British Journal of Pharmacology (2008) 154, 327–342
 0007–1188/08 $30.00
www.brjpharmacol.org

REVIEW

Neuroplasticity in the mesolimbic dopamine system and cocaine addiction

MJ Thomas[1,2], PW Kalivas[3] and Y Shaham[4]

[1]*Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA;* [2]*Department of Psychology, University of Minnesota, Minneapolis, MN, USA;* [3]*Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA and* [4]*Behavioral Neuroscience Branch, IRP/NIDA/NIH/DHHS, Baltimore, MD, USA*

The main characteristics of cocaine addiction are compulsive drug use despite adverse consequences and high rates of relapse during periods of abstinence. A current popular hypothesis is that compulsive cocaine use and cocaine relapse is due to drug-induced neuroadaptations in reward-related learning and memory processes, which cause hypersensitivity to cocaine-associated cues, impulsive decision making and abnormal habit-like learned behaviours that are insensitive to adverse consequences. Here, we review results from studies on the effect of cocaine exposure on selected signalling cascades, growth factors and physiological processes previously implicated in neuroplasticity underlying normal learning and memory. These include the extracellular signal-regulated kinase (ERK) signalling pathway, brain-derived neurotrophic factor (BDNF), glutamate transmission, and synaptic plasticity (primarily in the form of long-term potentiation and depression, LTP and LTD). We also discuss the degree to which these cocaine-induced neuroplasticity changes in the mesolimbic dopamine system mediate cocaine psychomotor sensitization and cocaine-seeking behaviours, as assessed in animal models of drug addiction. Finally, we speculate on how these factors may interact to initiate and sustain cocaine psychomotor sensitization and cocaine seeking.
British Journal of Pharmacology (2008) **154,** 327–342; doi:10.1038/bjp.2008.77; published online 17 March 2008

Keywords: actin cycling; dopamine; extracellular signal-regulated kinase; long-term depression; long-term potentiation; glutamate; psychomotor sensitization; reinstatement; relapse; synaptic plasticity

Abbreviations: AMPAR, AMPA receptor; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mPFC, medial prefrontal cortex; MSNs, medium spiny neurons; NMDAR, NMDA receptor; VTA, ventral tegmental area

Introduction

The main characteristics of cocaine addiction are compulsive drug use despite adverse consequences and high rates of relapse during periods of abstinence (Mendelson and Mello, 1996). Despite decades of research, there are currently no effective medications for cocaine addiction (O'Brien, 2005). Results from many neuropharmacological studies in animal models indicate that neuronal activity in mesocorticolimbic dopamine system (which comprises cell bodies in ventral tegmental area (VTA) that project to medial and orbital prefrontal cortex, accumbens, amygdala and bed nucleus of stria terminalis (BNST)) underlies cocaine reward (Wise, 2004; Pierce and Kumaresan, 2006) and contributes to relapse to cocaine seeking (Shalev *et al*., 2002; Kalivas and McFarland, 2003). On the basis of these neuropharmacological studies, a current influential hypothesis is that cocaine addiction is due to drug-induced neuroadaptations in reward-related learning and memory processes in the mesocorticolimbic dopamine system and glutamatergic corticolimbic circuitry in which the dopamine projections are embedded (Nestler, 2002; Wolf *et al*., 2004; Everitt and Robbins, 2005; Kalivas and O'Brien, 2008). These neuroadaptations have been hypothesized to cause hypersensitivity to cocaine-associated cues (Di Chiara, 1998; Everitt and Wolf, 2002), impulsive decision making (Jentsch and Taylor, 1999; Volkow and Fowler, 2000) and abnormal habit-like learned behaviours (White, 1996) that are insensitive to adverse consequences (Wolffgramm and Heyne, 1995; Deroche-Gamonet *et al*., 2004; Vanderschuren and Everitt, 2004; Kalivas and Volkow,

Correspondence: Dr MJ Thomas, Departments of Neuroscience and Psychology, University of Minnesota, 6-145 Jackson Hall, 321 Church St. SE, Minneapolis, MN 55455, USA.
E-mail: tmhomas@umn.edu
Received 20 November 2007; revised 11 December 2007; accepted 13 February 2008; published online 17 March 2008

2005; Schoenbaum and Shaham, 2008). The 'drug-induced neuroadaptation' hypothesis has inspired many studies on the role of cellular events and signalling cascades that underlie SYNAPTIC PLASTICITY (see Boxes 1 and 2 for a glossary of terms that appear in small capital letters in the text) processes of learning and memory in cocaine behavioural effects (Nestler, 2002; Thomas and Malenka, 2003; Jones and Bonci, 2005).

Here, we review results from studies on the effect of acute and repeated cocaine exposure on selected signalling cascades, growth factors and physiological processes of excitatory transmission previously implicated in neuroplasticity underlying normal learning and memory. These include the extracellular signal-regulated kinase (ERK) signalling pathway (Sweatt, 2001), brain-derived neurotrophic factor (BDNF; Poo, 2001), glutamate transmission and synaptic plasticity (primarily in the form of LONG-TERM POTENTIATION (LTP) and LONG-TERM DEPRESSION (LTD; Malenka and Bear, 2004)). In recent years, several reviews were published on the roles of ERK (Lu *et al*., 2006; Girault *et al*., 2007; Zhai *et al*., 2007), BDNF (Pierce and Bari, 2001; Bolanos and Nestler, 2004; Corominas *et al*., 2007), glutamate transmission (Kalivas and Volkow, 2005) and synaptic plasticity (Thomas and Malenka, 2003; Wolf *et al*., 2004; Jones and Bonci, 2005) in cocaine behavioural and physiological effects. Therefore, our main goal here is not to provide a comprehensive review of this extant literature, but rather to critically discuss the degree to which cocaine-induced alterations in ERK, BDNF, glutamatergic transmission and synaptic plasticity in the mesolimbic dopamine system mediate cocaine PSYCHOMOTOR SENSITIZATION (Post and Rose, 1976), and cocaine-seeking behaviours, as assessed in the CONDITIONED PLACE PREFERENCE (CPP) (Van der Kooy, 1987; Bardo and Bevins, 2000), DRUG SELF-ADMINISTRATION (Schuster and Thompson, 1969; Yokel, 1987; Brady, 1991) and REINSTATEMENT (Stewart and de Wit, 1987; Shaham *et al*., 2003; Epstein *et al*., 2006) models. We also review data from studies on the roles of ERK and BDNF in INCUBATION OF COCAINE CRAVING (Grimm *et al*., 2001; Lu *et al*., 2004c).

Before reviewing the empirical data, an issue to consider in the context of our review is what experimental evidence is needed to conclude that a specific effect of cocaine exposure on neuroplasticity mediates a specific behavioural effect of cocaine rather than merely co-occurs or is associated with it. In this regard, a stringent criterion to infer causality between a specific physiological process that underwent cocaine-induced neuroplasticity and a specific behavioural effect of cocaine is that reversal of cocaine-induced neuroplasticity of the physiological process to a drug-naive state leads to decreases in the behavioural effect of cocaine (Kalivas, 2005; Shaham and Hope, 2005). This is a criterion that is increasingly being met in studies on drug-induced neuroplasticity and its role in drug-seeking behaviours (Baker *et al*., 2003; Bowers *et al*., 2004; Wang *et al*., 2005; Russo *et al*., 2007). We will use this criterion in evaluating the role of cocaine-induced changes in ERK, BDNF, glutamate transmission and synaptic plasticity in the VTA, accumbens and amygdala in cocaine psychomotor sensitization and cocaine-seeking behaviours.

Role of ERK

Extracellular signal-regulated kinase is a member of the MAPK (mitogen-activated protein kinase) intracellular signalling pathway family (Adams and Sweatt, 2002). Both acute and repeated cocaine injections increase ERK phosphorylation (a measure of ERK activity) in projection areas of the mesocorticolimbic dopamine system, including accumbens,

Box 1 Glossary of terminology: psychological terms

CONDITIONED PLACE PREFERENCE (CPP) MODEL: A classical (Pavlovian) conditioning model in which during the training phase one distinct context is paired with drug injections, while another context is paired with vehicle injections. During a subsequent drug-free CPP test, the animal chooses between the drug- and the vehicle-paired contexts. An increase in preference for the drug context serves as a measure of the drug's Pavlovian reinforcing effects.

DRUG SELF-ADMINISTRATION MODEL: An operant model in which laboratory animals typically lever press (or nose poke) for drug injections. The premise of this procedure is that psychoactive drugs control behaviour by functioning as operant-positive reinforcers. A high concordance exists between drugs self-administered by laboratory animals and those abused by humans.

INCUBATION OF COCAINE CRAVING: A hypothetical motivational process inferred from the findings of time-dependent increases in cue-induced cocaine seeking after withdrawal from cocaine self-administration in rats. In studies on the roles of ERK and BDNF in incubation of cocaine craving, cue-induced cocaine seeking was assessed in extinction tests in which rats were exposed to contextual cues previously associated with drug availability, and lever presses lead to contingent presentations of a discrete tone-light compound cue previously paired with cocaine injections.COCAINE CRAVING refers to an affective state that can be induced in human cocaine users by acute exposure to cocaine, cocaine-associated cues or stress.

PSYCHOMOTOR SENSITIZATION: A term that often refers to the progressive increase in locomotor activity or stereotypy with repeated drug (e.g., cocaine) administration. Typically, psychomotor sensitization studies include two phases: an initial phase (often referred to as 'DEVELOPMENT OF PSYCHOMOTOR SENSITIZATION' phase) in which laboratory subjects are injected repeatedly with drugs over days, and a subsequent test for 'EXPRESSION OF PSYCHOMOTOR SENSITIZATION' during which the subjects are injected acutely with drugs at different withdrawal days after the end of the 'development' phase and sensitized locomotor activity or stereotypy is assessed.

RECONSOLIDATION OF MEMORY: A hypothetical memory process in which previously consolidated memories become temporarily unstable after retrieval. This process requires protein synthesis and gene transcription, and is susceptible to pharmacological and brain lesion manipulations.

REINSTATEMENT MODEL: An animal model of relapse to drugs of abuse. In the operant conditioning version, animals are trained to respond to drug infusions (or oral solutions in the case of alcohol), typically by pressing a lever; then, following extinction of the responding, non-reinforced pressing on the drug-associated lever is induced by drug-priming injections, drug cues or stressors. In the classical conditioned version, CPP is induced by a drug, extinguished and then induced again by drug-priming injections or stressors.

Box 2 Glossary of terminology: physiological and molecular terms

ACTIN CYCLING: Actin filaments undergo depolymerization into monomeric G-actin and polymerization into F-actin. The cycling between these two forms of actin is termed actin cycling, and is a process regulated by various actin-binding proteins. Actin is the most abundant protein in the typical eukaryotic cell, accounting for about 15% in some cell types. The protein is highly conserved, and forms a variety of structures in cells, including dendritic spines, in concert with a numbers of actin-binding proteins.
AMPA/NMDA RATIO: This value is a sensitive measure for postsynaptic changes in synaptic strength (i.e. synaptic efficacy). It is defined as the peak synaptic AMPAR current relative to the peak synaptic NMDAR current. Comparison of synaptic strength from cell to cell and slice to slice is made difficult by several issues, including slice-to-slice variability in the density of afferent fibres and differences in the relative placements of recording and stimulating electrodes. Use of the ratio circumvents these problems, because for a given afferent pathway and cell type, it shows little to no dependence on the number of activated synapses and relatively low variability from cell to cell. Thus, treatment conditions that change AMPAR currents (which are dynamic) compared with NMDAR currents (which are relatively stable) can be readily identified through the use of the AMPA/NMDA ratio.
ERK1 AND ERK2 ISOFORMS: The two main 44 kDa (ERK1) and 42 kDa (ERK2) isoforms of ERK.
IMMEDIATE-EARLY GENES (IEG): Genes such as c-fos and *zif268* that are acutely induced (within 1 h) in response to neuronal stimulation in the absence of *de novo* protein synthesis.
LONG-TERM DEPRESSION (LTD): A form of synaptic plasticity defined by a persistent weakening of synaptic strength. It is often induced by an experimenter-delivered train of synaptic stimuli that produces a modest postsynaptic depolarization lasting from seconds to minutes.
LONG-TERM POTENTIATION (LTP): A form of synaptic plasticity defined by a persistent increase in synaptic strength. It is often induced by an experimenter-delivered train of synaptic stimuli that produces a strong postsynaptic depolarization lasting up to several seconds.
MAPK/ERK KINASE (MEK): The upstream kinase of ERK that is activated by the protein kinase Raf; Raf is activated by the small G protein Ras, and its activation depends on enhanced calcium influx. Until recently, ERK is the only known substrate of MEK. Selective pharmacological inhibitors of MEK include SL327, U0126 and PD98059; these inhibitors have been used in numerous studies to determine the role of ERK signalling in cellular and behavioural processes.
METAPLASTICITY: A form of synaptic plasticity in which the history of activity at a given neuron or synapse alters the direction or magnitude of plasticity in response to subsequent stimulation. Thus, metaplasticity does not necessarily involve direct changes in synaptic strength, but an altered capacity for future changes in synaptic strength. Metaplasticity may provide stability in neuronal circuits by limiting the overall degree of synaptic potentiation or depression.
MITOGEN-ACTIVATED PROTEIN KINASE (MAPK): Serine/threonine-specific protein kinases that are activated by extracellular stimuli (mitogens) such as neurotransmitters and growth factors. ERK is a member of the MAPK signal transduction family, which also includes p38 kinase and c-Jun N-terminal kinase (JNK).
MITOGEN AND STRESS ACTIVATED KINASE-1 (MSK-1): A kinase that phosphorylates histones and the transcription factor cyclic-AMP response element-binding protein (CREB). MSK1 can be activated by ERK and p38 kinase.
OCCLUSION: A term that refers to a test to determine whether cellular mechanisms are shared between two forms of synaptic plasticity that produce a common result (e.g., two forms of LTD). After one form of plasticity has been induced, a stimulus to induce the second form is administered. If the end result is a reduced response to the second stimulus, one interpretation is that an occlusion has occurred and that the forms of plasticity share common mechanisms. However, in practice, it is often difficult to distinguish an occlusion from a blockade of plasticity due to a disruption in mechanism.
POSTSYNAPTIC DENSITY (PSD): The scaffold of proteins clustered on the postsynaptic side of the synapse. Proteins in the PSD create a microenvironment that regulates short-term ion fluxes, medium-term changes in receptor signalling and enduring neuroplasticity. Proteins include receptors, receptor-binding proteins that regulate receptor signalling and trafficking, signalling molecules and actin.
SYNAPTIC PLASTICITY: A term that refers to activity-dependent, direct or indirect (see metaplasticity above) modifications of the strength of synaptic transmission at pre-existing synapses.
SYNAPTIC SCALING: A form of synaptic plasticity in which a chronic level of high or low neuronal activity drives a compensatory down- or upregulation (respectively) of synaptic strength in a cell-wide fashion. Although the overall average synaptic strength of the cell is altered, the relative synaptic strength (between synapses on the cell) is thought to be maintained. Like metaplasticity, synaptic scaling may provide stability in neuronal circuits by maintaining average firing rates within a normal dynamic range.
SYNAPTIC STRENGTH: The amount of postsynaptic current produced when a synapse has been activated.
TRANSCRIPTION FACTORS: Proteins that directly or indirectly bind to DNA at the promoter region of genes to stimulate or repress gene transcription.
VOLTAGE-GATED A-TYPE POTASSIUM CHANNEL SUBUNIT 4.2 (KV4.2): A voltage-gated potassium channel subunit that is localized in dendrites that allows outward flow of potassium ions, which produces a more negative membrane potential of neurons.

amygdala, BNST and prefrontal cortex. Upstream triggers of cocaine-induced ERK phosphorylation (a measure of ERK activation) are NMDA (*N*-methyl-D-aspartic acid) receptor (NMDAR), D1 dopamine receptors, PKA (cAMP-dependent protein kinase-A) and DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of M(r) 32000). Cocaine-induced ERK phosphorylation triggers downstream activation of MSK-1 (mitogen- and stress-activated protein kinase-1), the TRANSCRIPTION FACTORS CREB (cAMP response element-binding protein) and Elk-1, and enhanced expression of the IMMEDIATE EARLY GENES Fos and Zif268 (Lu *et al*., 2006; Girault *et al*., 2007). The role of ERK in cocaine's behavioural effects in rats and mice was assessed with U0126, SL327 and PD98059, inhibitors of MEK (MAPK/ERK kinase; an upstream activator of the ERK1 and ERK2 ISOFORMS) that decrease ERK phosphorylation.

ERK: psychomotor sensitization

Extracellular signal-regulated kinase activity and subsequent ERK-mediated downstream gene transcription is critical for the DEVELOPMENT OF PSYCHOMOTOR SENSITIZATION induced by cocaine exposure (Girault *et al*., 2007). In contrast, acute cocaine-induced ERK activity does not mediate the EXPRESSION OF PSYCHOMOTOR SENSITIZATION after withdrawal from the drug. Systemic injections of SL327 or VTA injections of PD98059 before daily cocaine injections (during the development of psychomotor sensitization) attenuate sensitized cocaine-induced locomotion during tests for expression of psychomotor sensitization, performed after several weeks of withdrawal (Pierce *et al*., 1999; Ferguson *et al*., 2006; Valjent *et al*., 2006b). The VTA is a critical site for the development of psychomotor sensitization (Vanderschuren and Kalivas, 2000; Vezina, 2004). However, in previously cocaine-sensitized mice,

acute systemic pretreatment with SL327 prior to a cocaine injection did not alter the expression of drug psychomotor sensitization (Valjent *et al*., 2006b). Recently, Boudreau *et al*. (2007) reported that in rats demonstrating cocaine psychomotor sensitization after several weeks of withdrawal from the drug, increased ERK2 activity is associated with increased accumbens AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (AMPAR) surface expression. No increases in ERK2 activity and AMPAR surface expression were observed in rats that did not demonstrate cocaine psychomotor sensitization after repeated non-contingent cocaine exposure and a period of withdrawal. The relevance of these interesting correlational findings to enduring cocaine psychomotor sensitization is a subject for future research.

ERK: conditioned place preference

Accumbens ERK activity likely serves two distinct roles in mediating the rewarding effects of psychostimulant in the CPP procedure: during CPP training, accumbens activity mediates consolidation of learned associations between the drug's unconditioned rewarding effects and the drug-paired context; during CPP testing, ERK activity mediates acute expression of cocaine-cue-conditioned responses. Systemic SL327 injections before cocaine CPP training prevent cocaine-induced accumbens (and dorsal striatum) ERK phosphorylation and subsequent expression of cocaine CPP (Valjent *et al*., 2000). PD98059 accumbens injections given either before or after CPP training sessions block subsequent amphetamine CPP expression (Gerdjikov *et al*., 2004). Exposure to the cocaine-paired context during CPP testing increases ERK phosphorylation in accumbens core, and U0126 accumbens core injections block both ERK phosphorylation and expression of cocaine CPP in rats (Miller and Marshall, 2005). In addition, methamphetamine CPP expression is associated with increased accumbens (and dorsal striatum) ERK phosphorylation, and PD98059 accumbens injections prevent this CPP expression. The CPP procedure was also used to demonstrate a role of accumbens ERK in RECONSOLIDATION of memories for cocaine cues. Here, if rats are injected with U0126 or PD98059 into accumbens core immediately after the test for the expression of cocaine CPP, subsequent preference for the drug is impaired (Miller and Marshall, 2005). Valjent *et al*. (2006a) also provided evidence for a role of accumbens ERK in reconsolidation of memory for cocaine cues.

ERK: cocaine self-administration and cocaine seeking

On the basis of limited clinical evidence, Gawin and Kleber (1986) hypothesized that cue-induced cocaine craving progressively increases over the first several weeks of abstinence and remains high over extended periods. An analogous phenomenon, which was termed incubation of cocaine craving, has been demonstrated in rats and mice: time-dependent increases in cue-induced cocaine seeking over the first months of withdrawal from cocaine (Neisewander *et al*., 2000; Grimm *et al*., 2001; Lu *et al*., 2004b; Lee *et al*., 2006; Mead *et al*., 2007). Glutamate-mediated ERK activity in the central amygdala plays an important role in the expression and persistence of incubation of cocaine craving (Lu *et al*., 2005). Exposure to cocaine cues in extinction tests increases ERK phosphorylation in the central but not basolateral amygdala after 30 but not 1 withdrawal days. After 30 withdrawal days, inhibition of central amygdala ERK phosphorylation by U0126 or the NMDAR antagonist AP-5 decreased cue-induced cocaine seeking; the behavioural effect of AP-5 is mimicked by LY379268 (Lu *et al*., 2007), an mGluR2/3 agonist that decreases glutamate transmission. After 1 withdrawal day, stimulation of central amygdala ERK phosphorylation by NMDA increased cocaine seeking, an effect reversed by U0126. Exposure to cocaine cues in extinction tests also increases ERK activity in the accumbens (L Lu and Y Shaham, unpublished data) and ventral and dorsal medial prefrontal cortex (mPFC; Koya *et al*., 2008) after 30 days (but not 1 day) of withdrawal. However, the relevance increased ERK activity in accumbens, and mPFC to incubation of cocaine craving is currently unknown.

ERK: conclusions

The role of ERK in cocaine's behavioural effects involves at least two distinct mechanisms with different time courses (Lu *et al*., 2006; Girault *et al*., 2007). One mechanism, which mediates cocaine psychomotor sensitization, and both consolidation and reconsolidation of memories for drug cues in the CPP model, may involves long-term stable alterations in molecules that can influence synaptic plasticity. These alterations may result from ERK-mediated activation of its downstream targets, including CREB, Elk-1, c-Fos and Zif268 (Valjent *et al*., 2000; Mattson *et al*., 2005; Miller and Marshall, 2005; Radwanska *et al*., 2006). The second mechanism involves rapid ERK-mediated effects that mediate acute expression of cocaine CPP and the expression of incubation of cocaine craving (Lu *et al*., 2006). Here, ERK activity mediates the acute behavioural effects of cocaine cues over short time periods (minutes) that likely do not involve gene transcription or stable changes in synaptic plasticity. For example, in hippocampal pyramidal neurons, ERK can acutely increase neuronal excitability via ERK-mediated inactivation of VOLTAGE-GATED POTASSIUM CHANNEL SUBUNIT KV4.2 (Yuan *et al*., 2002) or ERK-mediated potentiation of excitatory neurotransmission via AMPAR membrane insertion (Qin *et al*., 2005). Whether either of these mechanisms is engaged in neurons in mesocorticolimbic regions is unknown, although it is intriguing to speculate that this is the case based on evidence discussed above for parallel changes in AMPAR trafficking and ERK activation in accumbens in rats that demonstrated cocaine psychomotor sensitization after prolonged withdrawal from the drug (Boudreau *et al*., 2007).

Cocaine-induced ERK-mediated neuroplasticity is also critical for cocaine psychomotor sensitization because repeated blockade of cocaine-induced ERK activation in mesocorticolimbic areas prevents the development of cocaine psychomotor sensitization; thereby, satisfying the criterion outline above that reversal of cocaine-induced neuroplasticity of the physiological process to a drug-naive

state leads to decreases in a specific behavioural effect of a drug. In the case of cocaine CPP and incubation of cocaine craving, whereas ERK activity plays a critical role in both phenomena, the available data do not satisfy this criterion. Both CPP (Figlewicz *et al*., 2007) and incubation of craving (Grimm *et al*., 2002, 2005) are reliably observed with non-drug reinforcers such as sucrose and other palatable foods. Thus, data from studies with cocaine-exposed rats may reflect a role of mesocorticolimbic ERK in the different learning, memory and motivational processes that underlie CPP and incubation of craving that are independent of cocaine-induced neuroplasticity of the ERK pathway. In the context of the hypothesis that ERK is a mediator of cocaine-induced neuroplasticity that contributes to cocaine-seeking behaviours, data from studies on the role of mesocorticolimbic ERK in CPP and incubation of craving with non-drug reinforcers is an important subject for future research.

Role of BDNF

Brain-derived neurotrophic factor is involved in different forms of synaptic plasticity (Thoenen, 1995) and the survival and function of midbrain dopamine neurons (Hyman *et al*., 1991). BDNF immunoreactive cells are expressed in VTA (where it is colocalized with dopamine neurons), basolateral amygdala, BNST and prefrontal cortex (Seroogy *et al*., 1994; Dawson *et al*., 2001; Meredith *et al*., 2002). BDNF mRNA and immunoreactive cell expression in striatum is very low under normal conditions (Meredith *et al*., 2002; Graham *et al*., 2007) and is often undetected by classical *in situ* hybridization and immunohistochemistry techniques (Altar *et al*., 1997). In early studies, Altar *et al*. (1992) reported that midbrain (substantia nigra) injections of BDNF increase amphetamine-induced activity (see also Martin-Iverson *et al*., 1994). Contingent (self-administration) and non-contingent acute cocaine exposure increase BDNF protein levels in striatum (Zhang *et al*., 2002a; Liu *et al*., 2006; Graham *et al*., 2007); acute non-contingent cocaine exposure also increases BDNF mRNA expression in mPFC (Le Foll *et al*., 2005). Repeated non-contingent exposure to cocaine increases BDNF protein levels in VTA after 15 days (but not 1 day) of withdrawal (Pu *et al*., 2006). Cocaine self-administration increases BDNF protein levels in the VTA, amygdala and accumbens after 30 and 90 days (but not 1 day) of withdrawal (Grimm *et al*., 2003). There is evidence that BDNF contributes significantly to cocaine behavioural effects (Schoenbaum *et al*., 2007).

BDNF: psychomotor sensitization

Daily BDNF injections into VTA or chronic BDNF administration via osmotic minipumps into VTA or accumbens potentiate the acute locomotor-activating effects of cocaine during the development of psychomotor sensitization phase (Horger *et al*., 1999; Pierce *et al*., 1999). Furthermore, BDNF heterozygote mice are less sensitive to the locomotor-activating effects of cocaine during this phase (Horger *et al*., 1999). However, the degree to which BDNF-induced potentiation of cocaine-induced locomotion is associated with cocaine-induced neuroplasticity that underlies enduring cocaine psychomotor sensitization is unclear. VTA injections of BDNF during the development of psychomotor sensitization phase had no effect on subsequent expression of this sensitization after withdrawal from cocaine (Pierce *et al*., 1999). Pu *et al*. (2006) recently reported that BDNF-mediated LTP in VTA dopamine neurons is associated with the expression of cocaine psychomotor sensitization in mice. However, the degree to which this interesting finding underlies enduring expression of psychomotor sensitization has not been established.

BDNF: conditioned place preference

Brain-derived neurotrophic factor heterozygote mice, which were less sensitive to the effects of acute cocaine-induced locomotion, were also less sensitive to the rewarding effects of cocaine in the CPP model (Hall *et al*., 2003). CPP is a contextual learning task, and there is evidence that hippocampal BDNF plays a role in contextual learning (Tyler *et al*., 2002). Thus, the decreased cocaine CPP in BDNF heterozygote mice may be due learning deficits in these mice. This possibility is unlikely because, although the heterozygote BDNF mice showed impaired CPP with $10\,mg\,kg^{-1}$ of cocaine, they demonstrated normal CPP with $20\,mg\,kg^{-1}$ cocaine (Hall *et al*., 2003). However, in the absence of data demonstrating lack of decreases in CPP induced by non-drug rewards, a potential interpretation of the data of Hall *et al*. is that decreased cocaine CPP in heterozygote BDNF mice reflects a more general reward deficit. Finally, additional evidence for a role of BDNF in psychostimulant CPP is that amphetamine CPP is associated with increased expression of TrkB (tyrosine receptor kinase-B; which mediates BDNF effects on intracellular signalling) in hippocampus (CA3/dentate gyrus) and accumbens shell, and that amphetamine CPP is blocked by CA3/DG injections of K-252a, a non-selective Trk inhibitor (Shen *et al*., 2006).

Taylor and colleagues (Horger *et al*., 1999) provided one of the most dramatic illustrations of the role of mesolimbic BDNF in cocaine behavioural effects. It is well established that systemic or accumbens injections of psychostimulant drugs potentiate the rat's response to cues previously paired with natural rewards (Robbins, 1975; Taylor and Robbins, 1984). Horger *et al*. showed that chronic injections of BDNF into accumbens (via minipumps) profoundly (3–4-fold) increased systemic cocaine-induced potentiation of responding for a conditioned cue previously paired with water in thirsty rats. Remarkably, this effect persisted for up to 5 weeks after cessation of BDNF administration. This seminal study was the inspiration for subsequent studies described below on the role of BDNF in cocaine self-administration, reinstatement of cocaine seeking and incubation of cocaine craving.

BDNF: cocaine self-administration and cocaine seeking

Results from a study by Self and colleagues (Graham *et al*., 2007) indicate that accumbens BDNF is an important modulator of cocaine's rewarding effects in the drug self-administration model. They injected BDNF or anti-BDNF

into the accumbens shell of rats immediately after cocaine self-administration training for 5 days, in rats that had already learned to self-administer cocaine. Three to seven days after the last injection, BDNF-exposed rats self-administered more cocaine over a range of cocaine doses (an upward shift in the dose–response curve), suggesting increases in the rewarding effects of cocaine. In contrast, exposure to anti-BDNF had a modest effect in the opposite direction. Injections of BDNF, but not anti-BDNF, also potently increased the rats' motivation to work for cocaine when the response requirement for each successive injection exponentially increased under a progressive ratio reinforcement schedule (Richardson and Roberts, 1996). Graham *et al*. also locally injected an adeno-associated viral vector to knock down local BDNF protein production in mice accumbens shell. This manipulation caused a modest downward shift in the dose–response curve, suggesting a decrease in the rewarding effects of cocaine.

Results from three studies indicate that mesocorticolimbic BDNF plays an important role in cocaine craving and relapse, as assessed in rat models. In an initial study on mechanisms underlying incubation of cocaine craving, Grimm *et al*. (2003) reported that the time-dependent increases in cue-induced cocaine seeking after withdrawal (incubation) is associated with time-dependent increases in BDNF in mesocorticolimbic areas. On the basis of these findings, Lu *et al*. (2004a) injected BDNF acutely into VTA and assessed cue-induced cocaine seeking in extinction tests after 3, 10 or 30 withdrawal days. They found that these BDNF injections enhanced responding for cocaine cues for up to 30 days after cessation of cocaine use, an effect that was reversed by U0126. The finding of reversal of BDNF effects by U0126 is not surprising in light of the role of ERK signalling in BDNF-mediated synaptic plasticity (Poo, 2001). Lu *et al*. also found that acute VTA BDNF injections 2 h before testing had no effect on cue-induced cocaine seeking, suggesting that BDNF effects on responding to cues involve stable long-term synaptic alterations rather than acute effects on synaptic transmission or short-term plasticity.

In the same study where Graham *et al*. (2007) showed that BDNF in the accumbens potentiates the rewarding effects of self-administered cocaine, they also assessed extinction responding and subsequent reinstatement of cocaine seeking induced by cocaine priming injections, discrete cues previously paired with cocaine injections or a footshock stressor. Accumbens BDNF injections potently increased lever responding during both the extinction test and the subsequent reinstatement tests, whereas anti-BDNF injections had effects in the opposite direction. In apparent contrast with these findings, Berglind *et al*. (2007) used the same BDNF injection procedure in dorsal mPFC that was employed by Lu *et al*. (2004a) in the VTA. Surprisingly, they reported that these injections, which increased BDNF levels in accumbens a day later (presumably via anterograde transport; Altar *et al*., 1997), decreased extinction responding after 1 or 6 withdrawal days, and also decreased discrete cue- and cocaine priming-induced reinstatement after 6 withdrawal days. The reasons for the potentially discrepant findings between Berglind *et al*. data and those of Graham *et al*. are unknown. A missing piece in interpreting Berglind *et al*. data is that although there is evidence that endogenous BDNF expression is upregulated in the VTA and accumbens after prolonged withdrawal from cocaine (Grimm *et al*., 2003; Pu *et al*., 2006), there is no such evidence for mPFC. However, it is interesting to consider the possibility that the release of BDNF into the accumbens following microinjection into the mPFC in the study by Berglind *et al*. (2007) may more closely mimic spatially localized, activity-dependent release of BDNF relative to the pharmacological manipulations made by Graham *et al*. (2007) directly into the accumbens. Furthermore, a methodological issue in these studies is that it is unknown whether the effect of exogenous injections of local high doses of BDNF mimics cocaine-induced neuroplasticity of endogenous BDNF systems. In this regard, the data of Graham *et al*. of opposite effects of accumbens injections of BDNF versus anti-BDNF and the adeno-associated viral vector manipulation to knock down BDNF protein production are important for interpreting the roles of BDNF in cocaine-seeking behaviours, because the anti-BDNF and the viral vector interfere with the ability of endogenous BDNF to regulate these behaviours.

BDNF: conclusions

The data reviewed above indicate that although BDNF contributes significantly to several behavioural effects of cocaine, only some of them likely involve cocaine-induced BDNF-mediated long-term neuroplasticity in mesocorticolimbic areas. Thus, for cocaine self-administration, extinction responding and reinstatement of cocaine seeking, either acutely increasing or decreasing BDNF levels in the accumbens during cocaine self-administration training lead to corresponding increases or decreases in cocaine reward and the motivation to seek cocaine in a drug-free state after cessation of BDNF injections. The observation that the time-dependent increases in cue-induced cocaine seeking (incubation) in mesocorticolimbic areas are associated with time-dependent increases in BDNF levels, and that acute BDNF VTA injections cause long-lasting potentiation of this incubation further support the notion that cocaine-induced BDNF-mediated long-term neuroplasticity contributes to cocaine craving and relapse. On the basis of the data of Pu *et al*. (2006) discussed above, it is tempting to speculate that cocaine-induced BDNF-mediated synaptic plasticity in VTA dopamine neurons causes enhanced responsiveness of these neurons to cocaine cues or other stimuli (for example, stress) that provoke cocaine craving and relapse. VTA neurons are critical for relapse to drug seeking induced by drug priming, drug cues and stress (Stewart, 1984; McFarland and Kalivas, 2001; Bossert *et al*., 2004; Sun *et al*., 2005; Wang *et al*., 2005).

In contrast, cocaine psychomotor sensitization likely does not involve enduring cocaine-induced BDNF-mediated neuroplasticity. Although BDNF administered into accumbens or VTA potentiate the acute locomotor-activating effects of cocaine, these manipulations had no effect on the expression of cocaine psychomotor sensitization after several weeks of withdrawal. It also has not been established that cocaine-induced BDNF-mediated neuroplasticity contributes to the rewarding effects of cocaine in the CPP model.

Role of glutamatergic transmission and synaptic plasticity

Acute or repeated non-contingent cocaine exposure, or self-administered cocaine results in electrophysiological changes in excitatory transmission, and these electrophysiological neuroadaptations are accompanied by changes in the content and function of proteins associated with excitatory synapses. We will provide a brief overview of the electrophysiological and neurochemical data on synaptic plasticity in the VTA and accumbens in response to cocaine exposure. Rather than providing a comprehensive overview (Wolf *et al*., 2004; Kauer and Malenka, 2007), our goal is to emphasize what is known and unknown about the relationship between this plasticity and addiction-related behaviours. Also, this electrophysiological and neurochemical overview of excitatory transmission will be placed in the context of pharmacological evidence implicating a role for neuroplasticity in glutamate transmission in cocaine psychomotor sensitization and drug seeking.

VTA: psychomotor sensitization

It has long been suspected that psychomotor sensitization to cocaine involves adaptations in excitatory transmission, including early work by Post and Kopanda (1976) characterizing sensitization as a 'kindling' phenomenon. Indeed, in 1988 an entire book was devoted to seeking parallels between cocaine sensitization, electrical kindling, LTP and other forms of sensitization (Kalivas and Barnes, 1988). Although subsequent neuropharmacological studies over the last 15 years demonstrated that excitatory transmission in the VTA is necessary for the development of cocaine-induced psychomotor sensitization (Kalivas and Alesdatter, 1993; Wolf, 1998; Wolf *et al*., 2004), the first direct demonstration of synaptic plasticity being induced by *in vivo* cocaine experience at excitatory synapses on dopamine neurons in the VTA was obtained by Ungless *et al*. (2001). This study demonstrated that with a single cocaine injection, a long-lasting potentiation of synaptic strength (LTP) ensues, an effect that lasts at least 5, but not 10 days. These findings built upon earlier work showing increased glutamate-induced single-unit firing of dopamine neurons after repeated non-contingent cocaine exposure (White *et al*., 1995), and increased content of the GluR1 AMPAR subunit in the VTA at 24 h, but not 2 weeks after withdrawal from cocaine (Fitzgerald *et al*., 1996; Churchill *et al*., 1999).

Since the initial description of synaptic potentiation in the VTA, studies have focused on the molecular and cellular mechanisms of this potentiation (Wolf *et al*., 2004; Kauer and Malenka, 2007), and how cocaine-induced synaptic potentiation may influence behaviour. Although a clear picture of the role of cocaine-induced VTA synaptic potentiation in behaviour has yet to emerge, several studies provide data to address this issue. For example, Borgland *et al*. (2004) found that although cocaine-induced synaptic potentiation was correlated with acute cocaine-induced locomotor activation, after repeated cocaine treatment this correlation was no longer observed. Combining these data with the fact that VTA potentiation does not last much beyond 5 days of withdrawal from cocaine (Ungless *et al*., 2001), suggests that this process is more likely to be involved in early rather than long-lasting changes in reward circuits underlying addiction. This deduction is consistent not only with conclusions drawn from earlier studies showing that cocaine psychomotor sensitization could be initiated by amphetamine injections directly into the VTA and depends on local stimulation of both NMDA and D1 dopamine receptors (Kalivas and Alesdatter, 1993; Vezina, 1996), but also that the expression of this sensitization depends upon AMPA and dopamine receptor stimulation in the accumbens (Vanderschuren and Kalivas, 2000). Also, it was generally observed that adaptations measured in the VTA tended to be transient, whereas those in the accumbens were more enduring (Wolf, 1998).

Given the apparent role of the VTA in the development of cocaine-induced psychomotor sensitization identified in these earlier studies, recent electrophysiological studies have endeavoured to determine if the potentiation of dopamine neurons in the VTA is necessary for cocaine-induced behaviours. First, in a study examining AMPA-type glutamate receptor subtype GluR1 null mutant mice, Dong *et al*. (2004) found that cocaine does not increase AMPA/NMDA ratio in dopamine neurons in these mice. At the same time, however, there is a strong trend towards an increase in the basal (saline control) AMPA/NMDA ratio in these knockout mice, suggesting that perhaps AMPA receptor-mediated synaptic strength is already functioning at a high level in the absence of cocaine. GluR1 null mutants exhibit a high degree of cocaine-induced locomotion after an acute drug injection and an equivalent degree of psychomotor sensitization after repeated cocaine exposure. These results suggest that cocaine-induced potentiation in VTA dopamine neurons may not be an absolute requirement for cocaine-induced enhancement of locomotion or for psychomotor sensitization. Importantly, a limitation of this study (and related constitutive knockout studies) is that when a gene is deleted throughout development, it is unknown whether the observed changes in synaptic plasticity are indicative of the normal role of a given gene in this plasticity or some unknown compensatory changes that result from the gene deletion. Indeed, an elegant study by Borgland *et al*. (2006) offers another perspective on this question. These authors established a necessary role for orexin receptor signalling in VTA in the initiation of cocaine-induced synaptic potentiation and development of cocaine psychomotor sensitization. These findings suggest that cocaine-induced VTA dopamine neuron synaptic potentiation may play an important role in the development of cocaine psychomotor sensitization.

Interestingly, earlier pharmacological studies also indicated a different role for the VTA in the acute locomotor response of psychostimulants versus the development of sensitization. For example, daily injections of amphetamine or D1 agonists into the VTA did not alter locomotor activity, but elicited sensitization to a subsequent systemic amphetamine or cocaine injection (Vezina, 1993, 1996; Pierce *et al*., 1996b). Moreover, if synaptic potentiation is supplied via artificial means, the necessity for the cocaine-induced enhancement is bypassed and psychomotor sensitization still proceeds. For example, psychomotor sensitization can

be induced by electrical stimulation of prefrontal cortical glutamatergic afferents to the VTA (Schenk and Snow, 1994), and AMPA receptor overexpression in the VTA facilitates morphine psychomotor sensitization (Carlezon *et al*., 1997).

In addition to the synaptic potentiation in dopamine neurons discussed above, it is interesting to consider the possibility that cocaine induces METAPLASTICITY at these neurons. In a seminal 1996 paper, Abraham and Bear (1996) defined the concept of metaplasticity to describe 'plasticity of synaptic plasticity'. Although it has only recently been suggested that metaplasticity may contribute to addiction (Kourrich *et al*., 2007), it is interesting to consider whether prior findings on cocaine-induced plasticity in the VTA can be interpreted in this light. For example, *in vitro* electrical synaptic stimulation in slices from cocaine-exposed mice elicited smaller LTP and greater LTD. These results are consistent with an 'OCCLUSION' interpretation of this metaplasticity. That is, having been potentiated by cocaine exposure itself, these synapses are closer to a maximal amount of potentiation (thus smaller *in vitro* LTP), but further from a maximal point of depression (thus larger *in vitro* LTD). Support for this interpretation comes from similar findings in other experimental systems such as cortical LTP and LTD (Allen *et al*., 2003). This interpretation suggests that at least some molecular and cellular mechanisms are shared between synaptic potentiation in the VTA induced by cocaine experience and experimenter-controlled electrical stimulation.

Consistent with the idea that cocaine-induced potentiation in VTA may induce a near-maximal potentiation that occludes further synaptic enhancement, Borgland *et al*. (2004) found that multiple cocaine injections do not cause any greater increase in synaptic strength than a single injection. Furthermore, the time course of the potentiation remained the same, such that the time to return to a basal level of synaptic strength was between 5 and 10 days after the last acute or repeated cocaine injection. These results demonstrate the remarkable stability of cocaine's effect on dopamine neuron excitatory synaptic transmission, especially in contrast to the dynamic changes in cocaine's effect on accumbens medium spiny neurons (MSNs; see below).

In addition to occlusion effects, other forms of cocaine-induced metaplasticity may result from changes in plasticity mechanisms themselves. For example, Liu *et al*. (2005) reported that repeated *in vivo* cocaine injections cause a decrease in inhibitory synaptic transmission in VTA dopamine neurons. This decrease in inhibition facilitates *in vitro* LTP induction. Because this form of metaplasticity results from a process other than changes in excitatory synaptic strength *per se*, it is by definition not an occlusion effect. The relationship between LTP decreases due to occlusion and the reported LTP increases due to reduced inhibition has not yet been resolved (Kauer and Malenka, 2007), and, thus, a credible analysis of the role of these forms of metaplasticity in behaviour is not yet feasible. However, it is interesting to note that if a cocaine-induced decrease in inhibition is engaged to facilitate LTP induction *in vivo*, as may be predicted from Liu *et al*. results, this process does not appear likely to be engaged by cocaine experience itself, because multiple cocaine injections do not produce additional detectable potentiation beyond a single injection (Borgland *et al*., 2004). Of course, this does not rule out the possibility that other types of *in vivo* stimuli may take advantage of reduced inhibition to induce dopamine neuron LTP in animals with repeated cocaine experience (Liu *et al*., 2005).

VTA: conditioned place preference

Data addressing a potential role for dopamine neuron potentiation in animal models of cocaine addiction with greater face validity than psychomotor sensitization are beginning to emerge. For example, GluR1 null mutant mice, which lack cocaine-induced potentiation in VTA, also do not exhibit robust cocaine CPP, suggesting a possible link between the two phenomena (Dong *et al*., 2004; Mead *et al*., 2005). More detailed behavioural analyses of these mice suggest that, in particular, they show deficits in the learning of certain stimulus–reward relationships (Mead *et al*., 2007). As discussed above, however, the results from studies using knockout mice should be interpreted with caution. For example, while GluR1 knockout mice demonstrate potentiated expression of incubation of cocaine craving (Mead *et al*., 2007), other evidence suggests a link between incubation of craving and increased transmission via GluR1-containing AMPAR in the accumbens (Conrad *et al*., 2007).

Another study provides potential evidence that dopamine neuron synaptic potentiation enhances both morphine CPP and CPA (conditioned place aversion) induced by the κ-agonist U69593 (Kim *et al*., 2004). In this study, cocaine exposure, known to induce dopamine neuron synaptic potentiation for 5, but not 10 days (Ungless *et al*., 2001), was followed at various time periods by a single session CPP procedure with either morphine or U69593. The cocaine-treated rats showed enhanced morphine CPP and U69593 CPA only during the time period (that is, up to 5 days) when dopamine neuronal potentiation is known to occur. This enhancement of CPP was absent if an NMDAR antagonist was injected into the VTA prior to cocaine exposure, a pharmacological manipulation known to disrupt dopamine neuron synaptic potentiation (Ungless *et al*., 2001). Moreover, CPP to morphine is dependent on orexin release into the VTA (Harris *et al*., 2005), which is consistent with the observations by Borgland *et al*. (2006) (discussed above) that synaptic potentiation of dopamine cells by cocaine depends on orexin-induced mobilization of NMDAR to the cell surface. Together, these data support the notion that dopamine neuron potentiation enhances the salience of rewarding or aversive stimuli, and thereby promotes learning about contexts associated with these stimuli.

VTA: self-administration and reinstatement

The role of dopamine neuronal potentiation in the self-administration model has not been examined. However, given the short-lived nature of measurable VTA synaptic potentiation after discontinuing cocaine administration, it is likely that its primary role is in facilitating the reward learning required to acquire drug self-administration rather

than maintaining cocaine self-administration or reinstatement of cocaine seeking after withdrawal. Indeed, glutamate transmission in the VTA mediates the potentiation effect of prior exposure to systemic and VTA injections of amphetamine on subsequent acquisition of drug self-administration, and responding on a progressive ratio reinforcement schedule (Suto *et al*., 2003; Vezina, 2004). Perhaps consistent with the idea that synaptic potentiation in the VTA is transient and underlying the acquisition and/or sensitization of drug-seeking, short-lived upregulation of AMPAR subunits were found in the VTA after binge cocaine self-administration (Tang *et al*., 2004), although more enduring changes were identified in another study (Lu *et al*., 2003).

Although we have focused on synaptic potentiation, other aspects of excitatory transmission may also undergo neuroplasticity following cocaine. For example, Wang *et al*. (2005) found that cocaine self-administration induces long-lasting potentiation of CRF (corticotrophin-releasing factor)-mediated stress-induced glutamate and dopamine release in the VTA, an effect critical for stress-induced reinstatement of cocaine seeking. Of course, CRF-induced release of glutamate can be synergistic with synaptic potentiation. Indeed, like cocaine, stress exposure increases AMPA/NMDA ratio in VTA dopamine neurons (Saal *et al*., 2003).

Other evidence suggesting that some forms of long-lasting alterations in VTA neurons contribute to cocaine-seeking behaviours includes an intriguing form of cocaine-induced metaplasticity in dopamine neurons that involves BDNF (Pu *et al*., 2006). This study shows that although BDNF application by itself does not enhance dopamine neuron synaptic strength, this application facilitates the induction of *in vitro* LTP. In addition, in mice given repeated non-contingent exposure to cocaine, subthreshold electrical stimuli delivered in slices taken from these mice are able to generate LTP after 2 weeks of withdrawal from the drug; at this time point but not during early withdrawal, BDNF VTA levels were increased. Also, interfering with TrkB signalling blocks the enhancement of LTP, suggesting that cocaine-enhanced plasticity may be due to the increases in BDNF. Coupled with the fact that the synaptic plasticity experiments were done in the presence of GABA receptor antagonists, these findings appear to demonstrate a form of cocaine-induced metaplasticity that is distinct from that seen by reducing inhibition (Liu *et al*., 2005; Pu *et al*., 2006). This phenomenon may provide an attractive candidate mechanism for the effect of VTA BDNF injections on potentiation of cue-induced cocaine seeking after prolonged withdrawal (incubation of craving) (Lu *et al*., 2004a).

Accumbens: psychomotor sensitization

Although cocaine-induced changes in VTA dopamine neuron synaptic efficacy are rapidly induced and short-lived, plasticity in excitatory transmission in accumbens neurons has a slower and longer lasting time course. Also, in contrast to the robust effect of a single cocaine injection on dopamine neuron synaptic function, this treatment does not change synaptic strength in accumbens neurons in drug-naive rodents (Thomas *et al*., 2001; Fourgeaud *et al*., 2004; Kourrich *et al*., 2007). With repeated exposure, however, synaptic strength in these neurons appears to be depressed initially (Kourrich *et al*., 2007). However, 10 days after withdrawal from non-contingent cocaine exposure, this depression has reversed course to reveal robust potentiation, evident from electrophysiological measures as well as increased AMPAR surface expression (Boudreau and Wolf, 2005; Boudreau *et al*., 2007; Kourrich *et al*., 2007). These data are consistent with earlier studies demonstrating that the locomotor stimulant effect of AMPA microinjection into the accumbens is markedly potentiated after withdrawal from repeated non-contingent cocaine exposure, and that accumbens AMPA-induced psychomotor potentiation only occurs in rats that develop this sensitization (Bell and Kalivas, 1996; Pierce *et al*., 1996a).

Little is yet known about the molecular and cellular mechanisms for cocaine-induced accumbens synaptic plasticity. However, an enduring upregulation in GluR1 was shown in whole-cell lysates only in the accumbens of cocaine-sensitized rats (Churchill *et al*., 1999), and more recent studies demonstrated an increase in surface expression of GluR1/2-containing AMPAR after repeated cocaine exposure that was present only in rats developing psychomotor sensitization (Boudreau and Wolf, 2005; Boudreau *et al*., 2007). This effect was paralleled by an increase in ERK2 activity in the accumbens (see ERK section above). Consistent with this behavioural pharmacology and biochemical evidence, direct electrophysiological measurement of synaptic AMPAR responses 2 weeks after withdrawal from repeated non-contingent cocaine exposure demonstrates a synaptic potentiation (Kourrich *et al*., 2007). This increase in synaptic AMPAR responses is correlated with the development of psychomotor sensitization (MJ Thomas, unpublished data).

The current status of experimental information allows for many interpretations of the role(s) that MSNs synaptic potentiation can have in psychomotor sensitization. For example, in many areas of neuroscience, including the study of learning, epilepsy and chronic pain, a similar systems level or behavioural output often emerges from different underlying substrates with the passage of time and/or experience with additional stimuli in the environment (e.g. Squire, 1987). Thus, it is possible that sensitized psychomotor activity is supported by different underlying mechanisms at different time points after withdrawal from cocaine. In other words, during late withdrawal from repeated cocaine, MSNs synaptic potentiation may be a mediator of sensitization whereas at earlier time points it is not. In contrast, accumbens synaptic potentiation, rather than making a direct contribution to behavioural output, may actually be a compensatory response to changes in other circuit elements. As first suggested by Boudreau and Wolf (2005), it may in fact be a form of homeostasis related to the 'SYNAPTIC SCALING' phenomenon. Synaptic scaling refers to an alteration in synaptic responses throughout a cell that compensates for chronic changes in activity (Turrigiano and Nelson, 2004). In this scenario, general decreases in accumbens neuronal excitability (Zhang *et al*., 1998, 2002b; Hu *et al*., 2004; Dong *et al*., 2006) or extracellular glutamate (Pierce *et al*., 1996a; Hotsenpiller *et al*., 2001; Baker *et al*., 2003; McKee and Meshul, 2005) known to occur after withdrawal

from repeated cocaine exposure may trigger a lasting compensatory enhancement in AMPAR trafficking to excitatory synapses.

Although there are no studies yet that directly tested the scaling hypothesis, the idea fits with the fact that the observed changes in synaptic strength (Kourrich *et al*., 2007) and AMPAR surface expression (Boudreau and Wolf, 2005; Boudreau *et al*., 2007) are widespread. Between-group differences are readily detected through analysis of accumbens tissue homogenates (Boudreau and Wolf, 2005; Boudreau *et al*., 2007) and recording from relatively small groups of individual MSNs (Kourrich *et al*., 2007). From the data outlined above, it is tempting to assume that the cocaine-induced synaptic potentiation in the accumbens underlies psychomotor sensitization. However, at present it remains possible that as overall excitability to accumbens MSNs is markedly reduced after withdrawal from cocaine, the synaptic potentiation is restoring normal excitability and that interfering with this synaptic potentiation may in fact facilitate addiction-related behaviours such as psychomotor sensitization. Although this seems contradictory to the fact that injections of AMPAR antagonists in the accumbens prevent the expression of psychomotor sensitization or the reinstatement of cocaine seeking (Pierce *et al*., 1996a; Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; Park *et al*., 2002), blocking accumbens AMPARs through pharmacological means can produce undesirable side effects such as blockade of cocaine-induced dopamine release (Moghaddam and Bolinao, 1994; Pap and Bradberry, 1995).

One aspect of plasticity in accumbens MSNs that has emerged as a potential contributor is the increase in dendritic spine density and ACTIN CYCLING produced by repeated cocaine exposure (Robinson and Kolb, 2004; Toda *et al*., 2006). Actin cycling regulates the growth, retraction and shape of dendritic spines, and is controlled by a number of binding proteins that determine the rate and direction of actin polymerization and depolymerization (Kasai *et al*., 2003; Carlisle and Kennedy, 2005; Lippman and Dunaevsky, 2005). Moreover, actin cycling is thought to be a necessary component in many forms of synaptic plasticity, including LTP (Malinow and Malenka, 2002; Lisman, 2003). Interestingly, the actin-binding proteins associated with the increase in actin cycling after repeated cocaine exposure predict that the majority of actin polymerization is in the form of filopodia rather than lamellipodia (Toda *et al*., 2006). Filopodia are generally thought to be less stable, and more amenable to neuroplastic changes than lamellipodia are (Carlisle and Kennedy, 2005). Thus, the increase in actin cycling and spine density may predict that more rapid or quantitatively larger alterations in POSTSYNAPTIC DENSITY (PSD) proteins, and, consequently, spine structure can be induced by subsequent experimental or environmental stimuli. In other words, this biochemical and morphological plasticity in dendritic spines may be one means by which metaplasticity is achieved.

Accordingly, and akin to the situation in the VTA, metaplasticity is produced in the accumbens. For example, *in vivo* cocaine exposure increases LTP in accumbens MSNs when induced by experimenter-controlled electrical stimulation (Yao *et al*., 2004; Goto and Grace, 2005), while decreasing LTD induced via these means (Thomas *et al*., 2001; Fourgeaud *et al*., 2004; Martin *et al*., 2006). In contrast, recent studies show that when cocaine experience itself is used as a plasticity-generating stimulus, it can become a potent initiator of accumbens synaptic depression in mice with a history of cocaine exposure and subsequent withdrawal (Kourrich *et al*., 2007). Two studies provide evidence that repeated cocaine exposure modifies the induction of tetanus-induced LTP *in vitro* (Yao *et al*., 2004) and *in vivo* (Goto and Grace, 2005). Interestingly, although LTP at PFC–accumbens synapses appears to be enhanced (Yao *et al*., 2004; Goto and Grace, 2005), LTP at hippocampal–accumbens synapses is reduced (Goto and Grace, 2005). Given that these two populations of afferents are thought to carry distinct types of information and serve distinct functions in modulating accumbens MSNs firing patterns (O'Donnell and Grace, 1995), the cocaine-induced imbalance between plasticity at PFC and hippocampal inputs is likely to have a dramatic, yet complex role in modulating accumbens function. Goto and Grace proposed that this plasticity imbalance may help to explain why cocaine-exposed rats have difficulty in set shifting during goal-directed learning tasks, and thus produce excessive perseveration errors—potentially a useful model for certain aspects of addiction.

In addition to enhanced experimenter-induced accumbens LTP, other data demonstrate decreased LTD induction after cocaine exposure. For example, a single exposure to cocaine is sufficient to block the *in vitro* induction of a presynaptic endocannabinoid-mediated form of LTD in accumbens MSNs (Fourgeaud *et al*., 2004). This blockade occurs in the absence of any detectable changes in excitatory synaptic strength induced by a single cocaine injection (Thomas *et al*., 2001; Fourgeaud *et al*., 2004; Kourrich *et al*., 2007), and thus provides another example of metaplasticity that cannot be explained by a simple occlusion effect.

The investigation of metaplasticity discussed thus far has involved testing for cocaine-induced changes in LTP or LTD by inducing these phenomena with experimenter-controlled electrical stimulation. One difficulty in extrapolating from these metaplastic effects to their potential roles in behaviour is that it is unclear under what circumstances these forms of plasticity are actually engaged during *in vivo* experience. In contrast, a form of metaplasticity was recently demonstrated by using *in vivo* cocaine itself (rather than electrical stimulation) as the plasticity-inducing stimulus (Boudreau *et al*., 2007; Kourrich *et al*., 2007). These studies demonstrated that a single cocaine injection in cocaine-experienced mice during an extended drug-free period (10–14 days) triggered a synaptic depression (Thomas *et al*., 2001; Kourrich *et al*., 2007) and AMPAR internalization (Boudreau *et al*., 2007), whereas the same treatment in drug-naive animals did not (Thomas *et al*., 2001; Fourgeaud *et al*., 2004; Boudreau *et al*., 2007; Kourrich *et al*., 2007). Cocaine re-exposure after withdrawal from the drug also provides a trigger for the expression of psychomotor sensitization.

Two lines of evidence suggest that this cocaine experience-induced form of accumbens metaplasticity may contribute to the expression of psychomotor sensitization. First, Boudreau *et al*. demonstrated that cocaine-exposed rats that do not exhibit psychomotor sensitization do not exhibit

cocaine-induced accumbens AMPAR internalization after withdrawal from the drug. Second, after withdrawal from amphetamine, infusion of an AMPAR endocytosis-blocking peptide into the accumbens 90 min prior to a drug challenge interferes with the expression of amphetamine psychomotor sensitization (Brebner *et al*., 2005). Because this peptide selectively interferes with the induction of LTD *in vitro* without decreasing basal AMPAR responses, one reasonable interpretation of these results is that an amphetamine challenge induces an acute synaptic depression in the accumbens *in vivo* and that this depression is necessary for the expression of psychomotor sensitization. However, an issue to consider in the interpretation of these data is that there are no electrophysiological data to confirm that acute exposure to amphetamine (or cocaine) induces synaptic depression during tests for the expression of psychomotor sensitization. Thus, although these data are suggestive, the relationship between accumbens synaptic depression and the expression of cocaine sensitization will require further exploration.

Accumbens: self-administration and reinstatement of drug seeking
A variety of data strongly suggest that the prefrontal glutamatergic afferents to the accumbens are critical for the reinstatement of cocaine seeking, as recently reviewed by Kalivas and O'Brien (2008). This includes increased synaptic release of glutamate in the accumbens during drug seeking (McFarland *et al*., 2003, 2004) and blockade of drug seeking by inhibiting AMPAR (Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; Park *et al*., 2002) or stimulating mGluR2/3 receptors, which reduces synaptic glutamate release (Bossert *et al*., 2006; Peters and Kalivas, 2006). These findings are by and large consistent with the synaptic potentiation of glutamatergic synapses after withdrawal from non-contingent cocaine exposure outlined above. In fact, recent evidence indicates that a profound increase in GluR1 surface and total expression in accumbens also occurs after withdrawal from cocaine self-administration, a phenomenon that may mediate the incubation of cocaine craving (Conrad *et al*., 2007).

However, on the surface these collective data would seem to be at odds with the electrophysiological demonstrations of an enduring decrease in LTD in the accumbens of mice withdrawn from daily sessions of cocaine self-administration (Martin *et al*., 2006). Importantly, these investigators demonstrated that enduring loss of LTD was not observed in several control conditions (yoked cocaine, food self-administering or naive). Given the synaptic potentiation apparent from other electrophysiological and biochemical studies, one might have expected an occlusion of LTP rather than diminished LTD. Similarly, another study reports decreased excitatory field potential responses in response to stimulation of glutamatergic afferents after withdrawal from daily self-administered cocaine (Schramm-Sapyta *et al*., 2006). Finally, another finding, which on the surface appears inconsistent with the possibility that synaptic potentiation in accumbens MSNs mediates cocaine-seeking behaviour, is that inhibition of actin cycling by accumbens injections of latrunculin (which prevents actin polymerization) or a Lim-kinase inhibitor (which stabilizes actin structure) potentiates cocaine-induced reinstatement of drug seeking (Toda *et al*., 2006). Thus, the increased potential for metaplasticity inherent in high actin cycling may be protective and limiting to the behavioural effect of an acute cocaine injection. However, understanding the relationship between actin cycling, loss of LTD and synaptic potentiation requires significant additional experimentation, and conclusions drawn from the available data should be considered speculative.

Potential roles for ERK, BDNF and synaptic potentiation in cocaine addiction

This review describes several cellular components of cocaine-induced neuroplasticity, including elevated ERK and BDNF signalling, alterations in actin cycling and changes in excitatory synaptic transmission. These forms of plasticity can be evaluated in terms of two distinct categories of plasticity (1) transient plasticity associated with the development of more enduring cellular changes and (2) relatively enduring baseline plasticity that is measurable in unstimulated conditions, and the accompanying metaplasticity that is revealed by different challenges (for example, cocaine, conditioned cue, electrical stimulation and stress) imposed onto basal plasticity. Below, we attempt to integrate the plasticity and metaplasticity described above into these two general categories of plasticity.

Transient plasticity
The potentiation of synaptic strength in VTA dopamine cells by a single injection of cocaine has emerged as a key observation regarding a potential transient mechanism for initiating enduring neuroplasticity (Ungless *et al*., 2001; Borgland *et al*., 2004, 2006; Wolf *et al*., 2004; Bellone and Luscher, 2006; Dong *et al*., 2006). This potentiation of synaptic AMPARs appears mediated in part by an increase in NMDAR signalling that involves orexin (Borgland *et al*., 2006). Importantly, the facilitation of dopamine cell firing by potentiating synaptic strength at glutamate synapses would increase dopamine signalling in terminal fields known to harbour enduring forms of cocaine-induced neuroplasticity. Increased ERK activity in these dopamine terminal fields by acute cocaine may also initiate cellular events that mediate the enduring changes in gene expression and protein function that underlie cocaine psychomotor sensitization and cocaine seeking (Lu *et al*., 2006; Girault *et al*., 2007). Non-transcriptional ERK-mediated alterations in dendritic plasticity (Wu *et al*., 2001) may also account for the role of ERK in cocaine psychomotor sensitization, and consolidation and reconsolidation of memory for cocaine cues. In this regard, morphological changes in dendritic spines of neurons in dopamine axon terminal fields (Robinson and Kolb, 2004) and associated increases in actin cycling (Toda *et al*., 2006) are induced by drug exposure regimens that induce ERK-dependent psychomotor sensitization (Ferguson *et al*., 2006), posing a potential role for ERK-stimulated signalling in these forms of enduring plasticity.

Furthermore, a recent study directly linked ERK2 activation to increased AMPAR surface expression in the accumbens of cocaine-sensitized rats (Boudreau *et al*., 2007).

Enduring basal plasticity and metaplasticity

These forms of cocaine-induced plasticity are probably the most widely described, and are manifested more in dopamine axon terminal fields such as the accumbens, mPFC and amygdala than in the VTA (but see Pu *et al*., 2006 regarding enduring effects of BDNF in the VTA to facilitate the excitability of dopamine cells). Although recent reviews provide an overview of plasticity in dopamine terminal fields in many cellular domains ranging from gene expression and protein function to neurotransmission (Hyman *et al*., 2006; Kauer and Malenka, 2007; Kalivas and O'Brien, 2008), the topics in the present review focus on the accumbens and enduring baseline changes in ERK, BDNF and glutamatergic synaptic activity. In this regard, the concept of glutamatergic synaptic potentiation in MSNs is probably most relevant. Thus, a collision of findings from behavioural pharmacology with glutamate receptor agonists and antagonists (Pierce *et al*., 1996a; Suto *et al*., 2004), neurochemical measures of glutamate receptor subunit surface expression (Churchill *et al*., 1999; Boudreau and Wolf, 2005; Boudreau *et al*., 2007; Conrad *et al*., 2007) and electrophysiological analysis of synaptic currents (Kourrich *et al*., 2007) all support the perspective that withdrawal from repeated cocaine exposure causes increased responsiveness of glutamatergic synapses to AMPAR stimulation in the accumbens.

Determining the role of synaptic potentiation in mediating the augmented behavioural responding associated with repeated cocaine exposure, such as locomotor sensitization or cocaine seeking, will require further experimentation employing pharmacological or behavioural treatments that reverse synaptic potentiation and also antagonize or potentiate behavioural responding. The fact that blocking accumbens AMPAR inhibits both the expression of cocaine psychomotor sensitization and cocaine seeking (Vanderschuren and Kalivas, 2000; Kalivas and McFarland, 2003; Bossert *et al*., 2005) can be viewed as a first step towards such a proof. However, eliminating excitatory transmission is far too general a manipulation to be considered as evidence directly supporting a role for synaptic potentiation. Similarly, BDNF treatments in the accumbens potentiated cocaine seeking, while inhibiting BDNF reduced subsequent cocaine seeking (Graham *et al*., 2007). BDNF treatment is known to promote manifestations of synaptic potentiation, such as LTP (Poo, 2001). Moreover, the incubation of cocaine craving is associated with accumulating BDNF in the accumbens (Grimm *et al*., 2003). However, these observations fall short of directly linking synaptic potentiation with BDNF and augmented behavioural responding after cocaine self-administration.

Another aspect of dendritic physiology that shows enduring basal alterations in the accumbens after chronic cocaine exposure is the increase in dendritic spine density and actin cycling (Robinson and Kolb, 2004; Toda *et al*., 2006). Given the important role of spine morphology and actin cycling regulation of PSD proteins in synaptic strength (Kasai *et al*., 2003; Lisman, 2003; Carlisle and Kennedy, 2005), it is tempting to link these changes to synaptic potentiation and increased AMPAR surface expression in accumbens (Boudreau and Wolf, 2005; Boudreau *et al*., 2007). However, in contrast to predictions of this hypothesis, accumbens injections of latrunculin (a compound that inhibits actin cycling and has been shown to change spine structure *in vitro*) potentiated cocaine seeking (Toda *et al*., 2006) at a dose that caused a rapid loss of GluR1 from the PSD subfraction (S Toda and PW Kalivas, unpublished observations). Thus, if these findings are indeed related to synaptic potentiation, they argue that synaptic potentiation may be compensatory, because reducing GluR1 expression in the PSD (and presumably reducing synaptic potentiation as well) by disrupting actin cycling promoted cocaine seeking. One possible account of the data of Toda *et al*. is that they reflect a distinction between experimenter-administered and self-administered cocaine with regards to synaptic potentiation. Thus, while synaptic potentiation may be positively linked to psychomotor sensitization, it is negatively linked to self-administration behaviour. Indeed, a study examining LTD after self-administered cocaine found a loss of LTD in the accumbens (Martin *et al*., 2006). Assuming the validity of the occlusion hypothesis, which predicts that a loss of LTD occurs in synapses that are already depressed (Allen *et al*., 2003), these data argue that in the basal state after withdrawal from self-administered cocaine, glutamate synapses in the accumbens are not potentiated. However, more research is needed to address this question, as recent data of Conrad *et al*. (2007) indicate that extended withdrawal (45 days) from cocaine self-administration is accompanied by increased surface expression of the AMPAR subunit GluR1 in accumbens, and that this increased expression is associated with a progressive increase in cue-induced cocaine seeking (see above).

Conclusions

The effort made in this review to link cocaine-induced neuroplasticity in ERK and BDNF signalling with changes in glutamate synaptic physiology in mesocorticolimbic circuitry is clearly hampered by a dearth of experiments identifying cause and effect mechanisms. However, the potential associations between transient synaptic potentiation in the VTA, ERK-induced plasticity in dopamine terminal fields and the enduring neurochemical changes and synaptic potentiation in the accumbens highlight points where further experimentation may be most informative. For example, the pharmacological tools now exist to interfere with and/or promote BDNF or ERK activity and have been used to successfully link these signalling cascades with psychomotor sensitization and cocaine seeking. Therefore, these tools should also be applicable towards determining a causal linkage between BDNF, ERK and aspects of enduring synaptic potentiation, such as AMPAR subunit distribution and synaptic activity. Using systems that can be directly manipulated by relatively specific receptor or enzyme pharmacology, can help characterize the role of more integrated physiological forms of neuroplasticity such as

synaptic potentiation, actin cycling or spine morphology that are not as amenable to specific, reversible interventions. Not only will these types of studies increase our understanding of the neurobiological basis of cocaine addiction, but they can also establish more thorough assays for assessing the neurological impact and validity of emerging pharmacological treatments for cocaine addiction.

Acknowledgements

This review was supported by extramural NIH grants (DA03906, DA12513 and DA015369 to PWK; DA019666 to MJT), the McKnight Foundation (MJT) and by funds from the Intramural Research Program of the NIH, NIDA (YS).

Conflict of interest

The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the results discussed in this review.

References

Abraham WC, Bear MF (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci* **19**: 126–130.

Adams JP, Sweatt JD (2002). Molecular psychology: roles for the ERK MAP kinase cascade in memory. *Annu Rev Pharmacol Toxicol* **42**: 135–163.

Allen CB, Celikel T, Feldman DE (2003). Long-term depression induced by sensory deprivation during cortical map plasticity *in vivo*. *Nat Neurosci* **6**: 291–299.

Altar CA, Boylan CB, Jackson C, Hershenson S, Miller J, Wiegand SJ *et al*. (1992). Brain-derived neurotrophic factor augments rotational behavior and nigrostriatal dopamine turnover *in vivo*. *Proc Natl Acad Sci USA* **89**: 11347–11351.

Altar CA, Cai N, Bliven T, Juhasz M, Conner JM, Acheson AL *et al*. (1997). Anterograde transport of brain-derived neurotrophic factor and its role in the brain. *Nature* **389**: 856–860.

Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S *et al*. (2003). Neuroadaptations in cystine–glutamate exchange underlie cocaine relapse. *Nat Neurosci* **6**: 743–749.

Bardo MT, Bevins RA (2000). Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology* **153**: 31–43.

Bell K, Kalivas PW (1996). Context-specific cross sensitization between systemic cocaine and intra-accumbens AMPA infusion in rats. *Psychopharmacology* **127**: 377–383.

Bellone C, Luscher C (2006). Cocaine triggered AMPA receptor redistribution is reversed *in vivo* by mGluR-dependent long-term depression. *Nat Neurosci* **9**: 636–641.

Berglind WJ, See RE, Fuchs RA, Ghee SM, Whitfield Jr TW, Miller SW *et al*. (2007). A BDNF infusion into the medial prefrontal cortex suppresses cocaine seeking in rats. *Eur J Neurosci* **26**: 757–766.

Bolanos CA, Nestler EJ (2004). Neurotrophic mechanisms in drug addiction. *Neuromolecular Med* **5**: 69–83.

Borgland SL, Malenka RC, Bonci A (2004). Acute and chronic cocaine-induced potentiation of synaptic strength in the ventral tegmental area: electrophysiological and behavioral correlates in individual rats. *J Neurosci* **24**: 7482–7490.

Borgland SL, Taha SA, Sarti F, Fields HL, Bonci A (2006). Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* **49**: 589–601.

Bossert JM, Ghitza UE, Lu L, Epstein DH, Shaham Y (2005). Neurobiology of relapse to heroin and cocaine seeking: an update and clinical implications. *Eur J Pharmacol* **526**: 36–50.

Bossert JM, Gray SM, Lu L, Shaham Y (2006). Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. *Neuropsychopharmacology* **31**: 2197–2209.

Bossert JM, Liu SY, Lu L, Shaham Y (2004). A role of ventral tegmental area glutamate in contextual cue-induced relapse to heroin seeking. *J Neurosci* **24**: 10726–10730.

Boudreau AC, Reimers JM, Milovanovic M, Wolf ME (2007). 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.

Boudreau AC, Wolf ME (2005). Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci* **25**: 9144–9151.

Bowers MS, McFarland K, Lake RW, Peterson YK, Lapish CC, Gregory ML *et al*. (2004). Activator of G-protein signaling 3: a gatekeeper of cocaine sensitization and drug-seeking. *Neuron* **42**: 269–281.

Brady JV (1991). Animal models for assessing drugs of abuse. *Neurosci Biobehav Rev* **15**: 35–43.

Brebner K, Wong TP, Liu L, Liu Y, Campsall P, Gray S *et al*. (2005). Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* **310**: 1340–1343.

Carlezon Jr WA, Boundy VA, Haile CN, Lane SB, Kalb RG, Neve RL *et al*. (1997). Sensitization to morphine induced by viral-mediated gene transfer. *Science* **277**: 812–814.

Carlisle HJ, Kennedy MB (2005). Spine architecture and synaptic plasticity. *Trends Neurosci* **28**: 182–187.

Churchill L, Swanson CJ, Urbina M, Kalivas PW (1999). 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.

Conrad KL, Uejima JM, Shaham Y, Marinelli M, Wolf ME (2007). Role of nucleus accumbens GluR2-lacking AMPA receptors in incubation of cocaine craving. *SFN Abstr* **33** 815.20.

Cornish J, Kalivas P (2000). Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci* **20**: RC89 (81–85).

Corominas M, Roncero C, Ribases M, Castells X, Casas M (2007). Brain-derived neurotrophic factor and its intracellular signaling pathways in cocaine addiction. *Neuropsychobiology* **55**: 2–13.

Dawson NM, Hamid EH, Egan MF, Meredith GE (2001). Changes in the pattern of brain-derived neurotrophic factor immunoreactivity in the rat brain after acute and subchronic haloperidol treatment. *Synapse* **39**: 70–81.

Deroche-Gamonet V, Belin D, Piazza PV (2004). Evidence for addiction-like behavior in the rat. *Science* **305**: 1014–1017.

Di Chiara G (1998). A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *J Psychopharmacol* **12**: 54–67.

Di Ciano P, Everitt BJ (2001). 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.

Dong Y, Green T, Saal D, Marie H, Neve R, Nestler EJ *et al*. (2006). CREB modulates excitability of nucleus accumbens neurons. *Nat Neurosci* **9**: 475–477.

Dong Y, Saal D, Thomas M, Faust R, Bonci A, Robinson T *et al*. (2004). Cocaine-induced potentiation of synaptic strength in dopamine neurons: behavioral correlates in GluRA(−/−) mice. *Proc Natl Acad Sci USA* **101**: 14282–14287.

Epstein DH, Preston KL, Stewart J, Shaham Y (2006). Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology* **189**: 1–16.

Everitt BJ, Robbins TW (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* **8**: 1481–1489.

Everitt BJ, Wolf ME (2002). Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci* **22**: 3312–3320.

Ferguson SM, Fasano S, Yang P, Brambilla R, Robinson TE (2006). Knockout of ERK1 enhances cocaine-evoked immediate early gene expression and behavioral plasticity. *Neuropsychopharmacology* **31**: 2660–2668.

Figlewicz DP, Naleid AM, Sipols AJ (2007). Modulation of food reward by adiposity signals. *Physiol Behav* **91**: 473–478.
Fitzgerald LW, Ortiz J, Hamedani AG, Nestler EJ (1996). Drugs of abuse and stress increase the expression of GluR1 and NMDAR1 glutamate receptor subunits in the rat ventral tegmental area: common adaptations among cross-sensitizing agents. *J Neurosci* **16**: 274–282.
Fourgeaud L, Mato S, Bouchet D, Hemar A, Worley PF, Manzoni OJ (2004). A single *in vivo* exposure to cocaine abolishes endocannabinoid-mediated long-term depression in the nucleus accumbens. *J Neurosci* **24**: 6939–6945.
Gawin FH, Kleber HD (1986). Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. *Arch Gen Psychiatry* **43**: 107–113.
Gerdjikov TV, Ross GM, Beninger RJ (2004). Place preference induced by nucleus accumbens amphetamine is impaired by antagonists of ERK or p38 MAP kinases in rats. *Behav Neurosci* **118**: 740–750.
Girault JA, Valjent E, Caboche J, Herve D (2007). ERK2: a logical AND gate critical for drug-induced plasticity? *Curr Opin Pharmacol* **7**: 77–85.
Goto Y, Grace AA (2005). Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron* **47**: 255–266.
Graham DL, Edwards S, Bachtell RK, Dileone RJ, Rios M, Self DW (2007). Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse. *Nat Neurosci* **10**: 1029–1037.
Grimm JW, Fyall AM, Osincup DP (2005). Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. *Physiol Behav* **84**: 73–79.
Grimm JW, Hope BT, Wise RA, Shaham Y (2001). Incubation of cocaine craving after withdrawal. *Nature* **412**: 141–142.
Grimm JW, Lu L, Hayashi T, Hope BT, Su TP, Shaham Y (2003). Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. *J Neurosci* **23**: 742–747.
Grimm JW, Shaham Y, Hope BT (2002). Effect of the cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. *Behav Pharmacol* **13**: 379–388.
Hall FS, Drgonova J, Goeb M, Uhl GR (2003). Reduced behavioral effects of cocaine in heterozygous brain-derived neurotrophic factor (BDNF) knockout mice. *Neuropsychopharmacology* **28**: 1485–1490.
Harris GC, Wimmer M, Aston-Jones G (2005). A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* **437**: 556–559.
Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ, Taylor JR (1999). Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor. *J Neurosci* **19**: 4110–4122.
Hotsenpiller G, Giorgetti M, Wolf ME (2001). Alterations in behaviour and glutamate transmission following presentation of stimuli previously associated with cocaine exposure. *Eur J Neurosci* **14**: 1843–1855.
Hu XT, Basu S, White FJ (2004). Repeated cocaine administration suppresses HVA-Ca^{2+} potentials and enhances activity of K^+ channels in rat nucleus accumbens neurons. *J Neurophysiol* **92**: 1597–1607.
Hyman C, Hofer M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP *et al.* (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. *Nature* **350**: 230–232.
Hyman SE, Malenka RC, Nestler EJ (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci* **29**: 565–598.
Jentsch JD, Taylor JR (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* **146**: 373–390.
Jones S, Bonci A (2005). Synaptic plasticity and drug addiction. *Curr Opin Pharmacol* **5**: 20–25.
Kalivas PW (2005). How do we determine which drug-induced neuroplastic changes are important? *Nat Neurosci* **8**: 1440–1441.
Kalivas PW, Alesdatter JE (1993). Involvement of NMDA receptor stimulation in the VTA and amygdala in behavioral sensitization to cocaine. *J Pharmacol Exp Ther* **267**: 486–495.
Kalivas PW, Barnes CD (1988). *Sensitization in the Nervous System*. Telford Press: Caldwell, NJ.
Kalivas PW, McFarland K (2003). Brain circuitry and the reinstatement of cocaine-seeking behavior. *Psychopharmacology* **168**: 44–56.
Kalivas PW, O'Brien C (2008). Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* **33**: 166–180.
Kalivas PW, Volkow ND (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* **162**: 1403–1413.
Kasai H, Matsuzaki M, Noguchi J, Yasumatsu N, Nakahara H (2003). Structure–stability–function relationships of dendritic spines. *Trends Neurosci* **26**: 360–368.
Kauer JA, Malenka RC (2007). Synaptic plasticity and addiction. *Nat Rev Neurosci* **8**: 844–858.
Kim JA, Pollak KA, Hjelmstad GO, Fields HL (2004). A single cocaine exposure enhances both opioid reward and aversion through a ventral tegmental area-dependent mechanism. *Proc Natl Acad Sci USA* **101**: 5664–5669.
Kourrich S, Rothwell PE, Klug JR, Thomas MJ (2007). Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J Neurosci* **27**: 7921–7928.
Koya E, Uejima JM, Bossert JM, Shaham Y, Hope BT (2008). Role of ventral medial prefrontal cortex in incubation of cocaine craving. *Neuropharmacology* (in press).
Le Foll B, Diaz J, Sokoloff P (2005). A single cocaine exposure increases BDNF and D3 receptor expression: implications for drug-conditioning. *NeuroReport* **16**: 175–178.
Lee JL, Milton AL, Everitt BJ (2006). Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. *J Neurosci* **26**: 5881–5887.
Lippman J, Dunaevsky A (2005). Dendritic spine morphogenesis and plasticity. *J Neurobiol* **64**: 47–57.
Lisman J (2003). Actin's actions in LTP-induced synapse growth. *Neuron* **38**: 361–362.
Liu QR, Lu L, Zhu XG, Gong JP, Shaham Y, Uhl GR (2006). Rodent BDNF genes, novel promoters, novel splice variants, and regulation by cocaine. *Brain Res* **1067**: 1–12.
Liu QS, Pu L, Poo MM (2005). Repeated cocaine exposure *in vivo* facilitates LTP induction in midbrain dopamine neurons. *Nature* **437**: 1027–1031.
Lu L, Dempsey J, Liu SY, Bossert JM, Shaham Y (2004a). A single infusion of brain-derived neurotrophic factor into the ventral tegmental area induces long-lasting potentiation of cocaine seeking after withdrawal. *J Neurosci* **24**: 1604–1611.
Lu L, Grimm JW, Dempsey J, Shaham Y (2004b). Cocaine seeking over extended withdrawal periods in rats: different time courses of responding induced by cocaine cues versus cocaine priming over the first 6 months. *Psychopharmacology* **176**: 101–108.
Lu L, Grimm JW, Hope BT, Shaham Y (2004c). Incubation of cocaine craving after withdrawal: a review of preclinical data. *Neuropharmacology* **47** (Suppl 1): 214–226.
Lu L, Grimm JW, Shaham Y, Hope BT (2003). Molecular neuroadaptations in the accumbens and ventral tegmental area during the first 90 days of forced abstinence from cocaine self-administration in rats. *J Neurochem* **85**: 1604–1613.
Lu L, Hope BT, Dempsey J, Liu SY, Bossert JM, Shaham Y (2005). Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. *Nat Neurosci* **8**: 212–219.
Lu L, Koya E, Zhai H, Hope BT, Shaham Y (2006). Role of ERK in cocaine addiction. *Trends Neurosci* **29**: 695–703.
Lu L, Uejima JL, Gray SM, Bossert JM, Shaham Y (2007). Systemic and central amygdala injections of the mGluR(2/3) agonist LY379268 attenuate the expression of incubation of cocaine craving. *Biol Psychiatry* **61**: 591–598.
Malenka RC, Bear MF (2004). LTP and LTD: an embarrassment of riches. *Neuron* **44**: 5–21.
Malinow R, Malenka RC (2002). AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* **25**: 103–126.

Martin M, Chen BT, Hopf FW, Bowers MS, Bonci A (2006). Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nat Neurosci* **9**: 868–869.

Martin-Iverson MT, Todd KG, Altar CA (1994). Brain-derived neurotrophic factor and neurotrophin-3 activate striatal dopamine and serotonin metabolism and related behaviors: interactions with amphetamine. *J Neurosci* **14**: 1262–1670.

Mattson BJ, Bossert JM, Simmons DE, Nozaki N, Nagarkar D, Kreuter JD *et al.* (2005). Cocaine-induced CREB phosphorylation in nucleus accumbens of cocaine-sensitized rats is enabled by enhanced activation of extracellular signal-related kinase, but not protein kinase A. *J Neurochem* **95**: 1481–1494.

McFarland K, Davidge SB, Lapish CC, Kalivas PW (2004). Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* **24**: 1551–1560.

McFarland K, Kalivas PW (2001). The circuitry mediating cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* **21**: 8655–8663.

McFarland K, Lapish CC, Kalivas PW (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* **23**: 3531–3537.

McKee BL, Meshul CK (2005). Time-dependent changes in extracellular glutamate in the rat dorsolateral striatum following a single cocaine injection. *Neuroscience* **133**: 605–613.

Mead AN, Brown G, Le Merrer J, Stephens DN (2005). Effects of deletion of gria1 or gria2 genes encoding glutamatergic AMPA-receptor subunits on place preference conditioning in mice. *Psychopharmacology (Berl)* **179**: 164–171.

Mead AN, Zamanillo D, Becker N, Stephens DN (2007). AMPA-receptor GluR1 subunits are involved in the control over behavior by cocaine-paired cues. *Neuropsychopharmacology* **32**: 343–353.

Mendelson JH, Mello NK (1996). Management of cocaine abuse and dependence. *N Engl J Med* **334**: 965–972.

Meredith GE, Callen S, Scheuer DA (2002). Brain-derived neurotrophic factor expression is increased in the rat amygdala, piriform cortex and hypothalamus following repeated amphetamine administration. *Brain Res* **949**: 218–227.

Miller CA, Marshall JF (2005). Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* **47**: 873–884.

Moghaddam B, Bolinao ML (1994). Glutamatergic antagonists attenuate ability of dopamine uptake blockers to increase extracellular levels of dopamine: implications for tonic influence of glutamate on dopamine release. *Synapse* **18**: 337–342.

Neisewander JL, Baker DA, Fuchs RA, Tran-Nguyen LT, Palmer A, Marshall JF (2000). Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. *J Neurosci* **20**: 798–805.

Nestler EJ (2002). Common molecular and cellular substrates of addiction and memory. *Neurobiol Learn Mem* **78**: 637–647.

O'Brien CP (2005). Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry* **162**: 1423–1431.

O'Donnell P, Grace AA (1995). Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J Neurosci* **15**: 3622–3639.

Pap A, Bradberry CW (1995). Excitatory amino acid antagonists attenuate the effects of cocaine on extracellular dopamine in the nucleus accumbens. *J Pharmacol Exp Ther* **274**: 127–133.

Park WK, Bari AA, Jey AR, Anderson SM, Spealman RD, Rowlett JK *et al.* (2002). 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.

Peters J, Kalivas PW (2006). The group II metabotropic glutamate receptor agonist, LY379268, inhibits both cocaine- and food-seeking behavior in rats. *Psychopharmacology (Berl)* **186**: 143–149.

Pierce RC, Bari AA (2001). The role of neurotrophic factors in psychostimulant-induced behavioral and neuronal plasticity. *Rev Neurosci* **12**: 95–110.

Pierce RC, Bell K, Duffy P, Kalivas PW (1996a). Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci* **16**: 1550–1560.

Pierce RC, Born B, Adams M, Kalivas PW (1996b). Repeated intral-ventral tegmental area administration of SKF-38393 induces behavioral and neurochemical sensitization to a subsequent cocaine challenge. *J Pharmacol Exp Ther* **278**: 384–392.

Pierce RC, Kumaresan V (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? *Neurosci Biobehav Rev* **30**: 215–238.

Pierce RC, Pierce-Bancroft AF, Prasad BM (1999). Neurotrophin-3 contributes to the initiation of behavioral sensitization to cocaine by activating the Ras/Mitogen-activated protein kinase signal transduction cascade. *J Neurosci* **19**: 8685–8995.

Poo MM (2001). Neurotrophins as synaptic modulators. *Nat Rev Neurosci* **2**: 24–32.

Post RM, Kopanda RT (1976). Cocaine, kindling, and psychosis. *Am J Psychiatry* **133**: 627–634.

Post RM, Rose H (1976). Increasing effects of repetitive cocaine administration in the rat. *Nature* **260**: 731–732.

Pu L, Liu QS, Poo MM (2006). BDNF-dependent synaptic sensitization in midbrain dopamine neurons after cocaine withdrawal. *Nat Neurosci* **9**: 605–607.

Qin Y, Zhu Y, Baumgart JP, Stornetta RL, Seidenman K, Mack V *et al.* (2005). State-dependent Ras signaling and AMPA receptor trafficking. *Genes Dev* **19**: 2000–2015.

Radwanska K, Valjent E, Trzaskos J, Caboche J, Kaczmarek L (2006). Regulation of cocaine-induced activator protein 1 transcription factors by the extracellular signal-regulated kinase pathway. *Neuroscience* **137**: 253–264.

Richardson NR, Roberts DC (1996). Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. *J Neurosci Methods* **66**: 1–11.

Robbins TW (1975). The potentiation of conditioned reinforcement by psychomotor stimulant drugs: a test of Hill's hypothesis. *Psychopharmacologia* **45**: 103–114.

Robinson TE, Kolb B (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* **47** (Suppl 1): 33–46.

Russo SJ, Bolanos CA, Theobald DE, DeCarolis NA, Renthal W, Kumar A *et al.* (2007). IRS2-Akt pathway in midbrain dopamine neurons regulates behavioral and cellular responses to opiates. *Nat Neurosci* **10**: 93–99.

Saal D, Dong Y, Bonci A, Malenka RC (2003). Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* **37**: 577–582.

Schenk S, Snow S (1994). Sensitization to cocaine's motor activating properties produced by electrical kindling of the medial prefrontal cortex but not of the hippocampus. *Brain Res* **659**: 17–22.

Schoenbaum G, Shaham Y (2008). The role of orbitofrontal cortex in drug addiction: a review of preclinical studies. *Biol Psychiatry* **63**: 256–262.

Schoenbaum G, Stalnaker TA, Shaham Y (2007). A role for BDNF in cocaine reward and relapse. *Nat Neurosci* **10**: 935–936.

Schramm-Sapyta NL, Olsen CM, Winder DG (2006). Cocaine self-administration reduces excitatory responses in the mouse nucleus accumbens shell. *Neuropsychopharmacology* **31**: 1444–1451.

Schuster CR, Thompson T (1969). Self administration of and behavioral dependence on drugs. *Annu Rev Pharmacol* **9**: 483–502.

Seroogy KB, Lundgren KH, Tran TM, Guthrie KM, Isackson PJ, Gall CM (1994). Dopaminergic neurons in rat ventral midbrain express brain-derived neurotrophic factor and neurotrophin-3 mRNAs. *J Comp Neurol* **342**: 321–334.

Shaham Y, Hope BT (2005). The role of neuroadaptations in relapse to drug seeking. *Nat Neurosci* **8**: 1437–1439.

Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* **168**: 3–20.

Shalev U, Grimm JW, Shaham Y (2002). Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol Rev* **54**: 1–42.

Shen F, Meredith GE, Napier TC (2006). Amphetamine-induced place preference and conditioned motor sensitization requires activation of tyrosine kinase receptors in the hippocampus. *J Neurosci* **26**: 11041–11051.

Squire LR (1987). *Memory and Brain*. Oxford University Press: New York.

Stewart J (1984). Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. *Pharmacol Biochem Behav* **20**: 917–923.

Stewart J, De Wit H (1987). Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth MA (ed). *Methods of Assessing the Reinforcing Properties of Abused Drugs*. Springer-Verlag: New York. pp 211–227.

Sun W, Akins CK, Mattingly AE, Rebec GV (2005). Ionotropic glutamate receptors in the ventral tegmental area regulate cocaine-seeking behavior in rats. *Neuropsychopharmacology* **30**: 2073–2081.

Suto N, Tanabe LM, Austin JD, Creekmore E, Pham CT, Vezina P (2004). Previous exposure to psychostimulants enhances the reinstatement of cocaine seeking by nucleus accumbens AMPA. *Neuropsychopharmacology* **29**: 2149–2159.

Suto N, Tanabe LM, Austin JD, Creekmore E, Vezina P (2003). Previous exposure to VTA amphetamine enhances cocaine self-administration under a progressive ratio schedule in an NMDA, AMPA/kainate, and metabotropic glutamate receptor-dependent manner. *Neuropsychopharmacology* **28**: 629–639.

Sweatt JD (2001). The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memory. *J Neurochem* **76**: 1–10.

Tang W, Wesley M, Freeman WM, Liang B, Hemby SE (2004). Alterations in ionotropic glutamate receptor subunits during binge cocaine self-administration and withdrawal in rats. *J Neurochem* **89**: 1021–1033.

Taylor JR, Robbins TW (1984). Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. *Psychopharmacology* **84**: 405–412.

Thoenen H (1995). Neurotrophins and neuronal plasticity. *Science* **270**: 593–598.

Thomas MJ, Beurrier C, Bonci A, Malenka RC (2001). Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci* **4**: 1217–1223.

Thomas MJ, Malenka RC (2003). Synaptic plasticity in the mesolimbic dopamine system. *Philos Trans R Soc Lond B Biol Sci* **358**: 815–819.

Toda S, Shen HW, Peters J, Cagle S, Kalivas PW (2006). Cocaine increases actin cycling: effects in the reinstatement model of drug seeking. *J Neurosci* **26**: 1579–1587.

Turrigiano GG, Nelson SB (2004). Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci* **5**: 97–107.

Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD (2002). From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learn Mem* **9**: 224–237.

Ungless MA, Whistler JL, Malenka RC, Bonci A (2001). Single cocaine exposure *in vivo* induces long-term potentiation in dopamine neurons. *Nature* **411**: 583–587.

Valjent E, Corbille AG, Bertran-Gonzalez J, Herve D, Girault JA (2006a). Inhibition of ERK pathway or protein synthesis during reexposure to drugs of abuse erases previously learned place preference. *Proc Natl Acad Sci USA* **103**: 2932–2937.

Valjent E, Corvol JC, Pages C, Besson MJ, Maldonado R, Caboche J (2000). Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. *J Neurosci* **20**: 8701–8709.

Valjent E, Corvol JC, Trzaskos JM, Girault JA, Herve D (2006b). Role of the ERK pathway in psychostimulant-induced locomotor sensitization. *BMC Neurosci* **7**: 1–11.

Van der Kooy D (1987). Place conditioning: a simple and effective method for assessing the motivational properties of drugs. In: Bozarth MA (ed). *Methods of Assessing the Reinforcing Properties of Abused Drugs*. Springer-Verlag: New York. pp 229–240.

Vanderschuren LJ, Everitt BJ (2004). Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* **305**: 1017–1019.

Vanderschuren LJ, Kalivas PW (2000). Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology* **151**: 99–120.

Vezina P (1993). Amphetamine injected into the ventral tegmental area sensitizes the nucleus accumbens dopaminergic responses to systemic amphetamine: an *in vivo* microdialysis study in the rat. *Brain Res* **605**: 332–337.

Vezina P (1996). D_1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. *J Neurosci* **16**: 2411–2420.

Vezina P (2004). Sensitization of midbrain dopamine neuron reactivity and the self-administration of psychostimulant drugs. *Neurosci Biobehav Rev* **27**: 827–839.

Volkow ND, Fowler JS (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* **10**: 318–325.

Wang B, Shaham Y, Zitzman D, Azari S, Wise RA, You ZB (2005). Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. *J Neurosci* **25**: 5389–5396.

White FJ, Hu XT, Zhang XF, Wolf ME (1995). Repeated administration of cocaine or amphetamine alters neuronal responses to glutamate in the mesoaccumbens dopamine system. *J Pharmacol Exp Ther* **273**: 445–454.

White NM (1996). Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* **91**: 921–949; discussion 951–965.

Wise RA (2004). Dopamine, learning and motivation. *Nat Rev Neurosci* **5**: 483–494.

Wolf ME (1998). The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Prog Neurobiol* **54**: 679–720.

Wolf ME, Sun X, Mangiavacchi S, Chao SZ (2004). Psychomotor stimulants and neuronal plasticity. *Neuropharmacology* **47** (Suppl 1): 61–79.

Wolffgramm J, Heyne A (1995). From controlled drug intake to loss of control: the irreversible development of drug addiction in the rat. *Behav Brain Res* **70**: 77–94.

Wu GY, Deisseroth K, Tsien RW (2001). Spaced stimuli stabilize MAPK pathway activation and its effects on dendritic morphology. *Nat Neurosci* **4**: 151–158.

Yao WD, Gainetdinov RR, Arbuckle MI, Sotnikova TD, Cyr M, Beaulieu JM *et al.* (2004). Identification of PSD-95 as a regulator of dopamine-mediated synaptic and behavioral plasticity. *Neuron* **41**: 625–638.

Yokel RA (1987). Intravenous self-administration: response rates, the effects of pharmacological challenges, and drug preference. In: Bozarth MA (ed). *Methods of Assessing the Reinforcing Properties of Abused Drugs*. Springer-Verlag: New York. pp 1–34.

Yuan LL, Adams JP, Swank M, Sweatt JD, Johnston D (2002). Protein kinase modulation of dendritic K^+ channels in hippocampus involves a mitogen-activated protein kinase pathway. *J Neurosci* **22**: 4860–4868.

Zhai H, Li Y, Wang X, Lu L (2008). Drug-induced alterations in the extracellular signal-regulated kinase (ERK) signalling pathway: implications for reinforcement and reinstatement. *Cell Mol Neurobiol* **28**: 157–172.

Zhang D, Zhang L, Lou DW, Nakabeppu Y, Zhang J, Xu M (2002a). The dopamine D1 receptor is a critical mediator for cocaine-induced gene expression. *J Neurochem* **82**: 1453–1464.

Zhang XF, Cooper DC, White FJ (2002b). Repeated cocaine treatment decreases whole-cell calcium current in rat nucleus accumbens neurons. *J Pharmacol Exp Ther* **301**: 1119–1125.

Zhang XF, Hu XT, White FJ (1998). Whole-cell plasticity in cocaine withdrawal: reduced sodium currents in nucleus accumbens neurons. *J Neurosci* **18**: 488–498.