Neurobiology of craving, conditioned reward and relapse
Friedbert Weiss

Chronic vulnerability to relapse is a formidable challenge for the treatment of drug addiction. The neurobiological basis of relapse and its prevention has, therefore, attracted major attention in addiction research. Current conceptualizations of addiction recognize craving as a central driving force for ongoing drug use, as well as for relapse following abstinence. Progress has been made in understanding experiential factors, neurocircuitry components and signaling mechanisms that mediate conditioned drug-seeking behaviour, craving and long-lasting susceptibility to relapse. Importantly, stress contributes to drug craving, and there is evidence for overlap between the neural and neuroendocrine mechanisms implicated in drug desire evoked by drug cues and stress. Recent research has substantially advanced our understanding of the neurobiological factors responsible for drug craving and relapse, with promising therapeutic implications.

Addresses
The Scripps Research Institute, Department of Neuropharmacology (CVN-15), 10550 North Torrey Pines Road, La Jolla, CA 92037, USA
Corresponding author: Weiss, F (bweiss@scripps.edu)

Current Opinion in Pharmacology 2005, 5:9–19
This review comes from a themed issue on Neurosciences
Edited by Graeme Henderson, Hilary Little and Jenny Morton
Available online 21st December 2004
1471-4892/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
DOI 10.1016/j.coph.2004.11.001

Abbreviations
BDNF brain-derived neurotrophic factor
BLA basolateral amygdala
CRF corticotropin-releasing factor
CS conditioned stimuli
HPA hypothalamic-pituitary-adrenal
LH lateral hypothalamus
MAPK mitogen-activated protein kinase
mGluR metabotropic glutamate receptor
NAC nucleus accumbens
N/OFQ nociceptin/ orphanin FQ
OFC orbitofrontal cortex
PFC prefrontal cortex
PLC prelimbic cortex
VTA ventral tegmental area

Introduction
Relapse is a phenomenon pivotal for the understanding and treatment of drug addiction. The focus of addiction research has, therefore, shifted towards identifying the experiential and neurobiological mechanisms responsible for the chronically relapsing nature of addiction. Major precipitating factors for relapse include drug craving and stress [1,2], with an increasing recognition of cognitive factors such as pre-attentive automatic reactions, and attentional bias related to previous drug experiences [3,4,5]. These risk factors are further aggravated by protracted withdrawal symptoms resulting from drug-induced neuroadaptation, but also by conditions such as psychiatric comorbidity, socioeconomic conditions and perceived drug availability [1,6,7].

Here, recent advances in both the neurocircuitry and the neurochemical and molecular bases of craving and relapse are reviewed, with emphasis on two fundamental questions: firstly, what factors are responsible for the distinctly compulsive nature of drug-seeking and craving, as opposed to behaviour motivated by natural rewards essential for survival and well-being; and secondly, what long-term changes develop in the brain during chronic drug use that maintain craving and relapse risk through years of abstinence and rapidly re-establish full-blown dependence after resumption of drug use? This review focuses predominantly on cocaine and ethanol as examples.

Associative learning as a factor in craving and relapse
Critical for craving and relapse is the process of associative learning, whereby environmental stimuli repeatedly paired with drug consumption acquire incentive-motivational value, evoking expectation of drug availability and memories of past drug euphoria [8–10]. Conditioned responses to such stimuli can activate brain reward mechanisms [11] and have been implicated both in maintaining ongoing drug use and in eliciting drug desire during abstinence, precipitating relapse. The definition of craving and its measurement, as well as the predictive link between craving and relapse, is still a matter of some debate [12,13,14]. Moreover, as a hypothetical construct, craving is difficult to model with functional equivalence in animals [14]. However, reactivity to drug cues has established significance for craving in clinical settings. These conditioned responses represent a mechanism leading to craving, and can therefore be exploited to study this specific aspect of craving in animals [8].

Functional brain imaging in humans ([15–17]; see review by Lingford-Hughes, this issue) as well as lesion and site-specific pharmacological manipulations in animals [9,10,18] have implicated an interconnected set of cortical
and limbic brain regions in associative learning underlying craving and relapse (see Table 1). Major components of this circuitry include the orbitofrontal cortex (OFC), anterior cingulate, prelimbic cortex (PLC), basolateral amygdala (BLA), hippocampus, nucleus accumbens (NAc) and, more recently, the dorsal striatum, which is thought to participate in consolidating stimulus-response habits via the engagement of corticostriatal loops [10].

Substantial advances have been made in elucidating key components and signaling mechanisms within this circuitry that regulate specific aspects of drug-seeking using animal models of conditioned reinforcement and conditioned reinstatement (see Boxes 1–3). The NAc, a functionally heterogeneous structure consisting of core and shell subregions (for review, see [23]), has long been considered critical for drug-seeking and reinforcement. Existing evidence favours a differential role for these subregions in reinstatement and second-order schedule performance maintained by discrete conditioned stimuli (CS) versus reinstatement elicited by contextual stimuli. Selective inactivation of the NAc core, but not shell, abolished cocaine CS-induced reinstatement [24*], and blockade of glutamate receptors in the NAc core eliminated conditioned reinforcement by cocaine CS on a second order schedule [25**]. Moreover, functional integrity of the core is required for the acquisition of conditioned cocaine reinforcement, whereas the shell appears essential for the psychomotor stimulant effects of cocaine [26**]. Furthermore, the glutamatergic projection from the BLA to the NAc core was found to be critical for the expression of cocaine CS-maintained second order schedule performance [25**,27]. Novel data also implicate the dopaminergic projection from the ventral tegmental area (VTA) to the NAc core in associative processes that influence conditioned responding under second order schedules [28*]; however, in contradiction to the effects of dopamine receptor blockade in the BLA [25**], inactivation of the dopaminergic projection from the VTA to the BLA failed to interfere with the conditioned reinforcing effects of cocaine CS [28*]. Thus, dopaminergic terminals in the NAc core and the BLA might differentially regulate CS-maintained cocaine reinforcement [28*], the behavioural significance of which awaits clarification.

In contrast to CS-maintained conditioned reinforcement and reinstatement, recovery of extinguished drug-seeking by contextual stimuli is dependent upon the NAc shell. During reinstatement evoked by a cocaine-predictive contextual stimulus, neurons in the shell exhibited significantly greater activity than those in the core, the latter responding indiscriminately to the drug cue or neutral stimulus [29*]. Shell neuron responses to the drug cue were still evident after four weeks of abstinence, illustrating that the neural representation of the motivational significance of these stimuli is highly resistant to decay [29*]. Importantly, inactivation of the dorsomedial prefrontal cortex (PFC) and BLA impaired reinstatement by cocaine CS [30,31*], whereas inactivation of the dorsal hippocampus was selective for contextual reinstatement [30]. However, recent data also implicate the BLA in contextual reinstatement [30,32*,33*] through its rostral subdivision [34]. Thus, input from the rostral BLA to the NAc shell is a neural link essential for encoding the motivational value of drug-associated contextual stimuli [29*,35]. Overall, neural substrates for reinstatement associated with contextual and explicit CS overlap, but also show distinct differences.

New understanding has accrued on the function of the OFC and PLC in drug-related learning. The OFC has been found to modulate cocaine-seeking in a subregion-specific manner, with CS-maintained reinstatement controlled by the lateral OFC and drug-induced (i.e. ‘priming’) reinstatement by the medial OFC [31*]. In the PLC, rats expressing conditioned preference for a cocaine-paired environment (i.e. a contextual stimulus) showed increased activation of inhibitory GABAergic interneurons, paired with decreased excitatory output from this site [36]. The decreased activation of excitatory PLC efferents may add to the functional defects in prefrontal cortical regions that develop with chronic cocaine use [37–40]. Considering the ‘executive function’ of the PFC that includes risk-benefit analysis and suppression of limbic impulses, the shift in activation patterns of PLC cell populations could contribute to impaired impulse control, and lack of judgement and risk assessment [41], which are defining features of addiction.

Determinate of craving and relapse as persistent and compulsive phenomena

Clinically, a ‘slip’ into limited drug use is unimportant for ultimate therapeutic success, such that modeling craving and reinstatement alone is not sufficient for investigating the chronic and compulsive nature of addiction [8]. Evidence has accumulated that drug-seeking in animals resembles along several dimensions the compulsive nature of addiction in humans. Reinstatement by drug cues is resistant to extinction and persists over months of abstinence [42*,43,44**]. Even stimuli present during a single cocaine experience elicited drug-seeking for up to one year [45*]. Importantly, the ‘intensity’ of conditioned reinstatement increases during the initial months of abstinence [42*,43,46,47]. The behavioural significance of this ‘incubation’ effect [48] was scrutinized by isolating the respective contribution to reinstatement of simply terminating access to cocaine versus subjecting rats to extinction of cocaine-reinforced responding with, or without, presentation of drug-associated CS. Extinction substantially decreased reinstatement (as measured by CS-maintained responding on a second order schedule)
<table>
<thead>
<tr>
<th>Brain region</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex</td>
<td>Executive and decision-making functions based on the recognition of survival-related challenges, and execution of goal-directed actions.</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>Associative learning linked to rewarding and aversive stimuli. Integration of emotion and natural drive states with behaviour. Assessment of reward value against previous experience influencing action and choice. CS-based reinstatement, Conditioned reinforcement, Stress-induced reinstatement, Cue-induced craving (human functional brain imaging).</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>Processing of pleasure and pain. Attention and cognitively demanding information processing. Conditioned emotional learning, including attribution of emotional and motivational value to internal and external stimuli guiding appropriate response selection. Regulation of autonomic and endocrine function. CS-based reinstatement, Contextual reinstatement, Cue-induced craving (human functional brain imaging).</td>
</tr>
<tr>
<td>Basolateral amygdala</td>
<td>Processing of emotionally significant stimuli guiding conditioned and unconditioned approach or avoidance behaviour. CS-based reinstatement, Contextual reinstatement, Cue-induced craving (human functional brain imaging).</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Limbic-motor interface, integrating converging input from limbic sites related to appetitive and motivational aspects of rewards for output to effector sites, initiating and sustaining behavioural responses. Participation in the translation of motivation into action. NAc core - Conditioned reinforcement, CS-based reinstatement, Contextual reinstatement. NAc shell - Contextual reinstatement, Molecular neuroadaptations following chronic cocaine with implications for craving and relapse, Cue-induced craving (human functional brain imaging).</td>
</tr>
<tr>
<td>Dorsal striatum</td>
<td>Part of the extrapyramidal motor system. Fine-tuning motoric functions. Consolidation of stimulus-response habits via corticostriatal loops. Presumed role in the switch from ‘action to habit’ (i.e. the transition from drug abuse to drug addiction).</td>
</tr>
<tr>
<td>Ventral tegmental area</td>
<td>Origin of the mesocorticolimbic dopamine projection. Site implicated in Group II mGluR-mediated contextual reinstatement. Molecular neuroadaptations following chronic cocaine with implications for craving and relapse.</td>
</tr>
<tr>
<td>Lateral hypothalamus</td>
<td>Regulation of ingestive behaviour. Sensitive site for the rewarding effects of electrical brain stimulation reward and changes in brain reward function as measured by intracranial self-stimulation reward thresholds. Increased in brain reward function by exposure to cocaine cues, Impaired brain reward function associated with escalated cocaine intake, Molecular neuroadaptations linked to escalated cocaine intake.</td>
</tr>
<tr>
<td>Central nucleus of the amygdala</td>
<td>Processing of behavioural and physiological responses to stress. Key component of the extrahypothalamic CRF stress system reciprocally connected to the BNST.</td>
</tr>
<tr>
<td>Bed nucleus of the stria terminalis (BNST)</td>
<td>Final common pathway processing stress and anxiety responses. Key component of the extrahypothalamic stress system. The BNST also projects heavily to the PVN, modulating HPA axis activity. CRF-rich nucleus and ‘apex’ of the HPA stress axis. CRF is the major stress-regulatory molecule in the brain and integrates behavioural, endocrine and autonomic responses to stress. Increase in CRF in the BNST in response to HPA axis activation leads to secretion of CRF, the major stress-regulatory molecule in the brain, and integrates behavioural, endocrine and autonomic responses to stress. Stress-related addictive behaviour is thought to be related to activation of the HPA axis by CRF. Drug cue exposure leads to HPA axis activation correlated with craving in cocaine- or ethanol-addicted individuals, Interference with HPA axis activation prevents cue-induced reinstatement.</td>
</tr>
<tr>
<td>Paraventricular nucleus of the hypothalamus</td>
<td>Release of CRF from PVN neurons projecting to the anterior pituitary results in secretion of ACTH (i.e. activation of the HPA axis) leading to secretion of glucocorticoids, predominantly corticosterone. Stress-related addictive behaviour is thought to be related to activation of the HPA axis by CRF. Drug cue exposure leads to HPA axis activation correlated with craving in cocaine- or ethanol-addicted individuals, Interference with HPA axis activation prevents cue-induced reinstatement.</td>
</tr>
<tr>
<td>Hypothalamic-pituitary-adrenal axis</td>
<td>Release of CRF from PVN neurons projecting to the anterior pituitary results in secretion of ACTH (i.e. activation of the HPA axis) leading to secretion of glucocorticoids, predominantly corticosterone. Stress-related addictive behaviour is thought to be related to activation of the HPA axis by CRF. Drug cue exposure leads to HPA axis activation correlated with craving in cocaine- or ethanol-addicted individuals, Interference with HPA axis activation prevents cue-induced reinstatement.</td>
</tr>
</tbody>
</table>
cessation of drug use might therefore be an important factor in determining the efficacy of cue extinction compared with one week of abstinence alone. However, after four weeks of abstinence, CS-maintained responding in the extinguished group was increased (i.e. showed ‘incubation’), and was identical to rats not subjected to extinction [46]. Consequently, eliminating drug availability following extinction might, with time, augment the efficacy of drug cues to facilitate reinstatement, diminishing the effects of extinction. The time since cessation of drug use might therefore be an important factor in determining the efficacy of cue extinction therapies. Drug-seeking in animals is also consistent with defining features of addiction other than persistence. Rats with a history of prolonged, but not limited, cocaine self-administration failed to show suppression of CS-maintained drug-seeking when concurrently presented with a conditioned stressor [44**,49**], in contrast with the well-established inhibition of appetitive behaviour by aversive stimuli (‘conditioned suppression’). Thus, drug-related cues in rats having experienced prolonged cocaine exposure sustain drug-directed behaviour despite adverse consequences, one of the hallmarks of substance dependence. Rats prone to ‘addiction’ on one index of vulnerability (cocaine ‘priming’) also proved more susceptible to other addiction-like behaviours, including escalation of cocaine intake, conditioned reinstatement and maintenance of cocaine-seeking despite increased work requirements [44**]. Thus, the inflexible dimension that characterizes addiction can readily be demonstrated in animals but requires prolonged drug access, confirming original findings that such exposure regimens are critical for the transition from drug use to dependence [50].

An important experiential factor (i.e. one related to personal experience) for the development of compulsive drug-seeking is that consumption of a drug during withdrawal, an event inextricably linked to addiction,
introduces learning about a previously latent incentive dimension of the drug — its capacity is to alleviate physically or emotionally adverse states. This experience can enhance the incentive value of the drug and, therefore, its reinforcing efficacy particularly during subsequent withdrawal states. Sound support for this hypothesis exists in animals [51]. This mechanism might also be relevant for cue-induced craving and relapse, considering that drug consumption during withdrawal is likely to increase not only the incentive value of the drug but also the conditioned incentive value of drug-related stimuli. Indeed, ethanol-dependent rats allowed to self-administer alcohol during withdrawal, and presented with ethanol CS three weeks after withdrawal [52], showed greater conditioned reinstatement, whereas this was not the case in dependent rats not having experienced ethanol during withdrawal [53,54]. The enhanced incentive value of drugs and associated environmental stimuli through withdrawal-related learning could generalize to other states of aversion and negative affect, because not only the ethanol CS but also footshock and a conditioned stressor exacerbated reinstatement in rats having consumed ethanol while in withdrawal, but not in rats without this drug history [52,55]. Such generalizations would dramatically contribute to the compulsive nature of drug addiction.

**Craving and ‘seeking-behaviour’ associated with drug versus natural rewards**

To understand drug compulsion, we must recognize differences that exist between the stimulus control of behaviour motivated by natural versus drug rewards (see chapter by Salamone et al., this issue). Prolonged exposure to cocaine, but not sucrose, eliminated conditioned suppression of ‘reward-seeking’ by a footshock-predictive cue, suggesting that the nature of the reward (drug versus natural) determines whether compulsive behaviour resistant to adverse environmental events develops [44*,49*]. Cocaine-associated contextual stimuli elicited reinstatement for one year, whereas the same stimuli paired with a palatable sweet solution remained effective for only three months [45*]. Conversely, incubation of CS-induced reinstatement developed with stimuli conditioned to either cocaine or sucrose [42*,47]. Thus, time-dependent variations in CS-induced reinstatement of reward-seeking might be common to drug and natural rewards but, by extrapolation from data above [46], could be driven by ‘incubation’ of ‘spontaneous recovery’ as an underlying process. Further understanding of the mechanisms contributing to the differential control of ‘normal’ appetitive versus compulsive drug-seeking behaviour might be gleaned from selective effects of pharmacological manipulations. A group II metabotropic glutamate receptor (mGluR) agonist and nociceptin/orphanin FQ (N/OFQ), a member of the opioid peptide family, reversed conditioned reinstatement by ethanol- or cocaine-associated contextual cues, without altering appetitive behaviour motivated by palatable sweet solutions [56*,57*].

**Neurobiological basis of long-lasting susceptibility to relapse**

Central to the understanding and treatment of craving and relapse are cellular and molecular neuroadaptations that mediate enduring associations between drugs and associated stimuli. Increased expression of brain-derived neurotrophic factor (BDNF) is a probable mechanism for the ‘incubation’ of conditioned reinstatement [42*], a hypothesis supported by long-lasting potentiation of reinstatement following intra-VTA application of BDNF [58*]. The role of BDNF in reinstatement appears to depend critically upon recruitment of mitogen-activated protein kinase (MAPK) signal transduction [58*], a pathway involved in long-term potentiation and synaptic plasticity, processes that have been implicated in development of addiction [59,60]. Withdrawal from prolonged cocaine self-administration is also associated with lasting increases in glutamate N-methyl-D-aspartate receptor 1 and GluR2 receptor subunits in the NAc and VTA, as well as transient elevation of cyclin-dependent protein kinase 5 in the VTA [61]. Increased BDNF expression initiates a plethora of signaling cascades with implications for addiction (for review, see [62*]), including changes in synaptic strength, neural signaling and dendrite formation. Repeated cocaine increases dendritic sprouting in the NAC, PFC and caudate-putamen that persists for months [63–65] — structural changes with a presumptive role in sensitization and the persistence of craving and relapse risk. The activation of cyclin-dependent protein kinase 5, also linked to proliferation of BNDF expression [61]. Increased BNDF expression shows significant elevation in the PFC and NAc after only one week of cocaine exposure, and was still evident after two months of abstinence [69]. Although a behavioural function for these neuroadaptations in two other regulatory systems are also of interest. The first — cocaine-induced alteration in cystine-glutamate exchange in the NAc — regulates basal extracellular glutamate levels, resulting in reduced levels of this amino acid during cocaine withdrawal, an effect implicated in susceptibility to relapse [68]. The second — upregulation of an activator of G protein signaling — showed significant elevation in the PFC and NAc after only one week of cocaine exposure, and was still evident after two months of abstinence [69].
targets to explore with respect to a role in cue-elicited craving and relapse.

Finally, an emerging neuropharmacological mechanism in craving and relapse is the endocannabinoid system that functionally interacts with numerous other brain neurotransmitter systems with established roles in drug-seeking and addiction [70]. The endocannabinoid system has been implicated in opiate, cocaine and alcohol addiction [71,72]. More importantly, pharmacological manipulation of this system modifies both heroin reinforcement and conditioned reinstatement [73].

Different neurocircuits for drug versus natural reward?
Conditioned responses, whether motivated by drugs of abuse or natural rewards, are thought to be processed via the same neurocircuitry [18,74,75]. It is unclear, however, what differentiates neural signaling regulating normal appetitive behaviour versus pathological behaviour resulting from drug-related conditioning. NAc neurons, activated during cocaine-reinforced responding, were also responsive to cocaine CS, whereas cell populations activated only by water reinforcement were not (reviewed in [76]). Positron emission tomography imaging data of craving in heroin addicts indicate that both drug and non-drug stimuli activate brain attentional and memory circuits (primarily the anterior cingulate and OFC) but with stronger effects evoked by drug cues [77**]. Brain regions activated by drug cues, therefore, might not be specific to addiction-related events but components of ‘normal’ circuits activated to a greater degree, and may reflect either the creation of new motivational states such as those produced by withdrawal-related learning [74] or the tilting of processes that normally govern responding for natural rewards towards drug-directed behaviour. Differential activation of BDNF-induced signaling might be a contributory factor, as increased BDNF expression is linked to incubation of conditioned cocaine- but not sucrose-seeking behaviour [42*].

Dysregulation of hedonic homeostasis
A widely held position in addiction theory views craving and relapse as an opponent motivational process to avoid negative affect (e.g. dysphoria, anhedonia and anxiety), which is a consequence of withdrawal from most drugs of abuse. The most recent conceptualization of this process focuses on the development of allostasis, defined as a state of progressive deviation of motivational regulatory systems by chronic drug use from their normal function, with the establishment of a new hedonic set point (for review, see [50,78]). Novel evidence shows that increased cocaine intake (‘escalation’) that develops with prolonged drug exposure [50] leads to long-lasting counteradaptive deficits in brain reward function which reduce the hedonic impact of cocaine [79]. Allostasis has also been linked to dysregulation in molecular signaling systems. Transcriptional profiling by DNA microarray revealed that escalated cocaine intake is associated with alterations in transcripts relevant for neurite extension and synaptogenesis, cell adhesion and nerve regeneration, as well as for neuronal excitability and glutamate transmission (cited as unpublished in [50]). Increases in ionotropic and mGluR subunits during withdrawal support such changes in glutamate transmission during prolonged cocaine exposure [80]. Interestingly, gene transcript changes in cocaine ‘escalated’ rats were confined largely to the lateral hypothalamus (LH); therefore, synaptic rearrangement and altered neural excitability in the LH could play a role in compulsive cocaine-seeking [50] (for related discussion, see [81]).

Stress as a source of craving
Stress, although complex and influenced by multiple factors, has an established role in relapse [2]. Footshock (as a model of stress) reinstates extinguished responding previously maintained by drugs of abuse. Several theoretical views exist on the motivational mechanisms by which stress provokes relapse as discussed in several excellent reviews [82,83,84**]. Of interest here is the growing evidence that drug cue and stress manipulations induce a similar pattern of craving and cue reactivity, including comparable increases in negative affect and anxiety [85,86**, findings that support the allostatic view of addiction. Exposure to drug cues in cocaine-dependent subjects produced increases in both craving and corticosterone synthesis inhibition and blockade of CRF₁ receptors in rats attenuated cocaine CS-induced reinstatement (i.e. a measure of ‘craving’), indicative of a role for stress (i.e. HPA axis activation) in the response-reinstating actions of drug cues [22]. These observations implicate overlap between neural substrates controlling craving evoked by drug cues and stress. Stress, via HPA axis activation, increases mesocorticolimbic dopamine transmission. Both aversive and appetitive events are processed by interactions among limbic subcortical and prefrontal cortical regions, including the BLA and OFC, with ultimate effects on extrahypothalamic and neuroendocrine stress responses through direct and indirect connections with the bed nucleus of the stria terminalis, central nucleus of the amygdala, and hypothalamic paraventricular nucleus (reviewed in [2]). Thus, activation of both brain motivational circuits and stress-regulatory systems by drug cues and stress implicates common neural substrates through which these challenges enhance drug-seeking. Transient lesion and site-specific pharmacological manipulation of PFC regions have implicated the PLC and OFC as components of a circuitry mediating footshock-induced drug-seeking, with the PLC representing a possible common pathway for stress-, cue- and drug-induced reinstatement [87*]. Lastly, evidence for overlap between the neural substrates mediating stress...
and drug cue effects exists also at the pharmacological level. Several agents that attenuate conditioned reinstatement [56*,57*] also have marked ‘anti-stress’ and anxiolytic profiles. These include Group II mGluR agonists [88–90] and N/OFQ, which exerts strong CRF antagonist actions in the bed nucleus of the stria terminalis [91].

Interactions among risk factors for craving and relapse

Although craving and stress are undoubtedly important for relapse, a predictive relationship between subjective reports of stress or craving and subsequent drug use is a matter of some dispute [2,12,13,14**]. Risk factors for relapse are typically studied in isolation, whereas abstinent drug users are frequently exposed to multiple external risk factors, while experiencing varying degrees of protracted withdrawal symptoms. Of relevance for this issue, reinstatement of alcohol-seeking was found markedly enhanced when rats were subjected to footshock stress before response-contingent exposure to ethanol CS [52,55]. Both the individual and interactive effects of stress and the ethanol cue were greatly augmented in previously ethanol-dependent rats tested three weeks after withdrawal, a time when behaviourally relevant neuroadaptive changes in CRF and endogenous opioid function are present [54,92]. It is therefore likely that the probability of relapse varies as a function of the number and intensity of risk factors operative at any given time, with relapse occurring when the sum of these motivating forces reaches a critical threshold. Systematic investigation of such interactions could substantially advance current understanding of the relapse process.

Conclusions

The past three years have seen major advances in understanding of the experiential and neurobiological basis of craving and vulnerability to relapse. Behaviourally, prolonged exposure to drugs of abuse in animals has consequences consistent with defining features of substance dependence in humans, providing crucial support for the utility of animal models as tools for investigating the neural basis of specific aspects of addiction. In particular, drug-related environmental stimuli, once conditioned to drug-taking experiences, acquire the ability to elicit craving and precipitate relapse in a manner that is resistant to extinction, impervious to punishment, and increases in strength over prolonged abstinence. Novel data indicate strong overlap between neural substrates controlling drug desire evoked by drug cues and stress, the latter emerging as an important factor in drug craving. Neuroadaptations previously implicated in addiction using forced drug administration regimens have been verified and extended in animals voluntarily self-administering drugs of abuse with findings of persistent perturbations in BDNF and its signaling cascades, as well as in glutamate receptor subunits and gene transcripts linked to regulation of excitatory neurotransmission. Data supporting the ‘allostatic’ view of craving and relapse show that repeated withdrawal from escalated cocaine intake leads to long-lasting deficits in brain reward function, possibly involving synaptic rearrangement and altered neural excitability in the LH.

Clearly, major gaps remain in our knowledge of the control of craving and relapse. For example, only the time profile of BDNF corresponded well with incubation of drug-seeking. The role of other molecular signaling mechanisms, both in incubation and vulnerability to relapse in general, remains to be established. Similarly, the presumptive role of the LH in the consequences of escalated drug intake will require demonstration of a link between gene expression changes and ‘allostic load’. The selective reversal of conditioned reinstatement by a Group II mGluR agonist (see also Update) and by N/OFQ warrants acceleration of research devoted to these systems, both with regard to a mechanistic role in addiction and as drug targets for relapse prevention. Furthermore, the important function postulated for the dorsal striatum in consolidating addiction-related stimulus-response habits would benefit from confirmation as to whether this role applies specifically to ongoing drug-seeking maintained by conditioned reinforcers or also to relapse. This question is important because inactivation of the dorsolateral striatum failed to interfere with conditioned reinstatement of cocaine-seeking following extinction and abstinence [93]. Lastly, investigation of how interactions among risk factors exacerbate the likelihood of resumption of drug use could substantially advance our current understanding of the relapse process.

Update

Recent work has confirmed that Group II mGluR activation by the mGlu2/3 agonist LY379268 attenuates context-induced reinstatement of heroin-seeking [94]. Moreover, these authors have identified Group II mGluR-mediated glutamate translocation in the VTA as important in contextual heroin reinstatement. Importantly, these results also verified the selectivity of Group II mGluR activation for drug-seeking behavior, as LY379268 had no effect on responding for oral sucrose.

Acknowledgements

The author acknowledges National Institutes of Health funding through National Institute on Drug Abuse grants DA07348, DA08467 and DA017097; National Institute on Alcohol Abuse and Alcoholism (NIAAA) grants AA10531 and AA014351; and a component of NIAAA Alcohol Research Center grant AA06420. The author would like to thank Mike Arends for his editorial assistance.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


An elegant study utilizing a neuropsychopharmacological disconnection procedure to investigate the neural control of conditioned cocaine-seeking on a second order schedule of reinforcement. Unilateral infusion of a dopamine receptor antagonist into the BLA (which on its own had no effect) and concurrent application into the contralateral NAc core of an AMPA-kainate receptor antagonist in the NAc core, but not the BLA, also diminished cocaine seeking. The results identify a BLA-NAc core neural link that regulates stimulus-controlled ongoing cocaine-seeking.


Selective excitotoxic lesion of the NAc core produced only minor impairments in acquisition of cocaine-reinforced responding under a second-order schedule of reinforcement, but profoundly interfered with acquisition of drug-seeking maintained by cocaine-paired conditioned reinforcers under a second-order schedule contingency. By contrast, selective lesion of the NAc shell did not impair cocaine self-administration or acquisition of conditioned cocaine-seeking, but attenuated cocaine's psychomotor stimulant effects.


Transient inactivation of the VTA or NAc core by a baclofen-muscimol mixture decreased conditioned cocaine-seeking. Inactivation of the BLA,
however, had no effect. Although these data further confirm a selective role for the NAc core in conditioned reinforcement, they are somewhat difficult to reconcile with an earlier finding by the same authors [26**] implicating dopaminergic transmission in the BLA as critical in CS-maintained cocaine-seeking.

29. Ghitza UE, Fabbricatore AT, Prokopenko V, Pawlik AP, West MC: Persistent cue-evoked activity of accumbens neurons after prolonged abstinence from self-administered cocaine. J Neurosci 2003, 23:7239-7245. Using single-unit recording in rats, the authors demonstrate that NAc shell neurons participate in the process of discriminating the motivational value of cocaine-predictive versus neutral contextual stimuli, whereas NAc core neurons do not. Importantly, NAc shell neurons process information on reward-related contextual stimuli even after weeks of abstinence.


This research examines the relationship between behavioural incubation of cocaine-seeking and changes in BDNF protein levels in the mesolimbic dopaminergic system. BDNF, but not nerve growth factor, levels in the NAc, amygdala, and VTA increased during cocaine, but not sucrose, withdrawal in parallel with behavioural incubation of cocaine-seeking. The correspondence between the time profiles of incubation of cocaine-seeking and BDNF expression was strongest in the NAc and weakest in the VTA.


A seminal paper reporting that behaviours reflective of three essential diagnostic criteria for addiction in humans can be demonstrated to develop with prolonged cocaine self-administration in rats: drug use despite adverse outcomes, difficulty in limiting drug intake, and preoccupation with procurement and consumption of the drug. This set of behaviors was evident only in a small proportion of rats, with the majority of animals being non-responsive to any of the addiction-like behaviours measured. These findings strikingly resemble human epidemiological data showing that only a small proportion of drug users progress to an addicted state.


This paper presents evidence that contextual stimuli associated with a single life-time cocaine self-administration experience in rats elicit strong drug-seeking that persists for up to one year. By contrast, contextual stimuli associated with availability of a highly palatable conventional reinforcer produced only modest ‘seeking’ behaviour that extinguished rapidly. Thus, conditioned responses to drug cues not only facilitate relapse during abstinence in drug-experienced subjects, but perhaps also provoke craving related to initial sporadic drug experiences, leading to more frequent drug use.


One of a series of recent seminal papers providing preclinical evidence for the progression from casual to compulsive drug use. Here, rats with an extended cocaine self-administration history no longer showed conditioned suppression of drug-seeking in the presence of aversive CS. The authors show that this effect was not accounted for by extinction, impaired fear conditioning or an increase in cocaine’s incentive value. As in [44**], the maintenance of drug-seeking by rats in the face of adverse consequences—a hallmark feature of addiction—is consistent with the establishment of compulsive behaviour.


Group II mGluRs have received attention with respect to a role in addiction and as potential treatment drug targets. The data in this report support this hypothesis in that pharmacological activation of Group II mGluRs preferentially reduced the reinforcing effects of cocaine compared with a potent natural reinforcer, which remained unaltered, and preferentially reduced conditioned reinstatement as primary reinforcement by cocaine and the natural reinforcer.


Evidence is presented that N/OFQ — the endogenous ligand of the opioid-like orphan receptor — reduces alcohol self-administration under continuous and progressive ratio reinforcement contingencies, and attenuates contextual conditioned reinstatement. Importantly, the effects of N/OFQ were selective for drug-related behaviour, because the peptide did not alter behaviour maintained by sucrose.


This report extends the findings in [42*] with data further supporting the view that neuroadaptation in BDNF and/or signaling cascades initiated by BDNF contribute to the incubation phenomenon during cocaine withdrawal.


An excellent brief review of the role of neurotrophins and other neurotrophic factors, as well as the signaling pathways they activate, in long-term molecular, cellular, and behavioural adaptations associated with drug addiction.


The authors employed positron emission tomography scanning to investigate connectivity patterns associated with the primary brain regions activated by drug-craving memories (the anterior cingulate) and correlated with opiate craving (the OFC). The data revealed an ability of drug-related stimuli to activate attentional and memory circuits to a greater degree than non-drug-related stimuli, leading the authors to conclude that neural circuits of dependence and craving are not specific ‘craving’ or ‘addiction’ circuits, but ‘normal’ circuits activated to a greater degree.


86. Sinha R, Talih M, Malison R, Cooney N, Anderson GM, Kreek MJ: Hypothalamic-pituitary-adrenal axis and sympatho-adrenergic responses during stress-induced and drug cue-induced cocaine craving states. Psychopharmacology (Berl) 2003, 170:62-72. An elaborate study that scrutinizes the response of brain stress circuits in cocaine-dependent subjects exposed to guided imagery procedures known to increase cocaine craving. Stress and drug imagery manipulations each produced significant increases in craving and subjective anxiety, pulse rate, systolic blood pressure and levels of adrenocorticotropic hormone, cortisol, prolactin and norepinephrine, compared with neutral imagery. Of interest, these data confirm not only that similar craving states are elicited by stress and drug cue exposure, but also that the neurobiological basis of these reactions is shared with a significant activation of the CRF/HPA axis and noradrenergic/sympathoadreno-medullary system response.


This paper addresses the issue of common neural substrates for cocaine craving associated with different risk factors, with a focus on the role of the PFC in cocaine-seeking induced by footshock stress and priming injections. Based on the effects of transient tetrodotoxin lesions, site-specific pharmacological manipulations and findings in related literature, a picture emerges that implicates the PLC and OFC as part of the circuitry specifically mediating the effects of footshock stress on reinstatement. The PLC is proposed as a possible common pathway for cue, foot-shock and cocaine-induced reinstatement of drug seeking.


89. Linden AM, Greene SJ, Bergeron M, Schoepp DD: Anxiolytic activity of the mGlu2/3 receptor agonist LY354740 on the elevated plus maze is associated with the suppression of stress-induced c-Fos in the hippocampus and increases in c-Fos induction in several other stress-sensitive brain regions. Neuropsychopharmacology 2004, 29:502-513.


