Neuroplastic Alterations in the Limbic System Following Cocaine or Alcohol Exposure

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Abstract Neuroplastic changes in the CNS are thought to be a fundamental component of learning and memory. While pioneering studies in the hippocampus and cerebellum have detailed many of the basic mechanisms that can lead to alterations in synaptic transmission based on previous activity, only more recently has synaptic plasticity been monitored after behavioral manipulation or drug exposure. In this chapter, we review evidence that drugs of abuse are powerful modulators of synaptic plasticity. Both the dopaminergic neurons of the ventral tegmental area as well medium spiny neurons in nucleus accumbens show enhanced excitatory synaptic strength following passive or active exposure to drugs such as cocaine and alcohol. In the VTA, both the enhancement of excitatory synaptic strength and the acquisition of drug-related behaviors depend on signaling through the *N*-methyl-D-aspartate receptors (NMDARs) which are mechanistically thought to lead to increased synaptic insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Synaptic insertion of AMPARs by drugs of abuse can be long lasting, depending on the route of administration,

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number of drug exposures, or whether the drugs are received passively or self-administered.

Keywords Plasticity · Dopamine · Glutamate · Accumbens · Ventral tegmental area · Amygdala · Drug abuse · Reward

1 Introduction

The mesolimbic dopamine (DA) system, formed in part by the ventral tegmental area (VTA) and nucleus accumbens (NAc), is an integral part of the brain's natural reward circuit. The VTA is a major source of DA for brain circuits involved in encoding of reinforcement and learning, and the NAc is a critical node that integrates limbic and motivational input (including DA signals from the VTA) to influence behavioral output. Thus, these brain regions, in concert with other areas such as the prefrontal cortex, thalamus, and amygdala, are considered to play a critical role in the control of motivated and goal-directed behaviors, including the development and expression of addictive behavior (Cardinal et al. 2002; Epstein et al. 2006; Kalivas and McFarland 2003; Mogenson et al. 1980). In addition, recent studies suggest that addiction is a form of maladaptive learning, where aberrant neural links are formed between the action of taking drugs and the "reward" or alleviation of withdrawal-related negative states produced by the drugs (Hyman et al. 2006). For this reason, this chapter will briefly address the consequences of passive versus active exposure to drugs. Repeated passive exposure to a given drug can enhance or "sensitize" the locomotor-activating effects of that drug (for review, see Robinson and Berridge 1993). Since locomotor sensitization can be long-lasting and can enhance subsequent drug self-administration, sensitization has been considered a model of enhanced drug seeking during abstinence. However, although pharmacological effects through passive drug exposure can produce enduring plastic changes, human drug intake is typically active and voluntary, and associative learning between such volitional drug taking and the positive or negative reinforcing consequences may be a critical component in the development of addiction. Overall, this chapter seeks to address the hypothesis that drugs of abuse produce persistent changes in neuronal function that may drive drug seeking following periods of abstinence.

The ability of drugs to alter neuronal function was originally investigated predominantly through biochemical methods such as Western Blot, which allows one to determine changes in protein levels or phosphorylation state of a given receptor or channel subunit. More recently, large-scale screening for changes in protein levels (using proteomics) or mRNA levels (using DNA microarrays) have shown great promise for indicating potential changes in receptor or channel function. Importantly, ex vivo electrophysiological techniques in brain slice have

allowed direct examination of functional changes in excitatory synaptic strength or ion channel activity after drug exposure. Electrophysiological studies are particularly critical because they provide detailed information about the functional state of a given receptor or channel, which can occur without concurrent alterations in total protein or mRNA in brain tissue. Thus, we will examine evidence that abused substances can cause long-term changes (after one day or more of withdrawal) in glutamate receptor and ion channel function in the VTA and NAc. While many other brain regions such as the prefrontal cortex play a very important role in drug-dependent behaviors (Kalivas et al. 2005), those brain regions will not be addressed here. Furthermore, we will focus here on cocaine and alcohol, although many interesting studies have also been performed in relation to other abused drugs such as morphine, nicotine, and amphetamine.

2 Ionotropic Glutamate Receptors

Ionotropic glutamate receptors are generally categorized into one of two distinct classes. Activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) by glutamate leads to fast onset/fast offset depolarization, which contributes to action potential induction in many cells (Bredt and Nicoll 2003). In contrast, *N*-methyl-D-aspartate receptors (NMDARs) have slower kinetics and are voltage-activated. That is, at resting membrane potentials they are blocked by Mg^{2+} and no current can pass. However, as the neuron becomes more depolarized, the Mg^{2+} block is alleviated, which allows for the passage of cations including Ca^{2+} when glutamate is bound to the receptor. Therefore, currents through the NMDAR both depolarize the neuron and elevate intracellular Ca^{2+}, which is critical for induction of many enduring forms of synaptic plasticity.

AMPARs are hetero or homomeric complexes composed of four subunit proteins (GluR1-4) (Hollmann and Heinemann 1994). In many brain regions including both the VTA and NAc, AMPARs are thought to exist as heteromeric complexes containing both GluR2/3 and GluR1 subunits in a basal state (Liu and Zukin 2007). At some synapses neuroplastic changes in AMPAR function are associated with the synaptic insertion of GluR1 subunits that form homomeric receptors lacking GluR2/3 (Bellone and Lüscher 2006; Plant et al. 2006). The formation and insertion of GluR2/3-lacking (GluR1 homomeric) receptors is of particular importance as these receptors pass more current while hyperpolarized at resting membrane potentials compared to when they are depolarized (rectification) as well be being permeable to Ca^{2+}, which can facilitate further Ca^{2+}-dependent changes in plasticity. To investigate the functional consequence of changes in GluR subunit composition of AMPARs, several compounds that are capable of selectively blocking GluR2-lacking AMPARs, such as 1-naphthylacetylsperimine (Naspm), Joro spider toxin, or philanthotoxin-7,4, have been used (Argilli et al. 2008; Conrad et al. 2008; Nilsen and England 2007).

3 Cocaine-Induced Synaptic Plasticity in Midbrain DA Neurons

There is a large body of literature demonstrating a role of DAergic transmission in learning and reinforcement (for reviews see Kelley 2004; Salamone et al. 2005; Schultz and Dickinson 2000; Wise 2004). Midbrain DA neurons exhibit bimodal firing rates (2–7 Hz tonic; 10–30 Hz Bursting) (Freeman and Bunney 1987; Schultz 1998). Tonic firing is hypothesized to lead to ambient, low levels of DA (~20 nM) capable of activating high affinity D2 receptors, while burst firing is hypothesized to cause transient surges in DA concentrations (>100 nM), which would be able to act on lower affinity D1 receptors (Missale et al. 1998). Burst firing of DA neurons in particular seems to be of distinct importance as cues that are associated with reward, which can serve to initiate goal-directed behavior, lead to phasic DA release after cue-reward learning (Phillips et al. 2003; Stuber et al. 2005). Thus, phasic activation of midbrain DA neurons is thought to promote goal-directed behavior, especially in relation to reward-predictive stimuli.

Importantly, glutamatergic signaling potently modulates DAergic neuronal activity. Ionotropic glutamate receptor agonists can potently increase firing rates of DAergic neurons in vivo (Chergui et al. 1993; Grace and Bunney 1984; Johnson et al. 1992; Murase et al. 1993), while ionotropic antagonists attenuate firing (Charlety et al. 1991; Chergui et al. 1993). Furthermore, modeling studies predict that changes in AMPAR number or function should lead to profound alterations in the firing pattern of DA neurons, perhaps by indirectly inducing NMDAR activity which could lead to burst firing (Canavier and Landry 2006). Consistent with this notion, synapses onto DA neurons are highly plastic, exhibiting NMDAR-dependent long-term potentiation (LTP) (Liu et al. 2005; Ungless et al. 2001) and long-term depression (LTD) (Bonci and Williams 1996), as well as short-term plasticity involving changes in the amount or function of synaptic AMPA receptors (Bonci and Malenka 1999). Thus, it is hypothesized that such plasticity could modify AMPAR responses during environmental events that increase glutamate release onto DA neurons, and significantly alter the firing of DA neurons during goal-directed behavior. Indeed, nonassociative learning in relation to behavioral sensitization to cocaine, and cocaine- and morphine-induced conditioned place preference, are both blocked by VTA NMDAR antagonists (Harris and Aston-Jones 2003; Harris et al. 2004; Kalivas and Alesdatter 1993).

Ungless et al. (2001) were the first to report that the ratio of AMPAR-mediated current to NMDAR-mediated current (termed the AMPAR/NMDAR ratio) is significantly elevated at excitatory synapses in the VTA relative to saline-injected controls 24 h after a single exposure to cocaine. The increase in the AMPAR/NMDAR current ratio after cocaine exposure occludes further potentiation and induction of LTP, suggesting that these synapses already exist in an LTP-like state. Importantly, LTP of VTA glutamatergic synapses is observed after a single exposure to many other drugs of abuse, demonstrating a convergence of cellular responses within the VTA by all abused drugs (Saal et al. 2003). The mechanism underlying LTP of excitatory synapses onto VTA DA neurons appears to be

mediated by the initial insertion of GluR2-lacking AMPARs (Bellone and Lüscher 2006; Lüscher and Bellone 2008; Mameli et al. 2007). This insertion of new GluR2-lacking AMPAR subunits is thought to be transient, so that the homomeric GluR1 AMPA receptors are eventually replaced by newly synthesized GluR2/3 after many hours. Furthermore, the insertion of GluR2-lacking AMPARs can be reversed by activation of the metabotropic glutamate receptor (mGluR) mGluR1, which induces replacement of GluR2-lacking receptors with GluR2-containing receptors. This is hypothesized to readjust synaptic strength back to basal levels and therefore prevent behavioral changes that could contribute to development of addiction.

Thus, LTP observed in VTA DA neurons after a single cocaine exposure is transient, exhibiting potentiated AMPAR currents 5 but not 10 days later (Ungless et al. 2001). The same time course for potentiated VTA AMPAR currents has also been observed following repeated cocaine injections (Borgland et al. 2004), suggesting that increased cocaine exposure does not increase the duration of the VTA AMPAR enhancement. It also is interesting that a single cocaine injection produces changes in opiate conditioned place preference and aversion with a similar time course (altered conditioning 5 but not 10 days after cocaine exposure), and these effects of cocaine were prevented by inhibition of NMDARs in the VTA during cocaine exposure (Kim et al. 2004). These studies suggest that many forms of LTP require Ca^{2+} influx through NMDARs, and enhanced AMPAR number or signaling in the VTA following cocaine exposure could act to facilitate DA-mediated learning. Consistent with this hypothesis, establishment of place preference for both cocaine and morphine depends on NMDAR signaling (Harris and Aston-Jones 2003; Harris et al. 2004), as does conditioned approach behavior to cues that predict natural rewards (Stuber et al. 2008b). Reinstatement of cocaine-seeking behavior (either by electrical stimulation or by cocaine priming) following cessation of self-administration also is blocked by intra-VTA glutamate antagonism (Sun et al. 2005; Vorel et al. 2001).

Pathological drug use is thought to highjack natural associative learning mechanisms in order to facilitate and exacerbate drug-seeking behavior (Hyman et al. 2006; Kelley 2004). Since the process of active drug-seeking behavior is very different from passive experimenter-delivered drug exposure, it is critical to investigate changes in synaptic plasticity in the VTA following voluntary drug-self administration. Chen and colleagues (2008) found that voluntary cocaine self-administration in rats increased excitatory synaptic strength in VTA DA neurons for up to 3 months following cessation of chronic self-administration, in stark contrast to passive involuntary cocaine administration that potentiates excitatory synaptic strength for ~1 week as described above. Interestingly, yoked rats that received the same amount and temporal pattern of involuntary cocaine did not show an increase in synaptic strength. Finally Changes in VTA NMDAR levels have also been observed during cocaine withdrawal (Lu et al. 2003; Hemby et al. 2005), although electrophysiological studies have not been performed to corroborate these results. Taken together, these data suggest that a number of behavioral conditions can produce short-term plasticity in the VTA (passive cocaine exposure, self-administration of natural reinforcers), but the combined outcome of cocaine's pharmacological effect with

the animal's volition to self-administer cocaine can produce a long-lasting potentiation of glutamate transmission onto VTA DA neurons.

4 Cocaine-Induced Synaptic Plasticity in the NAc

The NAc is another integral part of the brain's reinforcement circuit, and many studies indicate that synaptic plasticity in the NAc can be altered by cocaine exposure. Neuroplasticity of glutamatergic synapses onto medium spiny NAc neurons was first observed following passive, experimenter-administered cocaine injections (Thomas et al. 2001), which found LTD at these synapses. Interestingly, in contrast to the VTA where LTP is elicited after a single cocaine exposure, NAc synaptic plasticity was observed only after five daily cocaine injections (Kourrich et al. 2007; Thomas et al. 2001). However, after extended withdrawal from repeated cocaine exposure, mice show both cocaine-induced behavioral sensitization and LTP ex vivo in NAc shell but not core. This LTP is reversed back to the basal state if animals received a cocaine injection 24 h before recording. Thus, the history of cocaine exposure and withdrawal can readily change the direction of synaptic plasticity in the NAc. The behavioral consequence of NAc LTD after repeated amphetamine exposure was demonstrated in an elegant experiment whereby a GluR-trafficking modulator prevented both NAc LTD induction ex vivo and expression of behavioral sensitization to amphetamine (Brebner et al. 2005). In addition, unlike the VTA, AMPAR potentiation in the NAc following experimenter-administered amphetamine is not attributed to changes in the composition of AMPAR subunits, since analyses of rectification index revealed no rectification before or after amphetamine exposure. These results are consistent with the finding that blocking constitutive recycling of GluR2-containing AMPARs prevented NAc LTD and reduced expression of amphetamine-induced sensitization.

In parallel to studies on plasticity in the VTA, plasticity in the NAc following chronic cocaine revealed differences whether cocaine was administered passively or by voluntary self-administration (Martin et al. 2006). In cocaine self-administering rats, the ability to induce LTD in the core and shell of the NAc was occluded one day after chronic cocaine. However, after 21 days of forced abstinence, LTD induction remained occluded in the NAc core, but could be readily induced in the NAc shell, suggesting that LTD in shell synapses had reverted to normal. These results suggest that voluntary cocaine self-administration induces long-lasting glutamatergic neuroadaptations exclusively in the NAc core, a region associated with control of behavior by drug-related stimuli and relapse to drug seeking. In support of this finding, a number of studies have observed increased NAc GluR1 levels after cocaine self-administration. Importantly, a recent study found an increase in cell surface GluR1 subunits in the NAc, during abstinence from cocaine self-administration (Conrad et al. 2008). Increased GluR1 levels are associated with an increase in rectification in synaptic AMPAR currents, as would be expected from plasma

membrane insertion of GluR1-containing AMPARs. Importantly, to demonstrate that addition of GluR1-containing AMPARs plays a significant role in cue-induced cocaine relapse this study showed that intra-NAc injection of an antagonist selective for GluR1-containing AMPARs significantly reduced the enhancement in cocaine seeking that occurs after longer withdrawal times. In another recent study (Anderson et al. 2008), viral interference of GluR1 membrane insertion in the NAc shell attenuated drug-induced reinstatement. Although there are some differences in the methods used to elicit cocaine seeking in these studies (i.e., context re-exposure vs. drug-induced reinstatement), it is clear that accumbens GluR1 is important for the expression of cocaine-seeking behavior.

In addition to altered AMPAR function, recent work has shown the importance of changes in the Homer proteins, scaffolding proteins that bind directly to mGluRs and indirectly to NMDARs, as critical neuroadaptations that can drive cocaine seeking (Swanson et al. 2001). Repeated cocaine and abstinence is associated with reduced NAc protein levels of Homer1b/c and Homer2a/b isoforms, and group I mGluRs (mGluR1 and mGluR5) (see also Mitrano et al. 2008). Activation of group I mGluRs within the NAc can increase NAc glutamate levels and produce locomotor activation. However, mGluR enhancement of NAc glutamate levels and locomotor activation is blunted after 3 weeks but not 24 h of withdrawal from repeated cocaine injection, in agreement with reduced mGluR and Homer protein levels.

5 Amygdala Plasticity and Drugs of Abuse

Within the amygdala, there is a great degree of subregion heterogeneity. Two amygdala subregions have been of particular interest in the context of plasticity related to drug-seeking behavior. The basolateral amygdala (BLA; composed of the lateral, basomedial, basal and accessory basal nuclei) plays a critical role in associating environmental stimuli with primary rewards (Cador et al. 1989; Cardinal et al. 2002; Davis and Whalen 2001; LeDoux 2003, 2007; Maren and Quirk 2004), which may lead to relapse of drug seeking (Everitt et al. 1999; Robbins et al. 2008). The BLA is markedly different from the central nucleus of the amygdala (CeA) in both structure and function. The CeA is thought to play a critical role in the development of ethanol dependence, purportedly by modulating anxiety or stress that may increase ethanol intake (Bajo et al. 2008; Hyytia and Koob 1995; Koob, 2004, 2009; Rassnick et al. 1993b; Roberts et al. 1996).

Drug conditioning plays a tremendous role in the persistence of drug addiction, and understanding how these learned responses are encoded is critical to developing drug addiction treatments. The lateral amygdala (LA), a dorsal subnucleus of the BLA, is a site of initial convergence for afferents transmitting sensory information about conditioned and unconditioned stimuli (Azuma et al. 1984; Doron and Ledoux 1999; LeDoux 2003; Maren and Quirk 2004; McDonald 1998; Nakashima et al. 2000). This may explain why the LA typically exhibits plasticity upon the acquisition of the association between a conditioned stimulus and a primary reward

(Cador et al. 1989; Everitt et al. 1999; Jentsch et al. 2002; Thomas and Everitt 2001; Tronel and Sara 2002; Tye et al. 2008), while regions such as the VTA or NAc show robust molecular and synaptic changes after a single exposure to cocaine (Ghasemzadeh et al. 2003; Grignaschi et al. 2004; Ungless et al. 2001). It is likely that drugs act as powerful reinforcers by hijacking the natural reward circuitry, and that the amygdala-mediated formation of conditioned stimulus (CS) drug associations endows the CS with the power to maintain (Arroyo et al. 1998; Goldberg 1975; Goldberg et al. 1975), prolong (Ciccocioppo et al. 2004; Ranaldi and Roberts 1996) and induce reinstatement of drug-seeking behaviors (Fuchs et al. 2006; Grimm and See 2000; Kantak et al. 2002; Meil and See 1996; See et al. 2001).

Relapse, which is often triggered by exposure to the drug, stress, or to cues associated with the drug experience, is a major clinical problem and one of the greatest challenges of addiction. In cocaine addicts, the presentation of cocaine-associated stimuli during abstinence can elicit intense drug craving (O'Brien et al. 1998), which is accompanied by physiological arousal, including increased heart rate and skin conductance (Childress et al. 1988; Ehrman et al. 1992), which corresponds to amygdala activation (Childress et al. 1999). The amygdala activation evoked by self-reported craving in humans is also observed in animals during drug-seeking behaviors. Animal models can be utilized to explore the ability of environmental cues to guide reward-seeking behavior. Additionally, LTP has been observed in the lateral amygdala during cocaine withdrawal (Goussakov et al. 2006).

While rats will readily lever press to self-administer primary reinforcers, such as sucrose, cocaine, or alcohol, they will also respond for reward-paired cues in the absence of the primary reward (Davis and Smith 1976; Grimm et al. 2002; Meil and See 1997; Nie and Janak 2003). The BLA has been shown to be necessary for second-order conditioning for both natural and drug rewards (Cador et al. 1989; Cardinal et al. 2002; Davis and Whalen 2001; LeDoux 2003, 2007; Maren and Quirk 2004). Moreover, evidence suggests that BLA function is specific to reinforcing properties of the reward-associated cue and does not affect reinforcing properties of the reward itself (Balleine et al. 2003). BLA lesions attenuate responding to a cue associated with a natural reinforcer such as sexual interaction, but do not alter sexual behavior itself (Everitt 1990). Furthermore, BLA lesions do not alter cocaine self-administration but attenuate the ability of cocaine-associated cues to reinstate extinguished responses (Meil and See 1997). Acute inactivation of the BLA prevents both cue-induced and drug priming-induced reinstatement to heroin-seeking behavior (Fuchs and See 2002). Other manipulations of the BLA, including muscarinic receptor antagonism (See et al. 2003), and DA receptor antagonism (Berglind et al. 2006) also impair the ability of cocaine-associated cues to induce reinstatement of cocaine-seeking behavior. It is also noteworthy that electrical stimulation of the BLA is sufficient to reinstate cocaine-seeking behavior (Hayes et al. 2003) and that LTP has been observed in the lateral amygdala during cocaine withdrawal (Goussakov et al. 2006). Importantly, extracellular concentrations of DA in the amygdala are tightly correlated with cocaine self-administration (Hurd and Ponten 2000). Specifically, intra-amygdala administration of selective DA antagonists reduces cocaine self-administration (Caine et al. 1995), and increasing or reducing

the concentrations of DA in the amygdala can increase or reduce cocaine self-administration (Hurd et al. 1997; Hurd and Ponten 2000). Whether these findings pertain to the cocaine-associated cues that are presented during self-administration or to the drug itself remains to be determined, but they clearly delineate a critical role for the amygdala in cocaine self-administration.

The BLA is critically involved in the formation and expression of associations between sensory cues and rewarding or aversive stimuli (Davis and Whalen 2001; Gallagher 2000; LeDoux 2007; McGaugh 2002). Specifically, when animals are trained to respond to a reward that is paired with a predictive cue and responding is subsequently extinguished by the omission of the cue and reward, presentation of the cue alone increases responding. Evidence of BLA encoding of reward-associated cues has been observed via in vivo electrophysiological recordings. BLA neurons are phasically excited during cocaine self-administration and by cocaine-associated cues (Carelli et al. 2003) as well as in response to cues associated with natural rewards such as sucrose (Tye and Janak 2007).

Dynamic changes in local levels of immediate early genes indicate the occurrence of synaptic plasticity in the amygdala following activation or manipulation of stimulus-drug associations. For example, antagonism of the NMDAR has been shown to reduce the expression of the plasticity-related immediate early gene *Zif268* during classical conditioning (Mokin and Keifer 2005). Furthermore, the protein products of immediate early gene *Zif268* are upregulated in the BLA, but not the CeA, following exposure to discrete cues previously associated with cocaine self-administration (Thomas et al. 2003). The infusion of *Zif268* antisense oligodeoxynucleotides into the BLA abolished the previously acquired conditioned reinforcing properties of the drug-associated stimulus (Lee et al. 2005). Acute NMDAR antagonism in the BLA prior to memory reactivation also disrupted the drug-associated memory, impairing the ability of the cocaine-associated cue to exert its acquired conditioned reinforcing properties, and resulted in reduced expression of *Zif268* (Milton et al. 2008).

In contrast to the BLA, the CeA is widely considered to be critically involved in mediating the behavioral effects of ethanol (Gilpin et al. 2008; Koob, 1998, 2003, 2004, 2009; Koob et al. 1998; McBride et al. 2005; Richter et al. 2000; Roberto et al. 2004a, b). There is a strong connection between anxiety states and alcohol dependence (Heilig and Egli 2006; Koob 2003, Pandey et al. 2003). Acute ethanol exposure induces anxiolytic effects associated with increased brain-derived neurotrophic factor (BDNF) and tyrosine kinase B (trk B) expression, increased expression of the immediate early gene activity-regulated cytoskeleton-associated protein (Arc), and increased dendritic spine density in the CeA, but not the BLA (Pandey et al. 2008). The activation of neuropeptide Y (NPY) in the CeA can impair the motivational aspects associated with ethanol dependence (Pandey et al. 2003). Specifically, administration of NPY into the CeA attenuates the increase in drug intake associated with alcohol dependence (Gilpin et al. 2008; Thorsell et al. 2007). In vivo microdialysis and in vitro electrophysiological studies revealed that both acute and chronic ethanol alter glutamatergic transmission in the CeA (Roberto et al. 2004b). Taken together, this constellation of ethanol-related neuroadaptations

strongly implicates the critical involvement of the CeA in alcohol abuse and dependence.

The CeA is heavily involved in the anxiety related to ethanol withdrawal (Koob 2003; McBride et al. 2002), as multiple measurable changes occur in the CeA during withdrawal. Accumulating evidence shows that acute withdrawal from many drugs of abuse, including cocaine (Fu et al. 2007; Richter and Weiss 1999) and alcohol (Funk et al. 2006; Koob 2003; Merlo Pich et al. 1995; Olive et al. 2002) produce common increases in reward thresholds, anxiety-like responses, and extracellular levels of CRF in the CeA. Understanding the anxiety related to ethanol withdrawal involves a complex neurobiology involving the interaction of multiple systems. The CRF and norepinephrine systems have been shown to be closely entwined in the amygdala (Dunn et al. 2004; Emoto et al. 1993; Roozendaal et al. 2008; Smith and Aston-Jones 2008), as they reciprocally activate one another (Koob 1999a, b). Both ethanol and CRF enhance GABA release in the CeA (Nie et al. 2004) via a common pathway involving protein kinase C epsilon (Bajo et al. 2008). Another substrate for withdrawal-related anxiety is in cAMP-responsive element-binding (CREB) phosphorylation in the CeA, which is decreased during withdrawal following chronic ethanol exposure (Pandey et al. 2003). Additionally, partial deletions and deficits in amygdaloid (CREB) protein contribute to increased ethanol consumption and a predisposition to alcoholism and alcohol-related anxiety (Pandey 2004; Pandey et al. 2005).

6 Alcohol and Plasticity in Glutamate Receptors

Alcohol abuse is considered the third leading preventable cause of human death (Mokdad et al. 2004). Also, because it is legal to obtain and linked to increased aggression and violence, alcoholism extracts enormous social and economic costs relative to other drugs of abuse (see Buck and Harris 1991; Harwood et al. 1998; Larimer et al. 1999; Sanchis-Segura and Spanagel 2006). Thus, changes in neuronal function after long-term alcohol intake that contribute to pathological, compulsive alcohol seeking and relapse are of great interest. In particular, alcohol seeking and intake occurs even in the face of detrimental consequences, which represents a major clinical hurdle during the process of overcoming alcohol use disorders. Interestingly, in humans, relapse to alcohol seeking is commonly associated with the appearance of negative affective states or other stressful events, as well as to alcohol-related cues (Larimer et al. 1999; Sanchis-Segura and Spanagel 2006). Relapse can thus be associated with more stressful and psychological symptoms early during withdrawal, or can be associated with increased susceptibility for relapse even after prolonged abstinence. Further, rodent studies have suggested that stress- and cue-related enhancement of drug seeking are critically regulated by the VTA and by target regions of the VTA such as the NAc (see Kalivas and McFarland 2003; Wang et al. 2007), where DA release can interact with

glutamate-driven firing to modulate expression of behavior. Thus, we will first focus on changes in glutamatergic function in the VTA and NAc after alcohol.

A number of studies using diverse alcohol exposure models have examined the effect of repeated alcohol exposure on NMDA receptor function, and several brain regions, including the NAc/striatum, show enhanced NMDAR function during early withdrawal from alcohol (Buck and Harris 1991; Dodd et al. 2000; Gulya et al. 1991; Siggins et al. 2003; Szumlinski et al. 2008a, b; Wang et al. 2007; Zhao and Constantine-Paton 2007); but see (Winkler et al. 1999). In general, increased NMDAR function during withdrawal from alcohol is thought to increase neuronal excitability and drive aversive withdrawal symptoms that increase alcohol consumption. Given the role of negative emotional and physical states in promoting alcohol seeking, NMDAR inhibitors are an attractive clinical intervention to reduce early withdrawal symptoms and decrease relapse during early withdrawal.

The exact change in particular NMDAR subunit levels varies among brain regions and alcohol exposure. In the NAc, both NR1 and NR2B have been found to be increased during early withdrawal from alcohol, in addition to increased mGluR1 and Homer 2b (see below) (Szumlinski et al. 2008a, b; Zhao and Constantine-Paton 2007). Some studies have also observed alterations in NMDAR function without changes in subunit levels. For example, long-term alcohol intake can strongly upregulate the NR1-2 isoform in the NAc, which lacks an NR1 C1 cassette that is necessary for efficient trafficking or anchoring of NMDARs to the postsynaptic density, and the pattern of functional changes in NMDAR depends on whether alcohol exposure is intermittent or continuous (Zhao and Constantine-Paton 2007).

In the VTA, chronic forced alcohol is associated with increased NMDAR subunit levels (Ortiz et al. 1995), although one study found reduced NMDA excitation of VTA firing in vitro during withdrawal from alcohol (Bailey et al. 1998). In addition to NMDAR changes, VTA AMPAR function is enhanced after alcohol self-administration (Stuber et al. 2008a), in agreement with an earlier study showing increased VTA GluR1 levels after long-term forced alcohol intake (Ortiz et al. 1995). Although enhanced glutamate receptor function might increase VTA excitability (Canavier and Landry 2006), early withdrawal from alcohol is associated with a decrease in activity of VTA neurons and a decrease in DA release in VTA terminal regions (Bailey et al. 1998; Diana et al. 1993; Weiss et al. 1996). This hypoactivity of the DA system is reversed by systemic inhibition of NMDARs (Rossetti et al. 1992). Thus, NMDARs in a brain region other than the VTA may control VTA firing activity during early withdrawal from alcohol. Importantly, self-administration of alcohol during withdrawal continues until NAc DA levels are normalized (Weiss et al. 1996), in agreement with observations that modulation of alcohol intake is sensitive to altering DA signaling in the NAc (Hodge et al. 1997; Rassnick et al. 1993a; Rassnick et al. 1993b; Samson and Chappell 2004) or altering VTA DA neuron activity (Hodge et al. 1993; Rodd et al. 2004). Finally, although VTA DA neurons may exhibit hypoactivity during withdrawal from alcohol, enhanced NMDAR and AMPAR function in the VTA after chronic alcohol could facilitate VTA neuron activity during consumption of alcohol, since alcohol exposure can facilitate VTA neuron firing

(Brodie et al. 1990; Diana et al. 1993; Mereu et al. 1984) and increases DA release in the NAc (Gonzales and Weiss 1998).

Of potentially great interest are possible long-term changes in VTA glutamatergic function after longer withdrawal from alcohol that may parallel alterations in glutamatergic function in both the NAc and VTA after withdrawal from cocaine self-administration (see above). In particular, enhanced glutamatergic throughput could increase firing of NAc or VTA neurons and modulate alcohol intake or facilitate relapse in the presence of alcohol-related conditioned stimuli. Altered glutamatergic function after long-term withdrawal from alcohol has been found in the NAc, where a different pattern of changes is observed relative to cocaine exposure. After alcohol, the NAc shows increases rather than decreases in NR2B, mGluR1, and Homer2b (see Szumlinski et al. 2008a, b). These altered glutamate receptor levels are observed after 2 weeks withdrawal following 3 months of alcohol drinking; after 2 months withdrawal, only an increase in Homer2b is observed. Changes in all three glutamate receptor proteins also are observed after short-term passive exposure or binge drinking (Szumlinski et al. 2008a, b; Zhao and Constantine-Paton 2007), and thus the time course of glutamate receptor changes may vary depending upon the duration and route of alcohol exposure. Interestingly, viral overexpression of Homer2b in the NAc increases alcohol preference and alcohol-related place preference, suggesting that mimicking the drinking-induced enhancement in Homer2b is sufficient to increase alcohol preference and reinforcement. Interestingly, overexpression of Homer2b in the NAc increases alcohol-related NAc glutamate and DA release. This pattern has been associated with increased alcohol preference, and is also linked to regulation of glutamate release by mGluR1/5. Thus, increased NAc Homer2b levels, acting through trafficking of mGluRs and modulation of glutamate release, could facilitate the reinforcing effects of alcohol after chronic intake, and in this way promote alcohol seeking during withdrawal.

7 Altered Intrinsic Excitability After Alcohol or Cocaine

In addition to modulation of neuronal excitability through plastic changes in glutamate receptor function, a number of studies in recent years have investigated the possibility that plastic changes in ion channel function can occur and be long-lasting. Further, such intrinsic excitability changes could alter the ability of synaptically generated excitatory postsynaptic currents (EPSCs) to propagate along dendrites in order to influence action potential generation and neuronal firing. Thus, numerous ion channels in dendrites can amplify or retard passing EPSCs and greatly impact the ability of glutamate receptor activation to generate action potentials and generate LTD or LTP (Kauer and Malenka 2007). Particularly interesting is the possibility that persistent alterations in ion channel function could dramatically enhance the ability of relapse-inducing stimuli to drive firing of the VTA and NAc, and in this way promote craving and relapse.

L-type voltage-gated calcium channels (LVGCC) are notably interesting, since altered LVGCC function seems to occur during early withdrawal from many abused drugs including alcohol, and thus could represent a common mechanism (for review, see Brooks et al. 2008; Buck and Harris 1991; Little 1999). Chronic alcohol exposure increases LVGCC levels in brain regions such as the hippocampus, with more mixed results in the few studies from the striatum (Lucchi et al. 1985; Woodward and Gonzales 1990). Also, systemic administration of LVGCC antagonists decreases alcohol withdrawal symptoms and the decreased DA levels normally evident during early withdrawal from alcohol and other drugs. Human studies are less clear with regard to changes in LVGCC in the brains of alcoholics (Kril and Harper 1989; Marks et al. 1989). However, there are human preclinical studies indicating that LVGCC antagonists may ameliorate early withdrawal symptoms, as well as reducing tolerance and cravings, with clearer evidence for drugs other than alcohol (Altamura et al. 1990; Rosse et al. 1994; Rush and Pazzaglia 1998). Interestingly, LVGCC in the striatum are required for induction of LTD (see Adermark and Lovinger 2007), and NAc LTD is necessary for the expression of behavioral sensitization to amphetamine (Brebner et al. 2005). While the mechanism underlying this requirement for LTD in behavioral sensitization is unknown, increased LVGCC levels could promote LTD induction after drug exposure and facilitate the development or expression of behavioral sensitization. Thus, like the NMDARs, LVGCC inhibitors may be a useful clinical intervention to counteract early withdrawal symptoms, even though the brain regions where LVGCC plasticity occurs and is necessary for withdrawal symptoms have not been clearly identified (see Whittington and Little 1991).

Considerable work has examined changes in NAc ion channel activity after repeated cocaine injection and 3 days withdrawal. A number of functional changes that decrease intrinsic excitability are apparent in the NAc during withdrawal from cocaine, including increased potassium channel activity, decreased N- and R-type VGCC activity, and decreased sodium channel activity (Hu et al. 2004, 2005; Zhang et al. 2002). Also, calcium channels can regulate a number of physiological processes in addition to firing, including induction of glutamatergic plasticity, neurotransmitter release, and calcium-dependent activation of intracellular regulatory proteins such as kinases. These changes may reflect increased or decreased ion channel protein levels, but some cocaine-associated changes in channel function may be related to altered tonic activity of intracellular signaling molecules and ion channel phosphorylation or other modifications. Thus, as for NMDARs, investigations of plastic changes in receptor or channel function after chronic drug exposure need to carefully consider the many different regulatory steps that can impact activity of a receptor or channel, such as phosphorylation, trafficking, and membrane localization, since these might provide important information about potential therapeutic targets to reverse drug-related neuroadaptations that could facilitate relapse. Such psychostimulant-related changes in intrinsic excitability are not limited to the NAc, and have also been identified in the prefrontal cortex and subiculum (Cooper et al. 2003; Nasif et al. 2005).

VTA DA neuron firing after alcohol exposure has also been studied. A number of groups have observed a reduction in firing during the first 1–6 days of withdrawal from alcohol (Bailey et al. 1998; Brodie 2002; Diana et al. 1993), a pattern also observed after withdrawal from exposure to other drugs of abuse (Ackerman and White 1992; Rossetti et al. 1992). However, the possible contribution of particular ion channels in this decreased VTA neuron excitability is poorly understood. Nonetheless, given the possible involvement of DA receptors in the regulation of many forms of alcohol- and drug-related behaviors (see above), changes in VTA ion channel function that persist beyond the early withdrawal period are of great interest. A recent study found that the function of the apamin-sensitive, SK-type calcium-activated potassium channel was significantly reduced in VTA DA neurons after 7 days withdrawal following repeated alcohol exposure (Hopf et al. 2007). Although alcohol exposure did not alter baseline firing rates, NMDA receptor activation increased burst firing in alcohol-treated animals, but increased the spike firing rate of VTA neurons in control animals. These findings are consistent with reductions in SK-type potassium channels in alcohol-treated animals, since inhibition of these channels facilitates glutamate-induced bursting in midbrain DA neurons (Johnson and Seutin 1997; Seutin et al. 1993; Waroux et al. 2005). Since bursting is associated with increased DA release in VTA terminal regions (see Grace 2000; Marinelli et al. 2006), reduced SK function could enhance DA release in response to alcohol-related stimuli and promote relapse to alcohol seeking. A small reduction in the I_h current was also observed after 7 days withdrawal from alcohol (Hopf et al. 2007), which was also observed after one day of withdrawal (Okamoto et al. 2006). Reduced I_h function did not change burst firing, but decreased the ability of VTA DA neurons to recover from hyperpolarization.

Of particular importance are neuroadaptations that are evident after even longer periods of abstinence from alcohol. Alcoholism is considered a chronically relapsing disease (Larimer et al. 1999; Sanchis-Segura and Spanagel 2006), and neuroadaptations that persist for months to years of abstinence could play a critical role in the increased propensity for relapse in human alcoholics. In this regard, a recent study from our group observed reduced SK channel function in the NAc core after 3 weeks abstinence from alcohol self-administration, but not after abstinence from sucrose self-administration. Importantly, infusion of an SK activator into the NAc core reduced alcohol seeking but not sucrose seeking. In addition, the lateral dorsal striatum exhibited a strong basal SK regulation of firing (Pineda et al. 1992), which was not reduced during abstinence from alcohol self-administration, and SK activators infused into the lateral dorsal striatum did not reduce alcohol seeking. Thus, SK activators were only effective in modulating alcohol seeking in regions where SK function was reduced, suggesting that SK activators might represent a novel therapeutic intervention in abstinent alcoholics. We hypothesize that decreased SK function in NAc core will enhance firing in NAc core neurons during exposure to alcohol-related stimuli, and so reduced NAc core SK function could promote behavioral activation by these alcohol-related stimuli and drive relapse. In addition, SK inhibition in the NAc is in agreement

with an early study showing that abstinence after long-term alcohol exposure was associated with a reduced after hyperpolarization in the dentate gyrus (Durand and Carlen 1984) that is strongly although not uniquely mediated by SK potassium channels (Gu et al. 2005).

Thus, results from multiple complementary techniques, including in vitro electrophysiology, biochemistry, and gene chip and proteomic studies have identified changes in SK and other ion channels and receptors after alcohol exposure. Additional behavioral pharmacology experiments have suggested that at least some of these neuroadaptations could represent critical changes in the NAc and other brain regions that might promote alcohol seeking during abstinence from alcohol.

8 Conclusions and Future Directions

Although many important and tantalizing clues regarding the effect of chronic drug and alcohol exposure on plasticity in glutamate receptor and ion channel function have been demonstrated, many questions remain. Few studies have examined excitability changes beyond the period of early withdrawal, although recent studies of glutamate receptor and ion channel function have begun to characterize changes after long-term withdrawal from cocaine, alcohol, or heroin exposure. Identifying long-term changes is particularly critical since neuroadaptations persisting after weeks or months of abstinence may mediate long-term susceptibility to cravings and relapse. Importantly, these long-term neuroadaptations may also correlate with structural changes in spine density or dendritic architecture that can occur in the NAc after passive or active cocaine administration. It is also clear that self-administration and passive administration of abused drugs can differentially alter gene expression and protein function (see Jacobs et al. 2002, 2004), perhaps due to learned cues that come to be associated with the act of voluntary self-administration and that can reinforce further alcohol or drug seeking in a conditioned, involuntary manner. Fortunately, the field possesses a battery of powerful techniques including membrane isolation and traditional Western Blot protein analyses, large scale genomic and proteomic methods, optogenetics, and ex vivo brain slice electrophysiology from animals that have learned to self-administer cocaine or alcohol. Although laborious and technically challenging in adult animals, we believe that ex vivo electrophysiology is especially critical for uncovering and defining which neuroadaptations might persist during abstinence, in part because potent functional changes can occur without altered total protein or mRNA levels. The advent of localized knockdown or cell-specific over expression of proteins of interest will aid in determining their functional role in addictive behavior. In addition, a more clear delineation of the molecular alterations apparent after abstinence could allow one to utilize specific pharmacological or molecular agents to reverse that harmful effects of molecular change (e.g., reversing the plasma membrane trafficking of particular AMPAR subunits), and perhaps provide a novel therapeutic intervention for addiction and alcoholism.

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