means that cocaine-induced reductions in cystine–glutamate exchange not only reduce basal extracellular concentrations of glutamate, but also increase the synaptic release of glutamate by reducing the tone on release-regulating mGluR2/3 (BOX 3). Thus, modulation of mGluR2/3 through cystine–glutamate exchange accounts not only for the reduction in basal extrasynaptic levels of glutamate after chronic cocaine administration (that is, an effect of reduced cystine–glutamate exchange), but also for the increase in synaptic release of glutamate into the NAc core during cue-, stress- and/or drug-induced reinstatement of cocaine and/or heroin seeking (that is, a result of the reduced tone on synaptic glutamate release regulating mGluR2/3)[23,50–52,58]. The importance of this mechanism is revealed by the fact that both the reinstatement of extinguished drug seeking and the associated rise in synaptically released glutamate in the NAc core are abolished by inactivation of the prelimbic cortex, indicating that prelimbic afferents to the NAc core are the primary source of augmented synaptic glutamate release[50,58]. It was recently shown that glutamate uptake and membrane levels of GLT1 are downregulated in the NAc core after cocaine or nicotine self-administration[42–44]. The overflow of synaptic glutamate during the reinstatement of drug-seeking behaviour therefore arises not only from the enhanced release of synaptic glutamate, but also from reduced elimination of glutamate from the extracellular space.

FIGURE 2 illustrates the general relationship between cystine–glutamate exchange, GLT1 and synaptic glutamate release. Crucial to the potential importance of downregulated cystine–glutamate exchange and GLT1 in addiction are behavioural studies demonstrating that the mechanisms illustrated in FIG. 2 can be used to inhibit cocaine or heroin seeking. Activating cystine–glutamate exchange with *N*-acetylcysteine restores basal extracellular levels of glutamate and prevents the reinstatement of cocaine and heroin seeking[46,59,60] (BOX 3). Correspondingly, direct agonist stimulation of mGluR2/3 inhibits cocaine and heroin seeking[61–63], and a mechanistic link between cystine–glutamate exchange and mGluR2/3 was shown by preventing *N*-acetylcysteine-induced

Box 2 | **Animal models used to study enduring neuroplasticity in addiction**

Many animal models of addiction are currently used to study drug-induced changes in brain chemistry, physiology and behaviour. These models can be grouped into two subcategories: those that use a non-contingent, experimenter-delivered drug, and those that use a contingent, self-administered drug. Given that human addiction involves drug self-administration, the face validity of the latter models exceeds that of the former. However, non-contingent models are still used because of the relative ease of drug delivery and because of overlap in some of the biological changes elicited by contingent and non-contingent drug administration.

**Non-contingent models**

Two non-contingent addiction models are locomotor sensitization and conditioned place preference. Locomotor sensitization is defined as the locomotor response induced by acute drug administration, which is progressively augmented with repeated administration. The sensitized motor response generally persists for weeks or months after the last drug injection. This characteristic is similar to the enduring behavioural changes associated with addiction, indicating potential shared neuronal substrates[141]. Conditioned place preference is used to study the ability of addictive drugs to establish learnt contextual associations[142], and might better model the acquisition of addiction than the enduring drug-induced adaptations.

**Contingent models**

Drug self-administration requires an operant response, such as lever pressing, to initiate drug delivery. A common contingent model used to evaluate enduring drug-induced plasticity is the reinstatement of drug seeking[143]. In this model, animals are trained to self-administer the addictive drug, and then undergo extinction training to inhibit context-induced drug seeking or are forced into abstinence with no further drug-related training. After a withdrawal period, the animals are given a stimulus (for example, a drug-associated cue, stressor or non-contingent drug injection) that will overcome the extinction-induced inhibition of responding, thereby causing them to engage the previously learnt response to obtain the drug, even though no drug is available[16]. If the animal has not undergone extinction training, returning to the drug-paired context will initiate robust behaviours associated with obtaining drugs in the absence of actual drug delivery[18,143]. Another self-administration model often used to discern the neural substrates of drug seeking uses second-order training schedules in which animals are trained to provide a complex chain of responses to achieve a conditioned reinforcer that predicts drug delivery, typically without incorporating a withdrawal period[144].



© 2009 Macmillan Publishers Limited. All rights reserved

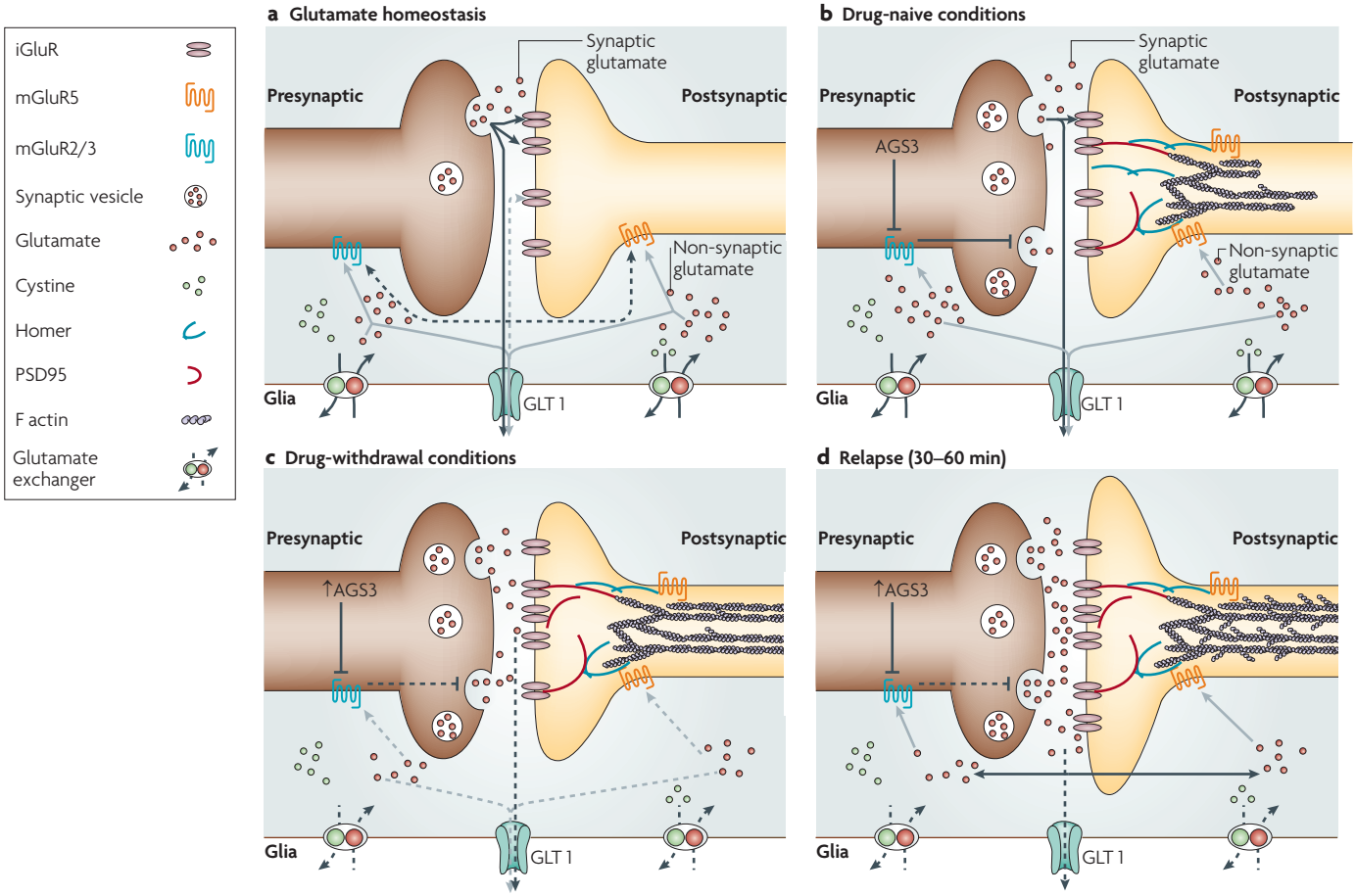



Figure 2 | **Neuroadaptations produced by the effects of chronic cocaine administration on protein content and function in excitatory synapses in the nucleus accumbens. a** | Glutamate uptake through glutamate transporter 1 (GLT1; also known as SLC1A2) limits the access of synaptically released glutamate to the non-synaptic extracellular space and metabotropic glutamate receptors (mGluRs), and limits the access of glutamate released non-synaptically (through cystine–glutamate exchange) to the synaptic cleft and ionotropic glutamate receptors (iGluRs). As a result, glutamate derived from cystine–glutamate exchange does not readily stimulate synaptic iGluRs[38]. Solid lines illustrate the physiological interactions under basal conditions; dotted lines illustrate minor interactions. **b** | In control (that is, drug-naive) conditions, glutamate homeostasis maintains concentrations of extracellular synaptic and non-synaptic glutamate that permit synaptic grading and the induction of long-term potentiation and long-term depression. **c** | Changes that occur after withdrawal from chronic cocaine administration. In this condition, reduced cystine–glutamate exchange results in a decrease in basal extrasynaptic glutamate levels. In addition, reduced tone on mGluR2 and mGluR3 (mGluR2/3), partially due to upregulation of activator of G protein signalling 3 (AGS3; also known as GPSM1), results in an increase in synaptically released glutamate. In the postsynaptic neuron, filamentous (F) actin, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) iGluRs and postsynaptic density protein 95 (PSD95; also known as DLG4) levels are elevated, whereas Homer levels are reduced. **d** | Changes in glutamate homeostasis and protein content in the nucleus accumbens seen 30 to 60 min following the induction of cocaine seeking by an acute cocaine injection (relapse). Synaptic glutamate levels are increased owing to enhanced release and to reduced elimination of glutamate from the extracellular space by GLT1. In addition, the surface expression of AMPA iGluRs is elevated and spine head diameter is further increased.

inhibition of cocaine seeking with an mGluR2/3 antagonist[55] (BOX 3). Finally, it was recently found that ceftriaxone restored GLT1 levels in the NAc core of rats trained to self-administer cocaine and prevented cue- and cocaine-induced reinstatement of cocaine seeking[44]. Interestingly, although *N*-acetylcysteine and ceftriaxone selectively target cystine–glutamate exchange and glutamate uptake through GLT1, respectively[64], daily treatment with either drug increases the membrane levels of both xCT and GLT1 (REF. 44). This indicates that glutamate homeostasis might involve co-regulation of glial glutamate release through cystine–glutamate exchange and elimination of glutamate by GLT1; this possibility is supported by results from earlier *in vitro* studies[65,66].

Ceftriaxone
A cephalosporin antibiotic in the β-lactam family that is used to treat pneumonia and bacterial meningitis. It was recently shown to also promote the synthesis and expression of the glial glutamate transporter.

***Morphological changes in dendritic spines.*** A decade ago, Robinson and Kolb demonstrated that chronic non-contingent amphetamine administration causes dendritic dysmorphisms and increased dendritic spine density in the NAc and prefrontal cortex of rats[67]. Subsequently, drug-induced dendritic changes were shown to be widespread in the striatum, although specific effects in

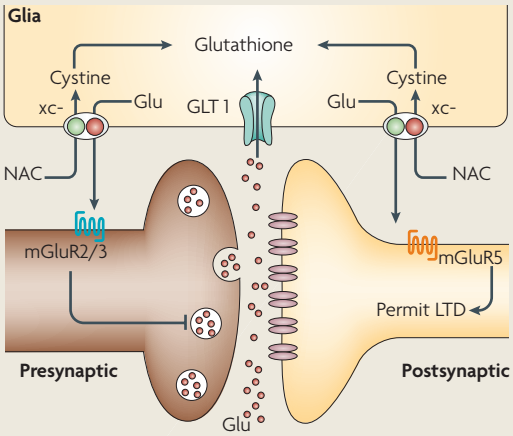


© 2009 Macmillan Publishers Limited. All rights reserved

**Prime-induced reinstatement of drug seeking behaviour**
Stimulating the reinstatement of lever pressing by an external stimulus. Examples of such a stimulus include presentation of a cue previously paired with the delivery of an addictive drug, presentation of an acute stressor, or acute administration of the addictive drug.

subcompartments have been associated with differences in drug exposure and environmental conditions[68–70]. Recently, it was shown that the distribution of spine head diameters in the NAc core or dorsal striatum was shifted to larger head diameters after withdrawal from chronic non-contingent cocaine or methamphetamine treatment[70,71]. Furthermore, in chronic non-contingent cocaine-treated subjects undergoing withdrawal, acute cocaine elicits dramatic changes over the first 120 min after administration, but it has no such effect in control animals (FIG. 3); this entails an increase in spine head diameter at 45 min and a reduction in diameter at 120 min after injection. Importantly, the changes also occur during prime-induced reinstatement of drug seeking in rats that have been trained to self-administer cocaine or heroin (P.W.K., unpublished observations). Thus, chronically administered cocaine or heroin results in marked neuroplasticity of dendritic spines during the reinstatement of drug seeking. However, it remains to be determined whether similar morphological plasticity is manifested during cue-, stress- or context-induced drug seeking.

Box 3 | **N-acetylcysteine regulation of drug seeking, LTP and LTD**




*N*-acetylcysteine (NAC) is a member of the procysteine drug class that has clinical utility because it increases glutathione synthesis[145]. It does this because it is deacetylated after administration and dimerizes to cystine, which is transported into cells by cystine–glutamate exchange (xc-) as the rate-limiting step in glutathione synthesis[41]. Intracellular glutamate (Glu) is exchanged with cystine, and downregulated cystine–glutamate exchange in the nucleus accumbens after chronic cocaine administration results in reduced extracellular glutamate. The figure illustrates the mechanism by which NAC-induced restoration of cystine–glutamate exchange might ameliorate drug seeking. Constitutive cystine–glutamate exchange maintains tone on perisynaptic metabotropic type 2 and 3 glutamate receptors (mGluR2/3), and blocking mGluR2/3 prevents NAC from inhibiting cocaine seeking[55]. This is thought to arise from mGluR2/3 stimulation by NAC administration, which in turn inhibits the synaptic release of glutamate. Moreover, NAC restores the bidirectional loss of long-term potentiation (LTP) and long-term depression (LTD) at prefrontal–nucleus accumbens synapses that is produced by chronic cocaine administration, an action that is inhibited by blocking mGluR2/3 (for LTP) or mGluR5 (for LTD)[60]. It is proposed that the action on mGluR2/3 decreases the probability of glutamate release, thereby depotentiating glutamate transmission and permitting the induction of LTP by high-frequency stimulation. Conversely, restoration of tone on mGluR5 promotes the capacity to induce LTD in response to low-frequency stimulation. Restoration of tone to both of these receptors by NAC administration might therefore re-establish the crucial homeostatic influence of mGluR2/3 on synaptic glutamate release and that of mGluR5 on synaptic grading. Importantly, given the capacity of NAC to elevate glutathione and the crucial role of glutathione in balancing intracellular redox potential, it is possible that some of the benefits of NAC in treating addiction might be related to elevating glutathione. This possibility has not been evaluated. GLT1, glutamate transporter 1.

***Alterations in synaptic proteins and proteins regulating dendritic spine morphology.*** Changes in the level or activity state of proteins after chronic drug administration have been intensively researched; for excellent reviews describing drug effects on transcriptional regulators and cell signalling proteins, see REFS 72,73. Here, I highlight specific proteins that illustrate how extracellular glutamate levels, glutamate transmission and synaptic physiology are dynamically affected by chronic administration of addictive drugs.

Glutamate receptors are the most thoroughly studied class of proteins affected by chronic drug administration. Whole-cell levels of the GluR1 (also known as GRIA1) subunit of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors[74] and the surface expression of GluR1 (REFS 75,76) are increased in the NAc after chronic contingent and non-contingent cocaine administration. Most recently, a cocaine self-administration paradigm showed that the increase in surface AMPA receptor levels after extensive withdrawal periods was due to addition of AMPA receptors that lack the GluR2 (also known as GRIA2) subunit[76]. Also, an acute injection of cocaine in animals withdrawn from self-administered cocaine rapidly induces the surface expression of GluR1 (REF. 77). The increase in both basal and cocaine-stimulated surface expression of AMPA receptors is consistent with the capacity of AMPA antagonists in the NAc to block heroin and cocaine seeking using second-order or reinstatement paradigms[58,77–80], and with augmentation of intra-NAc AMPA-induced locomotor activity and reinstatement of cocaine-seeking behaviour[45,81]. Interestingly, 24 h after a cocaine injection in chronic non-contingent cocaine-treated animals the surface expression of GluR1 is reduced[82], in apparent contrast to the initial rapid upregulation of surface AMPA receptors[77]. To some extent, this biphasic time course of surface GluR1 levels parallels the changes in spine head diameter and density of medium spiny neurons in the NAc after a cocaine injection in chronic cocaine-treated animals undergoing withdrawal (FIG. 3). The rapid increase in head diameter during the first 45 min after cocaine administration is consistent with an increase in AMPA receptor insertion[77]; the marked reduction in spine diameter at 120 min after injection is consistent with internalization of AMPA receptors[82]. Perhaps both processes are necessary for the expression of behavioural sensitization and reinstated drug seeking, with the two predominating at different times after a cocaine injection. Alternatively, as discussed below, the rapid trafficking of AMPA receptors might be part of a compensatory process that inhibits drug seeking.

Metabotropic glutamate receptors are also altered by repeated drug administration. Group II mGluR2/3 are downregulated after chronic non-contingent cocaine or self-administered nicotine administration[48,83]. Decreased mGluR2/3 function could result from reduced protein expression, increased receptor phosphorylation and/or upregulated expression of activator of G protein signalling 3 (AGS3; also known as GPSM1)[48,84,85]. mGluR2/3 are $G_i$-coupled, and AGS3 is a negative regulator of $G_i$ signalling[86]; therefore, inhibiting AGS3 restores mGluR2/3-mediated $G_i$ signalling and reduces cocaine, heroin and ethanol



© 2009 Macmillan Publishers Limited. All rights reserved

Synaptic grading
The capacity of synapses to potentiate and depotentiate the efficiency of communication between the pre- and postsynaptic components. It includes enduring plasticity in synaptic efficiency, such as long-term potentiation and long-term depression.

seeking[84,87,88]. Group I mGluR1 (also known as GRM1) and mGluR5 (also known as GRM5)(mGluR1/5) are also affected by chronic cocaine administration. mGluR1/5 and their intracellular binding protein Homer1b/c are downregulated in the NAc after withdrawal from chronic contingent or non-contingent cocaine[57,89–91]. The possibility that the downregulated Homer levels contribute to blunted mGluR1/5 signalling is supported by the fact that restoration of Homer1b in the NAc prevents acute cocaine injections inducing behavioural sensitization or increasing extracellular glutamate levels[47]. Interestingly, deletion of the *HOMER2* gene reduced the levels of xCT and elevated those of AGS3 in the NAc, indicating that reduced Homer levels might contribute to these effects of chronic cocaine[92]. The potential importance of the downregulation of mGluR1/5–Homer or mGluR2/3 signalling that occurs after chronic cocaine administration is indicated by the fact that pharmacologically inhibiting or deleting mGluR5 or downregulating Homer 1 levels attenuates cocaine, ethanol and nicotine seeking and locomotor sensitization[93–100], whereas stimulating mGluR2/3 signalling attenuates the reinstatement of nicotine, cocaine and heroin seeking[61–63,83]. These behavioural data point to the interesting possibility that drug-induced downregulation of mGluR5–Homer signalling is compensatory, whereas downregulation of mGluR2/3 signalling promotes drug seeking.

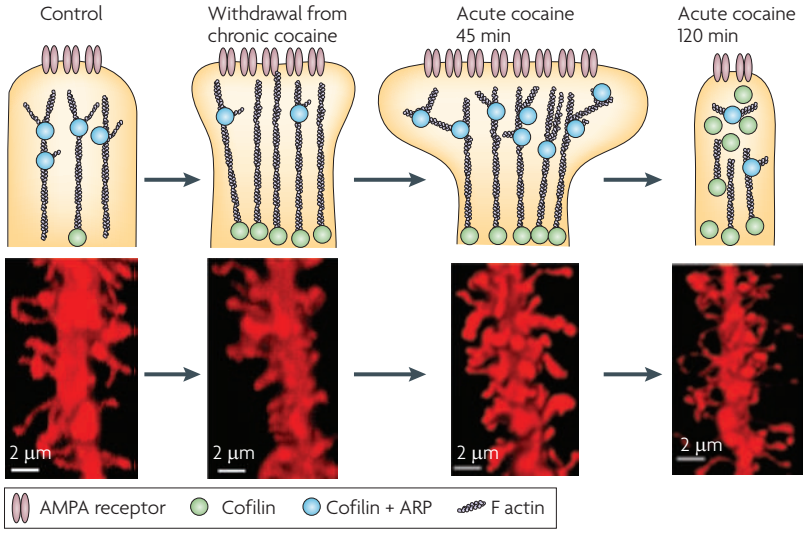



Figure 3 | **Changes in spine morphology and postsynaptic proteins produced by chronic cocaine and subsequent acute cocaine administration.** Withdrawal from chronic non-contingent cocaine administration causes a basal increase in spine head diameter that is associated with increased filamentous (F) actin levels. Withdrawal also produces alterations in actin-binding proteins that decrease F actin branching (for example, decreased levels of actin-related protein 3 (ARP3; also known as ACTR3)) but increase actin cycling (for example, reduced phosphorylation-induced inactivation of cofilin by Lim kinase (LIMK)[103])[71]. Acute cocaine administration to animals withdrawn from chronic cocaine exposure causes a bidirectional change in spine head diameter: soon after injection (45 min), spine head diameter is increased and this is associated with increased F actin branching and higher levels of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (an increase in surface AMPA receptors was shown as early as 30 min after acute cocaine administration)[77]. By 120 min, spine head diameter is markedly reduced in association with a marked increase in cofilin that promotes disassembly of F actin and, presumably, a reduction in AMPA receptors (although AMPA receptors have been examined only 24 h after injection)[82,111]. The micrographs show examples of changes in dendritic spines for each condition.

Given the changes in spine diameter and postsynaptic proteins, and the well-established role of actin in spine morphology[101], it is not surprising that filamentous (F) actin levels are elevated by chronic non-contingent morphine, cocaine and alcohol exposure[102,103] (however, see REF. 85). Perhaps more importantly, the changes in actin-binding proteins produced by a cocaine injection in the NAc of animals withdrawn from chronic cocaine parallel the changes in spine head diameter: an increase in actin-related protein 2 (ARP2; also known as ACTR2) at 45 min after injection is consistent with increased actin branching and increased spine head diameters, whereas an increase in cofilin and a decrease in F actin at 120 min after injection is consistent with shrinking of spines at 120 min[71] (FIG. 3). Indeed, actin cycling seems to be increased after chronic non-contingent cocaine or morphine administration (BOX 4), and if actin cycling is inhibited, cocaine-induced reinstatement of drug seeking is exacerbated and changes in spine head diameter are prevented[71,102]. This raises the interesting possibility that the increase in actin cycling, and corresponding rapid changes in spine morphology induced by an acute injection of cocaine, are compensatory and serve to attenuate cocaine seeking.

***Metaplasticity in glutamate synaptic physiology.*** Various changes induced by chronic drug treatment have been identified in the electrophysiological activity of medium spiny neurons in the NAc. These range from decreased excitability in dissociated spiny neurons from cocaine-withdrawn animals to increases and decreases in neuron firing that correlate with the act of cocaine seeking[104,105]. Here I focus on drug-induced changes in synaptic plasticity as it relates to glutamate homeostasis; for more general discussions of addiction and synaptic plasticity, see REFS 106,107. Changes in synaptic plasticity have been probed using two primary endpoints: induction of long-term depression (LTD) or potentiation (LTP), and the relative strength of AMPA- and NMDA (*N*-methyl-D-aspartate)-induced currents. The latter of these two measures is indicative of synaptic grading, in which an increase in the AMPA/NMDA current ratio indicates that the synapses are in a relatively potentiated state, whereas a decrease indicates a depotentiated state[107,108]. Metaplasticity is a change in the ability to generate synaptic plasticity: a priming activity alters the capacity of a subsequent high- or low-frequency stimulation protocol to induce LTP or LTD[109,110]; for the purposes of this Review the priming activity is chronic administration of an addictive drug.

Extended withdrawal from chronic cocaine produces two seemingly contradictory events in the NAc. First, and consistent with the previously mentioned increase in surface expression of AMPA receptors, it increases the AMPA/NMDA ratio, indicating potentiated synaptic strength[76,111]. Second, it attenuates LTD in the NAc core[112]. According to convention, the increase in AMPA/NMDA ratio would predict enhanced rather than reduced LTD, because already-potentiated synapses should have a greater dynamic range towards depotentiation[107]. In part to address these conflicting data, LTP or LTD was induced *in vivo* in the NAc core by electrical stimulation of the



© 2009 Macmillan Publishers Limited. All rights reserved

prelimbic cortex in animals withdrawn from cocaine self-administration; both LTP and LTD were found to be attenuated[60]. Although the loss of LTP is consistent with occlusion due to the increased AMPA/NMDA ratio, the inhibition of LTD is more difficult to account for. One explanation for the bidirectional loss of synaptic plasticity is indicated by the fact that increasing cystine–glutamate exchange with *N*-acetylcysteine restores the ability to induce both LTP and LTD. Cystine–glutamate exchange provides glutamatergic tone onto mGluRs (BOX 3), and presynaptic mGluR2/3 and postsynaptic mGluR5 regulate the expression of LTP and LTD, respectively[108,113,114]. Accordingly, the capacity of *N*-acetylcysteine to normalize LTP is blocked by inhibiting mGluR2/3, and the restoration of LTD is blocked by inhibiting mGluR5 (REF. 60). Thus, the tone on mGluRs provided by cystine–glutamate exchange facilitates the induction of both LTP and LTD, and the downregulation of cystine–glutamate exchange by chronic cocaine administration contributes to the bidirectional loss of synaptic plasticity.

The loss of LTP deserves further discussion, because a number of previous studies found that chronic non-contingent drug administration had no effect on LTP[115–117]. However, these studies used different experimental paradigms (non-contingent versus contingent drug administration (BOX 2)). In addition, two of them[115,117] were conducted in tissue slices, rather than *in vivo* (one using tissue from animals after non-contingent amphetamine administration[117]), and the other was conducted in mice, not rats[116]. The *in vivo* study was conducted in the NAc shell[115], where another study showed that animals trained to self-administer cocaine have no enduring impairment of LTD[113]. Moreover, LTP induced in the NAc shell by cortical stimulation was measured after conditioning tetanic stimulation of the hippocampus, which could have altered cortically induced LTP[116]. Interestingly, the LTP induced by hippocampal stimulation was inhibited by chronic non-contingent cocaine but not amphetamine administration[115,118]. These contradictory studies not only point to the important effects of the treatment paradigm used, but also indicate possible distinctions between the effects of amphetamine and cocaine[119].

***Caveats to consider.*** Before proceeding to an integrated model of how drug-induced adaptations in glutamate homeostasis might contribute to addiction, the reader should bear in mind four important caveats. First, the conclusions drawn here have been distilled from data using various animal models. Where possible the discussion has been restricted to the reinstatement models of drug seeking. However, in some instances potentially relevant data have been generated not by these models but by models using second-order schedules of drug self-administration or non-contingent drug administration. Second, although the neuroadaptations are described for drug addiction in general, most data are derived from the literature on cocaine and, to a lesser extent, that on opioids and nicotine. Third, even if one considers only cocaine self-administration and reinstatement, other differences between experimental protocols — such as the extent of total drug intake, the number of days of training or withdrawal, and the presence or absence of extinction training — might affect the presence or amplitude of a given drug-induced neuroadaptation[76,120,121]. Finally, to focus on prefrontal afferents to the NAc core is to oversimplify the circuit involved in drug seeking. Although abundant evidence — ranging from inactivation-induced inhibition of drug seeking[21–26,58] and immediate-early gene activation during drug seeking[122–125] to increased blood flow during craving in human addicts[126–129] — shows this pathway to be important, glutamatergic afferents from the amygdala to the NAc core also contribute to cue- and heroin-induced drug seeking, as do dopaminergic afferents to the NAc shell[130–132].

## Linking drug-induced adaptations

In an effort to link the various findings outlined above, FIG. 2c depicts the changes in glutamatergic synapses in the NAc following withdrawal from chronic cocaine administration. The key presynaptic adaptations include decreased mGluR2/3 signalling, due in part to elevated AGS3 and in part to reduced glutamatergic tone from diminished cystine–glutamate exchange. Importantly, under basal conditions metabolic activity in the prefrontal cortex of addicts[126] and the firing rate of prefrontal neurons projecting to the NAc are reduced[133], accounting for decreased basal synaptic glutamate release in the presence of reduced mGluR2/3-mediated inhibition of release. Diminished basal synaptic and non-synaptic release might contribute to the downregulation of GLT1 (REF. 42) and the basal increase in AMPA receptors in the postsynaptic membrane[75,76,111]. Indeed, cocaine-induced upregulation of AMPA receptors lacking GluR2 subunits has been interpreted as homeostatic synaptic scaling in response to decreased activity[76]. Moreover, the number and/or diameter of dendritic spines increases after chronic cocaine administration and is associated with an increase in F actin[69,71,102], which is also consistent with homeostatic synaptic scaling.

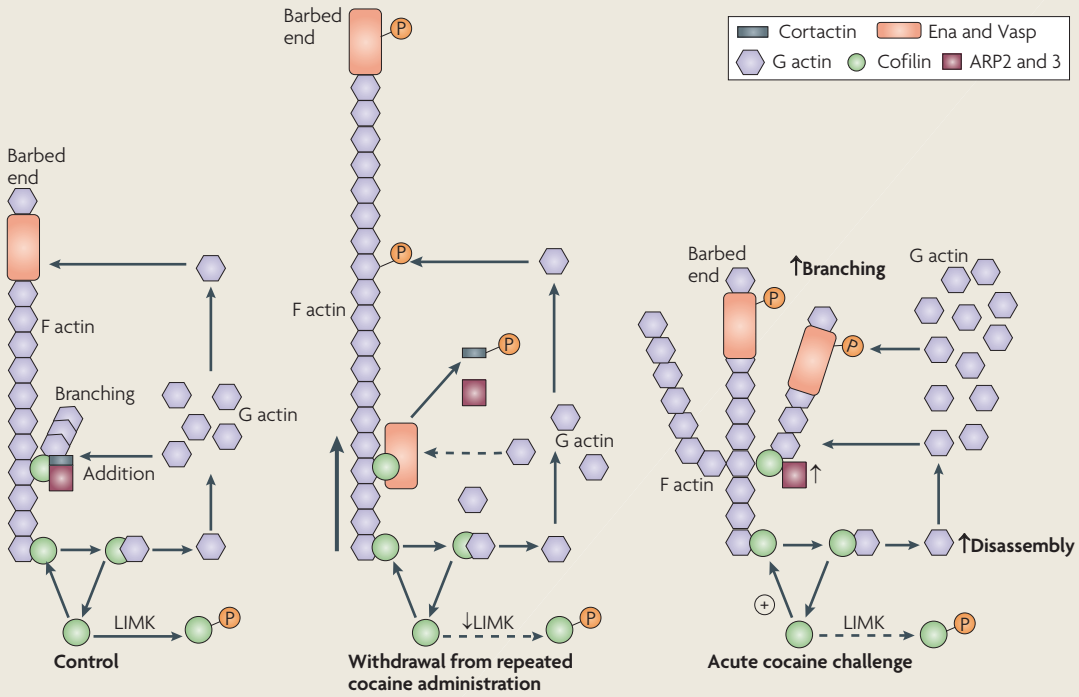
When drug seeking is reinstated in heroin- or cocaine-trained animals there is a large increase in both firing activity in prefrontal neurons and glutamate release in the NAc[50,51,58,133]. The release of glutamate is synaptic, derived from prefrontal afferents[50,58], and results in part from reduced tone on release-regulating mGluR2/3 caused by downregulated cystine–glutamate exchange[46,48,42]. In addition, the overflow of glutamate outside the synapse results in part from downregulation of GLT1 (REFS 42,44). Synaptic glutamate release evoked by drug seeking is associated with rapid changes in postsynaptic spine morphology and protein content: within 45 min of acute cocaine injection there is an increase in spine head diameter, AMPA receptor insertion and F actin levels[71,77,102]. However, by 120 min after injection, when extracellular glutamate is no longer elevated, spine diameter and levels of F actin are reduced. Consistent with shrinking spine head diameter, the number of surface AMPA receptors is reduced, and the AMPA/NMDA ratio and field potential amplitude stimulated from the prefrontal cortex 6–24 h after an acute cocaine injection are reduced in chronic non-contingent cocaine-treated animals[71,82,111,134].

Tetanic stimulation
A train of stimuli in which afferent axons are briefly activated at high frequency. In LTP experiments, a 1 s train of pulses delivered at a frequency of 100 Hz is commonly used to potentiate transmission.



© 2009 Macmillan Publishers Limited. All rights reserved

Box 4 | **Actin cycling and postsynaptic effects of chronic cocaine administration**




The morphology of dendritic spines is stabilized in large part by actin. To enlarge or shrink spines, actin undergoes a cycling process in which filamentous (F) actin is depolymerized to monomeric globular (G) actin at one end of the filament and elongated by addition of G actin monomers to the other, 'barbed' end of the filament[101] (see the left-hand side of the figure). The cycling of actin through depolymerization and elongation allows the actin filaments to grow, shrink and branch, which can change the shape of dendritic spines. This process is proximally regulated by actin-binding proteins (ABPs), and different ABPs control different aspects of disassembly, elongation and branching[101]. The exact role of many ABPs is only now becoming clear. Regarding enduring actin and ABP changes in models of addiction, certain observations indicate that actin cycling is increased after withdrawal from chronic non-contingent cocaine and morphine administration (see the middle part of the figure). A key cocaine-induced change is an increase in F actin content[102], which is consistent with the reported increase in spine density and head diameter after chronic cocaine exposure[69,71]. Cycling is promoted by a drug-induced reduction in Lim kinase (LIMK)[102]. LIMK phophorylates and inactivates cofilin, a key ABP that regulates both disassembly and branching[146]. Thus, after chronic cocaine administration cofilin inactivation is reduced, which in turn promotes the disassembly of actin. However, branching seems to be inhibited by a cocaine-induced reduction in actin-related protein 3 (ARP3; also known as ACTR3) and by an increase in phosphorylation of cortical actin-binding protein (cortactin), which impairs the ability of cofilin to induce branching[147]. How cocaine promotes elongation of F actin is not as clear, because the LIMK mechanism primarily affects disassembly; however, the cocaine-induced increase in the phosphorylation of Ena and Vasp proteins is expected to promote elongation[148]. After a cocaine challenge injection in chronically cocaine-treated animals (see the right-hand side of the figure) the increase in cofilin and ARP2 increases actin disassemby and branching, respectively. Figure is modified, with permission, from REF. 102 © (2006) Society for Neuroscience.

The bidirectional loss of LTP and LTD after self-administration of cocaine[60,112] suggests that the rapid changes in cytoskeletal proteins and dendritic spine morphology associated with the reinstatement of drug seeking might indicate impairment of mechanisms for inducing synaptic plasticity. Two findings relate to this possibility. First, actin cycling is elevated after chronic cocaine administration[102], potentially making it difficult to sustain the morphological changes in dendritic spines that accompany the induction of LTP or LTD. Second, increasing cystine–glutamate exchange with *N*-acetylcysteine, which normalizes tone on perisynaptic mGluRs (BOX 3), restores the induction of LTP and LTD in the NAc by prefrontal stimulation[60]. It is therefore possible to simultaneously normalize synaptic glutamate release, restore the ability to induce mGluR-dependent LTP and LTD, and prevent heroin or cocaine seeking[46,59], by restoring glutamatergic tone onto mGluRs that are crucial for inducing LTP and LTD[108,113,114].

The fact that reversal of the cellular and physiological adaptations wrought by chronic drug administration also restores the capacity to inhibit drug seeking is perhaps the best evidence that drug-induced neuropathologies in the NAc impair the ability of animals to inhibit drug seeking. The contention that altered neuroplasticity in the NAc is responsible for impaired regulation of behaviour by the limbic corticostriatal subcircuit gains further support from the finding that the drug-induced



© 2009 Macmillan Publishers Limited. All rights reserved

neuroadaptations outlined above can differentially promote and inhibit drug seeking. For example, the loss of glutamate homeostasis decreases tone and signalling at presynaptic mGluR2/3 and upregulates postsynaptic AMPA receptors, both of which promote the reinstatement of drug seeking[60,76]. By contrast, the loss of tone and signalling through postsynaptic mGluR5 is compensatory, as further decreasing mGluR5 signalling inhibits drug seeking and restoring mGluR5 tone promotes drug seeking[60,98,99]. Similarly, preventing the cocaine-induced increases in actin cycling and changes in spine morphology also promotes drug seeking[102], indicating that these are also compensatory adaptations. Thus, by manipulating specific cellular aspects of drug-induced plasticity it is possible to differentially potentiate or inhibit the reinstatement of drug seeking, raising the possibility that selective potentiation and inhibition of drug-induced plasticity could have therapeutic benefit in treating addiction.

## Clinical applications and conclusions

This Review argues that the diminished ability of drug addicts to control their drug seeking arises from a loss of glutamate homeostasis, which in turn impairs prefrontal regulation of striatal circuitry. The impairment is associated with several drug-induced changes in prefrontal glutamatergic synapses in the NAc that have the potential to reduce effective regulation of drug seeking. It is generally assumed that by examining the molecular underpinnings of the changes in spine morphology, extracellular glutamate concentration and synaptic plasticity, it might be possible to identify new targets for treating addiction[72,135,136].

There are two approaches to the therapeutic application of this emerging knowledge. First, we can target a specific drug-induced molecular change. As outlined above, some drug-induced changes are compensatory, and so pharmacologically exacerbating these drug-induced adaptations might be useful. For example, potentiating a compensatory adaptation is a rationale behind giving mGluR5 antagonists to inhibit drug seeking, as chronic drug administration downregulates mGluR5 function[98]. Conversely, stimulating mGluR2/3 or downregulating AGS3 prevents drug seeking[61,63,84,88], presumably by countermanding the drug-induced downregulation of mGluR2/3 function. A second therapeutic approach is to consider the imbalance in glutamate homeostasis as a potential root cause of these adaptations. Indeed, activating cystine–glutamate exchange with *N*-acetylcysteine restores non-synaptic glutamate release and the ability to induce LTP and LTD[51,60]. In addition, we recently found that *N*-acetylcysteine treatment reverses the changes in spine morphology and AMPA/NMDA ratio produced after withdrawal from self-administration of cocaine (P.W.K., unpublished observations) and also normalizes the membrane expression of GLT1 (REF. 44). The fact that *N*-acetylcysteine also prevents the reinstatement of cue-, cocaine- or heroin-induced drug seeking[51,59] and reduces the desire for cocaine and cigarette use in humans[43,137] supports targeting glutamate homeostasis as a therapeutic approach. A finding potentially very important to clinical applications is that two weeks of treatment with *N*-acetylcysteine produces a reduction in cocaine or heroin seeking that endures for more than one month after discontinuation of the *N*-acetylcysteine treatments[51,59].

The possibility of targeting addictive drug-induced changes in either specific molecules or more general physiological processes such as glutamate homeostasis provides an emerging and exciting avenue for new drug development in treating addiction. However, in contrast to the impact that all addictive drugs have on dopamine transmission to reinforce drug taking, and on the general role of corticostriatal circuitry in maintaining both drug use and relapse, substantial work remains to determine whether the neuroadaptations in glutamate homeostasis outlined here extend to all addictive drugs. Nonetheless, the data to date support further research in this direction, both in terms of the corticostriatal mechanisms underlying addiction and in terms of exploring the cellular mechanisms of glutamate homeostasis for treatments of addiction.


1. Berridge, K. & Robinson, T. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* **28**, 309–369 (1998).
2. Kelley, A. E. Memory and addiction: shared neural circuitry and molecular mechanisms. *Neuron* **44**, 161–179 (2004).
3. Cardinal, R. N. & Everitt, B. J. Neural and psychological mechanisms underlying appetitive learning: links to drug addiction. *Curr. Opin. Neurobiol.* **14**, 156–162 (2004).
4. Di Chiara, G. Drug addiction as dopamine-dependent associative learning disorder. *Eur. J. Pharmacol.* **375**, 13–30 (1999).
5. Wise, R. A. Dopamine, learning and motivation. *Nature Rev. Neurosci.* **5**, 483–494 (2004).
6. Barnes, T. D., Kubota, Y., Hu, D., Jin, D. Z. & Graybiel, A. M. Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories. *Nature* **437**, 1158–1161 (2005).
7. Yin, H. H. & Knowlton, B. J. The role of the basal ganglia in habit formation. *Nature Rev. Neurosci.* **7**, 464–476 (2006).
**An outstanding review that integrates the neuroanatomy of the corticostriatal pathways with behaviour, especially in terms of the roles played by the prefrontal cortical projections in action–outcome contingencies and motor cortex projections in stimulus–response habits.**
8. Everitt, B. J. & Robbins, T. W. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neurosci.* **8**, 1481–1489 (2005).
**A concise description of the underlying perspective in the field of addiction that drug seeking is progressively more habitual and guided by the motor subcircuit.**
9. Robbins, T. W. & Everitt, B. J. Limbic-striatal memory systems and drug addiction. *Neurobiol. Learn. Mem.* **78**, 625–636 (2002).
10. Everitt, B. J. *et al.* Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **363**, 3125–3135 (2008).
11. Belin, D. & Everitt, B. J. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* **57**, 432–441 (2008).
12. Haber, S. N. The primate basal ganglia: parallel and integrative networks. *J. Chem. Neuroanat.* **26**, 317–330 (2003).
13. Alexander, G. E., DeLong, M. R. & Strick, P. L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* **9**, 357–381 (1986).
14. Groenewegen, H. J., Wright, C. I. & Beijer, V. J. The nucleus accumbens: gateway for limbic structures to reach the motor system? *Prog. Brain Res.* **107**, 485–551 (1996).
15. Doya, K. Modulators of decision making. *Nature Neurosci.* **11**, 410–416 (2008).
16. Shaham, Y., Shalev, U., Lu, L., De Wit, H. & Stewart, J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl.)* **168**, 3–20 (2003).
17. Di Ciano, P., Robbins, T. W. & Everitt, B. J. Differential effects of nucleus accumbens core, shell, or dorsal striatal inactivations on the persistence, reacquisition, or reinstatement of responding for a drug-paired conditioned reinforcer. *Neuropsychopharmacology* **33**, 1413–1425 (2008).
18. Fuchs, R. A., Branham, R. K. & See, R. E. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J. Neurosci.* **26**, 3584–3588 (2006).
19. Kantak, K. M., Black, Y., Valencia, E., Green-Jordan, K. & Eichenbaum, H. B. Stimulus-response functions of the lateral dorsal striatum and regulation of behavior studied in a cocaine maintenance/cue reinstatement model in rats. *Psychopharmacology (Berl.)* **161**, 278–287 (2002).
20. Vanderschuren, L. J., Di Ciano, P. & Everitt, B. J. Involvement of the dorsal striatum in cue-controlled cocaine seeking. *J. Neurosci.* **25**, 8665–8670 (2005).




© 2009 Macmillan Publishers Limited. All rights reserved

21. Capriles, N., Rodaros, D., Sorge, R. E. & Stewart, J. A role for the prefrontal cortex in stress- and cocaine-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl.)* **168**, 66–74 (2003).
22. Fuchs, R. A., Eaddy, J. L., Su, Z. I. & Bell, G. H. Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. *Eur. J. Neurosci.* **26**, 487–498 (2007).
23. McFarland, K., Davidge, S. B., Lapish, C. C. & Kalivas, P. W. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J. Neurosci.* **24**, 1551–1560 (2004).
24. McFarland, K. & Kalivas, P. W. The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J. Neurosci.* **21**, 8655–8663 (2001).
25. McLaughlin, J. & See, R. E. Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. *Psychopharmacology (Berl.)* **168**, 57–65 (2003).
26. Park, W. K. *et al.* Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *J. Neurosci.* **22**, 2916–2925 (2002).
27. Peters, J., LaLumiere, R. T. & Kalivas, P. W. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. *J. Neurosci.* **28**, 6046–6053 (2008).
28. Koya, E. *et al.* Role of ventral medial prefrontal cortex in incubation of cocaine craving. *Neuropharmacology* **56** (Suppl. 1), 177–185 (2009).
29. Porrino, L. J., Lyons, D., Smith, H. R., Daunais, J. B. & Nader, M. A. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *J. Neurosci.* **24**, 3554–3562 (2004).
30. Ito, R., Dalley, J. W., Howes, S. R., Robbins, T. W. & Everitt, B. J. Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J. Neurosci.* **20**, 7489–7495 (2000).
31. Ito, R., Dalley, J. W., Robbins, T. W. & Everitt, B. J. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J. Neurosci.* **22**, 6247–6253 (2002).
32. Pelloux, Y., Everitt, B. J. & Dickinson, A. Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology (Berl.)* **194**, 127–137 (2007).
33. Vanderschuren, L. J. & Everitt, B. J. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* **305**, 1017–1019 (2004).
34. Herman, M. & Jahr, C. E. Extracellular glutamate concentration in hippocampal slice. *J. Neurosci.* **27**, 9736–9741 (2007).
35. Diamond, J. S. & Jahr., C. E. Transporters buffer synaptically released glutamate on a submillisecond time scale. *J. Neurosci.* **17**, 4672–4687 (1997).
36. Barbour, B. An evaluation of synapse independence. *J. Neurosci.* **21**, 7969–7984 (2001).
37. Timmerman, W. & Westerink, B. H. Brain microdialysis of GABA and glutamate: what does it signify? *Synapse* **27**, 242–261 (1997).
38. Warr, O., Takahashi, M. & Attwell, D. Modulation of extracellular glutamate concentration in rat brain slices by cystine-glutamate exchange. *J. Physiol.* **514**, 783–793 (1999).
39. Haydon, P. Glia: listening and talking to the synapse. *Nature Neurosci.* **2**, 185–191 (2001).
40. Baker, D. A., Xi, Z. X., Shen, H., Swanson, C. J. & Kalivas, P. W. The origin and neuronal function of *in vivo* nonsynaptic glutamate. *J. Neurosci.* **22**, 9134–9141 (2002).
41. McBean, G. J. Cerebral cystine uptake: a tale of two transporters. *Trends Pharmacol. Sci.* **23**, 299–302 (2002).
42. Pendyam, S., Mohan, A., Kalivas, P. W. & Nair, S. S. Computational model of extracellular glutamate in the nucleus accumbens incorporates neuroadaptations by chronic cocaine. *Neuroscience* **158**, 1266–1276 (2009).
43. Knackstedt, L., LaRowe, S. D., Malcolm, R., Markou, A. & Kalivas, P. Nicotine self-administration reduces the cystine-glutamate exchanger, and exchanger activation decreases cigarette smoking. *Biol. Psychiatry* **65**, 841–845 (2009).
44. Knackstedt, L., Melendez, R. & Kalivas, P. W. Ceftriaxone restores glutamate homeostasis and prevents relapse to cocaine seeking. *Biol. Psychiatry.* (in the press).
45. Pierce, R. C., Bell, K., Duffy, P. & Kalivas, P. W. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J. Neurosci.* **16**, 1550–1560 (1996).
46. Baker, D. A. *et al.* Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nature Neurosci.* **6**, 743–749 (2003).
47. Szumlinski, K. K. *et al.* Homer isoforms differentially regulate cocaine-induced neuroplasticity. *Neuropsychopharmacology* **31**, 768–777 (2006).
48. Xi, Z. X. *et al.* Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. *J. Pharmacol. Exp. Ther.* **303**, 608–615 (2002).
49. Xi, Z. X. *et al.* Cannabinoid CB1 receptor antagonist AM251 inhibits cocaine-primed relapse in rats: role of glutamate in the nucleus accumbens. *J. Neurosci.* **26**, 8531–8536 (2006).
50. McFarland, K., Lapish, C. C. & Kalivas, P. W. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J. Neurosci.* **23**, 3531–3537 (2003).
51. Madayag, A. *et al.* Repeated *N*-acetylcysteine administration alters plasticity-dependent effects of cocaine. *J. Neurosci.* **27**, 13968–13976 (2007). **This excellent paper provides definitive evidence that the capacity of *N*-acetylcysteine to regulate drug-seeking behaviour results from actions on the cystine–glutamate exchanger and is associated with preventing the large release of glutamate in the accumbens during drug seeking.**
52. Miguens, M. *et al.* Glutamate and aspartate levels in the nucleus accumbens during cocaine self-administration and extinction: a time course microdialysis study. *Psychopharmacology (Berl.)* **196**, 303–313 (2008).
53. Danbolt, N. C. Glutamate uptake. *Prog. Neurobiol.* **65**, 1–105 (2001).
54. Schoepp, D. D. & True, R. A. 1S,3R-ACPD-sensitive (metabotropic) [$^3$H]glutamate receptor binding in membranes. *Neurosci. Lett.* **145**, 100–104 (1992).
55. Moran, M. M., McFarland, K., Melendez, R. I., Kalivas, P. W. & Seamans, J. K. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J. Neurosci.* **25**, 6389–6393 (2005).
56. Alagarsamy, S., Sorensen, S. D. & Conn, P. J. Coordinate regulation of metabotropic glutamate receptors. *Curr. Opin. Neurobiol.* **11**, 357–362 (2001).
57. Mitrano, D. A., Arnold, C. & Smith, Y. Subcellular and subsynaptic localization of group I metabotropic glutamate receptors in the nucleus accumbens of cocaine-treated rats. *Neuroscience* **154**, 653–666 (2008).
58. LaLumiere, R. T. & Kalivas, P. W. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J. Neurosci.* **28**, 3170–3177 (2008).
59. Zhou, W. & Kalivas, P. W. *N*-Acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. *Biol. Psychiatry* **63**, 338–340 (2007).
60. Moussawi, K. *et al.* *N*-Acetylcysteine reverses cocaine-induced metaplasticity. *Nature Neurosci.* **12**, 182–189 (2009).
61. Peters, J. & Kalivas, P. W. The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology (Berl.)* **186**, 143–149 (2006).
62. Baptista, M. A., Martin-Fardon, R. & Weiss, F. Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. *J. Neurosci.* **24**, 4723–4727 (2004).
63. Bossert, J. M., Gray, S. M., Lu, L. & Shaham, Y. Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. *Neuropsychopharmacology* **31**, 2197–2209 (2006).
64. Rothstein, J. D. *et al.* β-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature* **433**, 73–77 (2005).
65. Murphy, T. H., Miyamoto, M., Sastre, A., Schnaar, R. L. & Coyle, J. T. Glutamate toxicity in a neuronal cell line involves inhibition of cystine transport leading to oxidative stress. *Neuron* **2**, 1547–1558 (1989).
66. Bannai, S. Exchange of cystine and glutamate across plasma membrane of human fibroblasts. *J. Biol. Chem.* **261**, 2256–2263 (1986).
67. Robinson, T. E. & Kolb, B. Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. *J. Neurosci.* **17**, 8491–8497 (1997).
68. Lee, K. W. *et al.* Cocaine-induced dendritic spine formation in D1 and D2 dopamine receptor-containing medium spiny neurons in nucleus accumbens. *Proc. Natl Acad. Sci. USA* **103**, 3399–3404 (2006).
69. Robinson, T. E. & Kolb, B. Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* **47** (Suppl. 1), 33–46 (2004).
70. Jedynak, J. P., Uslaner, J. M., Esteban, J. A. & Robinson, T. E. Methamphetamine-induced structural plasticity in the dorsal striatum. *Eur. J. Neurosci.* **25**, 847–853 (2007).
71. Shen, H. W. *et al.* Altered dendritic spine plasticity in cocaine-withdrawn rats. *J. Neurosci.* **29**, 2876–2884 (2009).
72. Hyman, S. E., Malenka, R. C. & Nestler, E. J. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu. Rev. Neurosci.* **29**, 565–598 (2006).
73. Nestler, E. J. Is there a common molecular pathway for addiction? *Nature Neurosci.* **8**, 1445–1449 (2005).
74. Churchill, L., Swanson, C. J., Urbina, M. & Kalivas, P. W. Repeated cocaine alters glutamate receptor subunit levels in the nucleus accumbens and ventral tegmental area of rats that develop behavioral sensitization. *J. Neurochem.* **72**, 2397–2403 (1999).
75. Boudreau, A. C. & Wolf, M. E. Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J. Neurosci.* **25**, 9144–9151 (2005).
76. Conrad, K. L. *et al.* Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* **454**, 118–121 (2008). **This paper clarifies the potential role of synaptic grading after chronic cocaine administration resulting in upregulated AMPA receptor signalling in the nucleus accumbens.**
77. Anderson, S. M. *et al.* CaMKII: a biochemical bridge linking accumbens dopamine and glutamate systems in cocaine seeking. *Nature Neurosci.* **11**, 344–353 (2008). **This paper demonstrates the rapid recruitment of AMPA receptors to the surface during cocaine seeking, and clarifies the manner in which D1 receptor signalling produces this effect.**
78. Backstrom, P. & Hyytia, P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl.)* (2007).
79. Cornish, J. & Kalivas, P. W. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J. Neurosci.* **20**, RC89 (2000).
80. Di Ciano, P. & Everitt, B. J. Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* **25**, 341–360 (2001).
81. Suto, N. *et al.* Previous exposure to psychostimulants enhances the reinstatement of cocaine seeking by nucleus accumbens AMPA. *Neuropsychopharmacology* **29**, 2149–2159 (2004).
82. Boudreau, A. C., Reimers, J. M., Milovanovic, M. & Wolf, M. E. Cell surface AMPA receptors in the rat nucleus accumbens increase during cocaine withdrawal but internalize after cocaine challenge in association with altered activation of mitogen-activated protein kinases. *J. Neurosci.* **27**, 10621–10635 (2007).
83. Liechti, M. E., Lhuillier, L., Kaupmann, K. & Markou, A. Metabotropic glutamate 2/3 receptors in the ventral tegmental area and the nucleus accumbens shell are involved in behaviors relating to nicotine dependence. *J. Neurosci.* **27**, 9077–9085 (2007).
84. Bowers, M. S. *et al.* Activator of G-protein signaling 3: a gatekeeper of cocaine sensitization and drug-seeking. *Neuron* **42**, 269–281 (2004).
85. Ghasemzadeh, M. B., Mueller, C. & Vasudevan, P. Behavioral sensitization to cocaine is associated with increased glutamate receptor trafficking to the postsynaptic density after extended withdrawal period. *Neuroscience* **159**, 414–426 (2009).
86. Takesono, A. *et al.* Receptor-independent activators of heterotrimeric G-protein signaling pathways. *J. Biol. Chem.* **274**, 33202–33205 (1999).




© 2009 Macmillan Publishers Limited. All rights reserved

87. Yao, L. *et al.* Activator of G protein signaling 3 regulates opiate activation of protein kinase A signaling and relapse of heroin-seeking behavior. *Proc. Natl Acad. Sci. USA* **102**, 8746–8751 (2005).
88. Bowers, M. S. *et al.* Nucleus accumbens AGS3 expression drives ethanol seeking through Gβγ. *Proc. Natl Acad. Sci. USA* **105**, 12533–12538 (2008).
89. Swanson, C., Baker, D., Carson, D., Worley, P. & Kalivas, P. W. Repeated cocaine administration attenuates group I metabotropic glutamate receptor-mediated glutamate release and behavioral activation: a potential role for Homer 1b/c. *J. Neurosci.* **21**, 9043–9052 (2001).
90. Ary, A. W. & Szumlinski, K. K. Regional differences in the effects of withdrawal from repeated cocaine upon Homer and glutamate receptor expression: a two-species comparison. *Brain Res.* **1184**, 295–305 (2007).
91. Ghasemzadeh, M. B., Vasudevan, P., Mueller, C., Seubert, C. & Mantsch, J. R. Neuroadaptations in the cellular and postsynaptic group 1 metabotropic glutamate receptor mGluR5 and Homer proteins following extinction of cocaine self-administration. *Neurosci. Lett.* **452**, 167–171 (2009).
92. Szumlinski, K. K. *et al.* Homer proteins regulate sensitivity to cocaine. *Neuron* **43**, 401–413 (2004).
93. Palmatier, M. I., Liu, X., Donny, E. C., Caggiula, A. R. & Sved, A. F. Metabotropic glutamate 5 receptor (mGluR5) antagonists decrease nicotine seeking, but do not affect the reinforcement enhancing effects of nicotine. *Neuropsychopharmacology* **33**, 2139–2147 (2008).
94. Olive, M. F. *et al.* The mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine decreases ethanol consumption via a protein kinase Cε-dependent mechanism. *Mol. Pharmacol.* **67**, 349–355 (2005).
95. Tessari, M., Pilla, M., Andreoli, M., Hutcheson, D. M. & Heidbreder, C. A. Antagonism at metabotropic glutamate 5 receptors inhibits nicotine- and cocaine-taking behaviours and prevents nicotine-triggered relapse to nicotine-seeking. *Eur. J. Pharmacol.* **499**, 121–133 (2004).
96. Ghasemzadeh, M. B., Permenter, L. K., Lake, R., Worley, P. F. & Kalivas, P. W. Homer1 proteins and AMPA receptors modulate cocaine-induced behavioural plasticity. *Eur. J. Neurosci.* **18**, 1645–1651 (2003).
97. Lee, B., Platt, D. M., Rowlett, J. K., Adewale, A. S. & Spealman, R. D. Attenuation of behavioral effects of cocaine by the metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)-pyridine in squirrel monkeys: comparison with dizocilpine. *J. Pharmacol. Exp. Ther.* **312**, 1232–1240 (2005).
98. Backstrom, P. & Hyytia, P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* **31**, 778–786 (2006).
99. Chiamulera, C. *et al.* Reinforcing and locomotor stimulant effects of cocaine are absent in *mGluR5* null mutant mice. *Nature Neurosci.* **4**, 873–874 (2001).
100. Paterson, N. E., Semenova, S., Gasparini, F. & Markou, A. The mGluR5 antagonist MPEP decreased nicotine self-administration in rats and mice. *Psychopharmacology (Berl.)* **167**, 257–264 (2003).
101. Cingolani, L. & Goda, Y. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. *Nature Rev. Neurosci.* **9**, 344–356 (2008).
102. Toda, S., Shen, H. W., Peters, J., Cagle, S. & Kalivas, P. W. Cocaine increases actin cycling: effects in the reinstatement model of drug seeking. *J. Neurosci.* **26**, 1579–1587 (2006).
103. Carpenter-Hyland, E. P. & Chandler, L. J. Homeostatic plasticity during alcohol exposure promotes enlargement of dendritic spines. *Eur. J. Neurosci.* **24**, 3496–3506 (2006).
104. Wheeler, R. A. & Carelli, R. M. Dissecting motivational circuitry to understand substance abuse. *Neuropharmacology* **56** (Suppl. 1), 149–159 (2008).
105. Kalivas, P. W. & Hu, X. T. Exciting inhibition in psychostimulant addiction. *Trends Neurosci.* **29**, 610–616 (2006).
106. Thomas, M. J., Kalivas, P. W. & Shaham, Y. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br. J. Pharmacol.* **154**, 327–342 (2008).
107. Kauer, J. A. & Malenka, R. C. Synaptic plasticity and addiction. *Nature Rev. Neurosci.* **8**, 844–858 (2007).
108. Malenka, R. C. & Bear, M. F. LTP and LTD: an embarrassment of riches. *Neuron* **44**, 5–21 (2004).
109. Abraham, W. C. Metaplasticity: tuning synapses and networks for plasticity. *Nature Rev. Neurosci.* **9**, 387–399 (2008).
110. Abraham, W. C. & Bear, M. F. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* **19**, 126–130 (1996).
111. Kourrich, S., Rothwell, P. E., Klug, J. R. & Thomas, M. J. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J. Neurosci.* **27**, 7921–7928 (2007).
112. Martin, M., Chen, B. T., Hopf, F. W., Bowers, M. S. & Bonci, A. Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nature Neurosci.* **9**, 868–869 (2006).
**This paper describes the loss of capacity to induce LTD in accumbens slices after cocaine self-administration, and raises the possibility that cocaine-induced changes might dissociate synaptic grading from synaptic plasticity.**
113. Wu, J., Rowan, M. J. & Anwyl, R. An NMDAR-independent LTP mediated by group II metabotropic glutamate receptors and p42/44 MAP kinase in the dentate gyrus *in vitro*. *Neuropharmacology* **46**, 311–317 (2004).
114. Grover, L. M. & Yan, C. Evidence for involvement of group II/III metabotropic glutamate receptors in NMDA receptor-independent long-term potentiation in area CA1 of rat hippocampus. *J. Neurophysiol.* **82**, 2956–2969 (1999).
115. Goto, Y. & Grace, A. A. Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron* **47**, 255–266 (2005).
116. Yao, W. D. *et al.* Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* **41**, 625–638 (2004).
117. Li, Y. & Kauer, J. A. Repeated exposure to amphetamine disrupts dopaminergic modulation of excitatory synaptic plasticity and neurotransmission in nucleus accumbens. *Synapse* **51**, 1–10 (2004).
118. Lodge, D. J. & Grace, A. A. Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. *J. Neurosci.* **28**, 7876–7882 (2008).
119. Nelson, C. L., Milovanovic, M., Wetter, J. B., Ford, K. A. & Wolf, M. E. Behavioral sensitization to amphetamine is not accompanied by changes in glutamate receptor surface expression in the rat nucleus accumbens. *J. Neurochem.* **109**, 35–51 (2009).
120. Lu, L. *et al.* Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. *Nature Neurosci.* **8**, 212–219 (2005).
121. Koob, G. & Kreek, M. J. Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *Am. J. Psychiatry* **164**, 1149–1159 (2007).
122. Neisewander, J. L. *et al.* Fos protein expression and cocaine seeking behavior in rats after exposure to a cocaine self-administration environment. *J. Neurosci.* **20**, 798–805 (2000).
123. Zavala, A. R., Biswas, S., Harlan, R. E. & Neisewander, J. L. Fos and glutamate AMPA receptor subunit coexpression associated with cue-elicited cocaine-seeking behavior in abstinent rats. *Neuroscience* **145**, 438–452 (2007).
124. Miller, C. A. & Marshall, J. F. Altered prelimbic cortex output during cue-elicited drug seeking. *J. Neurosci.* **24**, 6889–6897 (2004).
125. Hearing, M. C., Miller, S. W., See, R. E. & McGinty, J. F. Relapse to cocaine seeking increases activity-regulated gene expression differentially in the prefrontal cortex of abstinent rats. *Psychopharmacology (Berl.)* **198**, 77–91 (2008).
126. Goldstein, R. A. & Volkow, N. D. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* **159**, 1642–1652 (2002).
127. Volkow, N. D. *et al.* Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J. Neurosci.* **25**, 3932–3939 (2005).
128. George, M. S. *et al.* Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch. Gen. Psychiatry* **58**, 345–352 (2001).
129. Franklin, T. R. *et al.* Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. *Neuropsychopharmacology* **32**, 2301–2309 (2007).
130. Rogers, J. L., Ghee, S. & See, R. E. The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. *Neuroscience* **151**, 579–588 (2008).
131. Anderson, S. M., Schmidt, H. D. & Pierce, R. C. Administration of the D2 dopamine receptor antagonist sulpiride into the shell, but not the core, of the nucleus accumbens attenuates cocaine priming-induced reinstatement of drug seeking. *Neuropsychopharmacology* **31**, 1452–1461 (2006).
132. Di Ciano, P. & Everitt, B. J. Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. *J. Neurosci.* **24**, 7167–7173 (2004).
133. Sun, W. & Rebec, G. V. Repeated cocaine self-administration alters processing of cocaine-related information in rat prefrontal cortex. *J. Neurosci.* **26**, 8004–8008 (2006).
134. Thomas, M. J., Beurrier, C., Bonci, A. & Malenka, R. C. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nature Neurosci.* **4**, 1217–1223 (2001).
135. Kalivas, P. W. & O'Brien, C. Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* **33**, 166–180 (2008).
136. Vocci, F. & Ling, W. Medications development: successes and challenges. *Pharmacol. Ther.* **108**, 94–108 (2005).
137. LaRowe, S. D. *et al.* Is cocaine desire reduced by *N*-acetylcysteine? *Am. J. Psychiatry* **164**, 1115–1117 (2007).
138. Yin, H. H. *et al.* Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nature Neurosci.* **12**, 333–341 (2009).
139. Balleine, B. W., Liljeholm, M. & Ostlund, S. B. The integrative function of the basal ganglia in instrumental conditioning. *Behav. Brain Res.* **199**, 43–52 (2009).
140. Yin, H. H., Ostlund, S. B. & Balleine, B. W. Reward-guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks. *Eur. J. Neurosci.* **28**, 1437–1448 (2008).
141. Robinson, T. E. & Berridge, K. C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Rev.* **18**, 247–291 (1993).
142. Tzschentke, T. M. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addict. Biol.* **12**, 227–462 (2007).
143. Epstein, D. H., Preston, K. L., Stewart, J. & Shaham, Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology (Berl.)* **189**, 1–16 (2006).
144. Everitt, B. J. & Robbins, T. W. Second-order schedules of drug reinforcement in rats and monkeys: measurement of reinforcing efficacy and drug-seeking behaviour. *Psychopharmacology (Berl.)* **153**, 17–30 (2000).
145. Flanagan, R. J. & Meredith, T. J. Use of *N*-acetylcysteine in clinical toxicology. *Am. J. Med.* **91**, 131S–139S (1991).
146. Ono, S. Regulation of actin filament dynamics by actin depolymerizing factor/cofilin and actin-interacting protein 1: new blades for twisted filaments. *Biochemistry* **42**, 13363–13370 (2003).
147. May, R. C. The Arp2/3 complex: a central regulator of the actin cytoskeleton. *Cell. Mol. Life Sci.* **58**, 1607–1626 (2001).
148. Krause, M., Dent, E. W., Bear, J. E., Loureiro, J. J. & Gertler, F. B. Ena/VASP proteins: regulators of the actin cytoskeleton and cell migration. *Annu. Rev. Cell Dev. Biol.* **19**, 541–564 (2003).



**Acknowledgements**

I thank the members of my laboratory who made helpful editorial comments, including P. Hurt, R. LaLumiere, L. Knackstedt, K. Moussawi, A. Rocha, H. Shen, J. Uys and A. Wiggins. Much of the research incorporated into this Review was supported by NIDA (DA 015,369, DA 015,851, DA 012,513 and DA 003,906).


**DATABASES**

**Entrez Gene:** http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
AGS3 | Arp2 | GLT1 | GluR1 | GluR2 | Homer1b/c | Homer2 | mGluR1 | mGluR2 | mGluR3 | mGluR5 | xCT

**FURTHER INFORMATION**

**Peter W. Kalivas's homepage:** http://neurosciences.musc.edu/faculty/full_time/kalivas.html

**ALL LINKS ARE ACTIVE IN THE ONLINE PDF**



© 2009 Macmillan Publishers Limited. All rights reserved