Published in final edited form as:

Neuropharmacology. 2009 ; 56(Suppl 1): 122–132. doi:10.1016/j.neuropharm.2008.06.075.

Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis

William A. Carlezon Jr.¹ and Mark J. Thomas²

¹ Behavioral Genetics Laboratory, Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont MA 02478, USA

² Departments of Neuroscience and Psychology, University of Minnesota, Minneapolis MN 55455, USA

Abstract

The nucleus accumbens (NAc) is a critical element of the mesocorticolimbic system, a brain circuit implicated in reward and motivation. This basal forebrain structure receives dopamine (DA) input from the ventral tegmental area (VTA) and glutamate (GLU) input from regions including the prefrontal cortex (PFC), amygdala (AMG), and hippocampus (HIP). As such, it integrates inputs from limbic and cortical regions, linking motivation with action. The NAc has a well-established role in mediating the rewarding effects of drugs of abuse and natural rewards such as food and sexual behavior. However, accumulating pharmacological, molecular, and electrophysiological evidence has raised the possibility that it also plays an important (and sometimes underappreciated) role in mediating aversive states. Here we review evidence that rewarding and aversive states are encoded in the activity of NAc medium spiny GABAergic neurons, which account for the vast majority of the neurons in this region. While admittedly simple, this working hypothesis is testable using combinations of available and emerging technologies, including electrophysiology, genetic engineering, and functional brain imaging. A deeper understanding of the basic neurobiology of mood states will facilitate the development of well-tolerated medications that treat and prevent addiction and other conditions (e.g., mood disorders) associated with dysregulation of brain motivation systems.

The biological basis of mood-related states such as reward and aversion is not understood. Classical formulations of these states implicate the mesocorticolimbic system, comprising brain areas including the NAc, VTA, and PFC, in reward (Bozarth and Wise, 1981; Goeders and Smith, 1983; Wise and Rompré, 1989). Other brain areas, including the amygdala, periaqueductal gray, and the locus coeruleus, are often implicated in aversion (Aghajanian, 1978; Phillips and LePaine, 1980; Bozarth and Wise, 1983). However, the notion that certain brain areas narrowly and rigidly mediate reward or aversion is becoming archaic. The development of increasingly sophisticated tools and methodologies has enabled new approaches that provide evidence for effects that previously would have been difficult (if not impossible) to detect. As one example from our own work, we have found that a prominent neuroadaptation triggered in the NAc by exposure to drugs of abuse (activation of the transcription factor CREB) contributes to depressive-like and aversive states in rodents (for review, see Carlezon et al., 2005). Other work suggests that changes in the activity of

Corresponding author: William A. Carlezon, Jr. Department of Psychiatry, McLean Hospital, MRC 217, 115 Mill Street, Belmont, MA 02478 bcarlezon@mclean.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

dopaminergic neurons in the VTA—which provides inputs to the NAc that are integrated with glutamatergic inputs from areas such as the PFC, AMG, and HIP—can also encode both rewarding and aversive states (Liu et al., 2008).

In this review, we will focus on the role of the NAc in simple states of reward and aversion. The role of NAc activity in more complex states such as drug-craving and drug-seeking is beyond the scope of this review, since these states depend upon experience-dependent neuroadaptations and do not easily map onto basic conceptualizations of rewarding and aversive states. An improved understanding of the neurobiology of reward and aversion is critical to the treatment of complex disorders like addiction. This question is particularly important as the field utilizes accumulated knowledge from decades of research on drugs of abuse to move toward the rational design of treatments for addictive disorders. The requirement for new medications goes beyond the mere reduction of drug-craving, drug-seeking, or other addictive behaviors. To be an effective therapeutic, a medication must be tolerated by the addicted brain, or compliance (sometimes called adherence) will be poor. There are already examples of medications (e.g., naltrexone) that would appear on the basis of animal data to have extraordinary potential for reducing intake of alcohol and opiates—except that addicts often report aversive effects and discontinue treatment (Weiss et al., 2004). Methods to predict rewarding or aversive responses in normal and addicted brains would accelerate the pace of drug discovery, medication development, and recovery from addiction. Here we review evidence for the simple working hypothesis that rewarding and aversive states are encoded by the activity of NAc medium spiny GABAergic neurons.

II. The NAc

The NAc comprises the ventral components of the striatum. It is widely accepted that there are two major functional components of the NAc, the core and the shell, which are characterized by differential inputs and outputs (see Zahm, 1999; Kelley, 2004; Surmeier et al., 2007). Recent formulations further divide these two components into additional subregions (including the cone and the intermediate zone of the NAc shell) (Todtenkopf and Stellar, 2000). As in the dorsal striatum, GABA-containing medium spiny neurons (MSNs) make up the vast majority (~90–95%) of cells in the NAc, with the remaining cells being cholinergic and GABAergic interneurons (Meredith, 1999). Striatal regions contain subpopulations of these MSNs: those of so-called “direct” and “indirect” pathways (Gerfen et al., 1990; Surmeier et al., 2007). The MSNs of the direct pathway predominantly co-express dopamine D1-like receptors and the endogenous opioid peptide dynorphin, and project directly back to the midbrain (substantia nigra/VTA). In contrast, the MSNs of the indirect pathway predominantly co-express dopamine D2-like receptors and the endogenous opioid peptide enkephalin, and project indirectly to the midbrain via areas including the ventral pallidum and the subthalamic nucleus. Traditional formulations posit that dopamine actions at D1-like receptors, which are coupled to the G-protein G_s (stimulatory) and associated with activation of adenylate cyclase, tend to excite the MSNs of the direct pathway (Albin et al., 1989; Surmeier et al., 2007). Elevated activity of these cells would be expected to provide increased GABAergic and dynorphin (an endogenous ligand at κ -opioid receptors) input to the mesolimbic system and negative feedback on midbrain dopamine cells. In contrast, dopamine actions at D2-like receptors, which are coupled to G_i (inhibitory) and associated with inhibition of adenylate cyclase, tend to inhibit the MSNs of the indirect pathway (Albin et al., 1989; Surmeier et al., 2007). Inhibition of these cells would be expected to reduce GABAergic and enkephalin (an endogenous ligand at δ -opioid receptors) input to the ventral pallidum, a region that normally inhibits subthalamic cells that activate inhibitory inputs to the thalamus. Through multiple synaptic connections, inhibition of the indirect pathway at the level of the NAc would ultimately activate the thalamus (see Kelley, 2004).

Like neurons throughout the brain, MSNs also express glutamate-sensitive AMPA and NMDA receptors. These receptors enable glutamate inputs from brain areas such as AMG, HIP, and deep (infralimbic) layers of the PFC (O'Donnell and Grace, 1995; Kelley et al., 2004; Grace et al., 2007) to activate NAc MSNs. Dopamine and glutamate inputs can influence one another: for example, stimulation of D1-like receptors can trigger phosphorylation of glutamate (AMPA and NMDA) receptor subunits, thereby regulating their surface expression and subunit composition (Snyder et al., 2000; Chao et al., 2002; Mangiavacchi et al., 2004; Chartoff et al., 2006; Hallett et al., 2006; Sun et al., 2008). Thus the NAc is involved in a complex integration of excitatory glutamate inputs, sometimes excitatory dopamine (D1-like) inputs, and sometimes inhibitory dopamine (D2-like) inputs. Considering that VTA tends to have uniform a response—activation—to both rewarding (e.g., morphine; see DiChiara and Imperato, 1988; Leone et al., 1991; Johnson and North, 1992) and aversive (Dunn, 1988; Herman et al., 1988; Kalivas and Duffy, 1989; McFarland et al., 2004) stimuli, the ability of the NAc to integrate these excitatory and inhibitory signals downstream of mesolimbic dopamine neurons likely plays a key role in attaching valence and regulating mood.

III. Role of the NAc in rewarding states

It is well accepted that the NAc plays a key role in reward. Theories about its role in motivation have been a critical element in our understanding of addiction (e.g., Bozarth and Wise, 1987; Rompré and Wise, 1989). There are 3 primary lines of evidence implicating the NAc in reward, involving pharmacological, molecular, and electrophysiological approaches.

A. Pharmacological evidence

It is well established that drugs of abuse (Di Chiara and Imperato, 1988) and natural rewards (Fibiger et al., 1992; Pfaus, 1999; Kelley, 2004) have the common action of elevating extracellular concentrations of dopamine in the NAc. Moreover, lesions of the NAc reduce the rewarding effects of stimulants and opiates (Roberts et al., 1980; Kelsey et al., 1989). Pharmacology studies in rats (e.g., Caine et al., 1999) and monkeys (e.g., Caine et al., 2000) suggest that D2-like receptor function plays a critical role in reward. However, it has been studies involving the direct microinfusion of drugs into this area that have provided the strongest evidence for its role in rewarding states. For example, rats will self-administer the dopamine releasing agent amphetamine directly into the NAc (Hoebel et al., 1983), demonstrating the reinforcing effects elevating extracellular dopamine in this region. Rats will also self-administer the dopamine reuptake inhibitor cocaine into the NAc, although this effect is surprisingly weak in comparison to that reported with amphetamine (Carlezon et al., 1995). This observation has led to speculation that the rewarding effects of cocaine are mediated outside the NAc, in areas including the olfactory tubercle (Ikemoto, 2003). However, rats will avidly self-administer the dopamine reuptake inhibitor nomifensine into the NAc (Carlezon et al., 1995), suggesting that the local anesthetic properties of cocaine complicate studies in which the drug is applied directly to neurons. Co-infusion of the dopamine D2-selective antagonist sulpiride attenuates intracranial self-administration of nomifensine, demonstrating a key role for D2-like receptors in the rewarding effects intra-NAc microinfusions of this drug. When considered together with evidence from a variety of other studies (for review, see Rompré and Wise, 1989), these studies are entirely consistent with theories prevailing in the 1980's that dopamine actions in the NAc play a necessary and sufficient role in reward and motivation.

While there is little controversy that dopamine actions in the NAc is sufficient for reward, other work began to challenge the notion that they are necessary. For example, rats will self-administer morphine directly into the NAc (Olds, 1982), away from the trigger zone (the VTA) in which the drug acts to elevate extracellular dopamine in the NAc (Leone et al., 1991; Johnson and North, 1992). Considering that μ - and δ -opioid receptors are located directly on NAc MSNs (Mansour et al., 1995), these data were the first to suggest that reward can be triggered by

events occurring in parallel with (or downstream of) those triggered by dopamine. Rats will also self-administer phencyclidine (PCP), a complex drug that is a dopamine reuptake inhibitor and a non-competitive NMDA antagonist, directly into the NAc (Carlezon and Wise, 1996). Two lines of evidence suggest that this effect is not dopamine-dependent. First, intracranial self-administration of PCP is not affected by co-infusion of the dopamine D2-selective antagonist sulpiride; and second, rats will self-administer other non-competitive (MK-801) or competitive (CPP) NMDA antagonists with no direct effects on dopamine systems directly into the NAc (Carlezon and Wise, 1996). These data provided early evidence that blockade of NMDA receptors in the NAc is sufficient for reward and, by extension, reward can be dopamine-independent. Blockade of NMDA receptors would be expected to produce an overall reduction in the excitability of NAc MSNs without affecting baseline excitatory input mediated by AMPA receptors (Uchimura et al., 1989; Pennartz et al. 1990). Importantly, rats also self-administered NMDA antagonists into deep layers of the PFC (Carlezon and Wise, 1996), which project directly to the NAc (see Kelley, 2004) and have been conceptualized as a part of an inhibitory ("STOP!") motivational circuit (Childress, 2006). When considered together, these studies provided two critical pieces of evidence that have played a prominent role in the formulation of our current working hypothesis: first, that dopamine-dependent reward is attenuated by blockade of D2-like receptors, which are inhibitory receptors expressed predominately in the NAc on the MSNs of the indirect pathway; and second, that events that would be expected to reduce the overall excitability of the NAc (e.g., stimulation of G_i-coupled opioid receptors, reduced stimulation of excitatory NMDA receptors, reduced excitatory input) are sufficient for reward. This interpretation led to the development of a model of reward in which the critical event is reduced activation of MSNs in the NAc (Carlezon and Wise, 1996).

Other pharmacological evidence supports this theory, and implicates calcium (Ca²⁺) and its second messenger functions. Activated NMDA receptors gate Ca²⁺, an intracellular signaling molecule that can affect membrane depolarization, neurotransmitter release, signal transduction, and gene regulation (see Carlezon and Nestler, 2002; Carlezon et al., 2005). Microinjection of the L-type Ca²⁺ antagonist diltiazem directly into the NAc increases the rewarding effects of cocaine (Chartoff et al., 2006). The mechanisms by which diltiazem-induced alterations in Ca²⁺ influx affect reward are unknown. One possibility is that blockade of Ca²⁺ influx through voltage-operated L-type channels reduces the firing rate of neurons within the ventral NAc (Cooper and White, 2000). It is important to note, however, that diltiazem alone was not rewarding, at least at the doses tested in these studies. This might indicate that baseline levels of Ca²⁺ influx via L-type channels within the NAc are normally low, and difficult to reduce further. A related possibility is that microinjection of diltiazem reduces aversive actions of cocaine that are mediated within the NAc, unmasking reward. For example, activity of the transcription factor cAMP response element binding protein (CREB) within the NAc is associated with aversive states and reductions in cocaine reward (Pliakas et al., 2001; Nestler and Carlezon, 2006). The activation of CREB depends on phosphorylation, which can occur via activation of L-type Ca²⁺ channels (Rajadhyaksha et al., 1999). Phosphorylated CREB can induce expression of dynorphin, a neuropeptide that might contribute to aversive states via activation of κ -opioid receptors in the NAc (for review, see Carlezon et al., 2005). The potential role of intra-NAc Ca²⁺ in regulating rewarding and aversive states is a common theme in our work that will be explained in greater detail below.

B. Molecular evidence

Mice lacking dopamine D2-like receptors have reduced sensitivity to the rewarding effects of cocaine (Welter et al., 2007). Ablation of D2-like receptors also reduces the rewarding effects of morphine (Maldonado et al., 1997)—presumably by reducing the ability of the drug to stimulate dopamine via VTA mechanisms: Leone et al., 1991; Johnson and North, 1992—and

lateral hypothalamic brain stimulation (Elmer et al., 2005). One interpretation of these findings is that loss of D2-like receptors in the NAc reduces the ability of dopamine to inhibit the indirect pathway, a putative mechanism of reward. These findings, when combined with evidence that human addicts have reduced dopamine D2-like receptor binding in the NAc, suggest that this receptor plays an essential role in encoding reward (Volkow et al., 2007).

Other advances in molecular biology have enabled the detection of neuroadaptive responses to drugs of abuse and the ability to mimic such changes in discrete brain areas to examine their significance. One such change is in the expression of AMPA-type glutamate receptors, which are expressed ubiquitously in the brain and composed of various combinations of the receptor subunits GluR1-4 (Hollmann et al., 1991; Malinow and Malenka, 2002). Drugs of abuse can alter GluR expression in the NAc. For example, repeated intermittent exposure to cocaine elevates GluR1 expression in the NAc (Churchill et al., 1999). Furthermore, GluR2 expression is elevated in the NAc of mice engineered to express Δ FosB, a neuroadaptation linked with increased sensitivity to drugs of abuse (Kelz et al., 1999). Studies in which viral vectors were used to elevate GluR1 selectively in the NAc indicate that this neuroadaptation tends to make cocaine aversive in place conditioning tests, whereas elevated GluR2 in the NAc increases cocaine reward (Kelz et al., 1999). Potential explanations for this pattern of findings likely involve Ca^{2+} and its effect on neuronal activity and intracellular signaling. Increased GluR1 expression favors formation of GluR1-homomeric (or GluR1-GluR3 heteromeric) AMPARs, which are Ca^{2+} -permeable (Hollman et al., 1991; Malinow and Malenka, 2002). In contrast, GluR2 contains a motif that prevents Ca^{2+} influx; thus increased expression of GluR2 would favor formation of GluR2-containing Ca^{2+} -impermeable AMPARs (and theoretically decrease the number of Ca^{2+} -permeable AMPARs). Thus GluR2-containing AMPARs have physiological properties that render them functionally distinct from those lacking this subunit, particularly with respect to their interactions with Ca^{2+} (Fig. 1).

These early studies involved place conditioning studies, which generally require repeated exposure to drugs of abuse and presumably involve cycles of reward and aversion (withdrawal). More recent studies examined how alterations in GluR expression modeling those acquired through repeated drug exposure affect intracranial self-stimulation (ICSS), an operant task in which the magnitude of the reinforcer (brain stimulation reward) is precisely controlled (Wise, 1996). Elevated expression of GluR1 in NAc shell increases ICSS thresholds, whereas elevated GluR2 decreases them (Todtenkopf et al., 2006). The effect of GluR2 on ICSS is qualitatively similar to that caused by drugs of abuse (Wise, 1996), suggesting that it reflects increases in the rewarding impact of the stimulation. In contrast, the effect of GluR1 is qualitatively similar to that caused by prodepressive treatments including drug withdrawal (Markou et al., 1992) and κ -opioid receptor agonists (Pfeiffer et al., 1986; Wadenberg, 2003; Todtenkopf et al., 2004; Carlezon et al., 2006), suggesting that it reflects decreases in the rewarding impact of the stimulation. These findings indicate that elevated expression of GluR1 and GluR2 in NAc shell have markedly different consequences on motivated behavior. Moreover, they confirm previous observations that elevated GluR1 and GluR2 expression in NAc shell have opposite effects in cocaine place conditioning studies (Kelz et al., 1999), and extend the generalizability of these effects to behaviors that are not motivated by drugs of abuse. Perhaps most importantly, they provide more evidence to implicate Ca^{2+} flux within the NAc in reduced reward or elevated aversion. Because Ca^{2+} plays a role in both neuronal depolarization and gene regulation, alterations in GluR expression and AMPAR subunit composition in NAc shell likely initiate physiological and molecular responses, which presumably interact to alter motivation. Again, the mechanisms by which Ca^{2+} signal transduction might trigger genes involved in aversive states are described in detail below.

C. Electrophysiological evidence

Several lines of electrophysiological investigation support the idea that decreases in NAc firing may be related to reward. First, rewarding stimuli produce NAc inhibitions *in vivo*. Second, neurobiological manipulations that specifically promote inhibition of NAc firing appear to enhance rewarding effects of stimuli. Third, the inhibition of NAc GABAergic MSNs can disinhibit downstream structures such as the ventral pallidum to produce signals related to the hedonic qualities of stimuli. Each of these lines of investigation will be addressed in turn. The most substantial line of investigation involves studies of NAc single-unit activity in rodent paradigms where a wide variety of drug and non-drug rewards are delivered. A consistent finding across these studies is that the most commonly observed pattern of firing modulation is a transient inhibition. This has been observed during self-administration of many different types of rewarding stimuli including cocaine (Peoples and West, 1996), heroin (Chang et al., 1997), ethanol (Janak et al., 1999), sucrose (Nicola et al., 2004), food (Carelli et al., 2000) and electrical stimulation of the medial forebrain bundle (Cheer et al., 2005). Though not as commonly investigated as self-administration paradigms, the inhibition-reward effect is also present in awake, behaving animals where rewards are delivered without requirement for an operant response (Roitman et al., 2005; Wheeler et al., 2008). These studies indicate that the transient inhibitions need not be directly related to motor output, but may be more directly tied to a rewarding or motivationally activated state. As ubiquitous as the NAc inhibition-reward relationship seems to be, however, there are counterexamples. For instance, Taha and Fields (2005) found that of those NAc neurons that appeared to encode palatability in a sucrose solution-drinking discrimination task, excitations outnumbered inhibitions, and the total number of such neurons was small (~10% of all neurons recorded). This discrepancy from what appears to be the typical NAc activity pattern highlights the need for techniques to identify the connectivity and biochemical composition of cells recorded *in vivo*. As these techniques become available, unique functional subclasses of NAc neurons will most likely be identified and a more detailed model of NAc function can be constructed.

How are the transient reward-related inhibitions of NAc firing generated? Because rewarding stimuli are known to produce transient elevations in extracellular dopamine, one straightforward hypothesis is that dopamine may be responsible. In fact, findings from *in vitro* and *in vivo* studies using iontophoretic application and other methods indicate that dopamine is capable of inhibiting NAc firing (reviewed in Nicola et al., 2000, 2004). Recent studies examining simultaneous dopamine electrochemical and single unit responses (the majority of which are inhibitions) in an ICSS paradigm indicate that these parameters show a high degree of concordance in the NAc shell (Cheer et al., 2007). On the other hand, it is now clear that dopamine can have marked excitatory effects as well as inhibitory effects in behaving animals (Nicola et al., 2000, 2004). In addition, while inactivating VTA to interfere with dopamine release in NAc blocks both the cue-induced excitations and inhibitions, it does not affect reward-related inhibitions themselves (Yun et al., 2004a). The combination of these findings suggests that while dopamine may contribute to reward-related inhibition of NAc firing, there must be other factors that can drive it as well. Although there has been much less investigation of other potential contributors, additional candidates include the release of acetylcholine and the activation of μ -opioid receptors in the NAc, both of which have been shown to occur under rewarding conditions (Trujillo et al., 1988; West et al., 1989; Mark et al., 1992; Imperato et al., 1992; Guix et al., 1992; Bodnak et al., 1995; Kelley et al., 1996) and both of which have the ability to inhibit NAc firing (McCarthy et al., 1977; Hakan et al., 1989; de Rover et al., 2002).

Another newer line of electrophysiological evidence supporting the inhibition/reward hypothesis comes from experiments in which molecular genetics approaches have been used to manipulate the excitable properties of NAc neurons. The clearest example of this so far is for viral-mediated overexpression of mCREB (dominant negative CREB), a repressor of CREB

activity, in the NAc. This treatment was recently shown to cause decreases in the intrinsic excitability of NAc MSNs, as indicated by the fact that neurons recorded in the NAc exhibited fewer spikes in response to a given depolarizing current injection (Dong et al., 2006). As noted above, NAc mCREB overexpression is not only associated with enhanced rewarding effects of cocaine (Carlezon et al., 1998) but also with a decrease in depressive-like behavioral effects in the forced-swim task (Pliakas et al., 2001) and a learned-helplessness paradigm (Newton et al., 2002). The combination of these findings is consistent with the idea that conditions that facilitate a transition to lower firing rates in NAc neurons also facilitate reward processes and/or elevates mood.

On the other hand, deletion of the *Cdk5* gene specifically in the NAc core region produced an enhanced cocaine reward phenotype (Benavides et al., 2007). This phenotype correlated with an *increase* in excitability in NAc MSNs. This contrasts with the mCREB effect, which was most robust when CREB function was inhibited in the shell region, rather than the core (Carlezon et al., 1998). Considered along with other evidence, these studies highlight the importance of distinguishing between inhibition of NAc activity in the shell region, which appears to be associated with reward, versus the core region, where it may not.

Finally, the hypothesis relating NAc inhibition to reward is supported by the study of the relationship between neural activity in NAc target structures and reward. Considering that NAc MSNs are GABAergic projection neurons, inhibition of firing in these cells should disinhibit target regions. As mentioned above, one structure that receives a dense projection from the NAc shell is the ventral pallidum. Elegant electrophysiological studies have demonstrated that elevated activity in ventral pallidal neurons can encode the hedonic impact of a stimulus (Tindell et al., 2004, 2006). For example, among neurons that responded to sucrose reward (between 30–40% of total recorded units), receipt of a sucrose reward produced a robust, transient increase in firing—an effect that persisted throughout training (Tindell et al., 2004). In a subsequent study, the investigators used a clever procedure to manipulate the hedonic value of a taste stimulus to assess whether activity in pallidal neurons would track this change (Tindell et al., 2006). Although hypertonic saline solutions are typically aversive taste stimuli, in salt-deprived humans or experimental animals their palatability is increased. Both behavioral measures of positive hedonic response (i.e. facial taste reactivity measures) and increases in pallidal neuron firing occurred in response to a hypertonic saline taste stimulus in sodium-deprived animals, but not in animals maintained on a normal diet. Thus, increased firing of pallidal neurons, downstream targets of NAc efferents, appears to encode a key feature of reward. Of course, it is possible that other inputs to pallidal neurons could contribute to these reward-related firing patterns. However, recent studies have indicated a strong relationship between the ability of mu-opioid receptor activation (a factor which is known to inhibit MSN firing) in discrete regions of the NAc shell to drive increases in behavioral response to a hedonic stimulus and its ability to activate c-fos in discrete regions of ventral pallidum (Smith et al., 2007). This apparently tight coupling between NAc and pallidal “hedonic hotspots” is an intriguing new phenomenon that is just beginning to be explored.

IV. Role of the NAc in aversive states

The fact that the NAc also plays a role in aversion is sometimes underappreciated. Pharmacological treatments have been used to demonstrate aversion after NAc manipulations. In addition, molecular approaches have demonstrated that exposure to drugs of abuse and stress cause common neuroadaptations that can trigger signs (including anhedonia, dysphoria) that characterize depressive illness (Nestler and Carlezon, 2006), which is often co-morbid with addiction and involves dysregulated motivation.

A. Pharmacological evidence

Some of the earliest evidence that NAc plays a role in aversive states came from studies involving opioid receptor antagonists. Microinjections of a wide-spectrum opioid receptor antagonist (methylnaloxonium) into the NAc of opiate-dependent rats establishes conditioned place aversions (Stinus et al., 1990). In opiate-dependent rats, precipitated withdrawal can induce immediate-early genes and transcription factors in the NAc (Gracy et al., 2001; Chartoff et al., 2006), suggesting activation of MSNs. Selective κ -opioid agonists, which mimic the effects of the endogenous κ -opioid ligand dynorphin, also produce aversive states. Microinjections of a κ -opioid agonist into the NAc cause conditioned place aversions (Bals-Kubik et al., 1993) and elevate ICSS thresholds (Chen et al., 2008). Inhibitory (G_i -coupled) κ -opioid receptors are localized on the terminals of VTA dopamine inputs to the NAc (Svingos et al., 1999), where they regulate local dopamine release. As such, they are often in apposition to μ - and δ -opioid receptors (Mansour et al., 1995), and stimulation produces the opposite effects of agonists at these other receptors in behavioral tests. Indeed, extracellular concentrations of dopamine are reduced in the NAc by systemic (DiChiara and Imperato, 1988; Carlezon et al., 2006) or local microinfusions of κ -opioid agonist (Donzati et al., 1992; Spanagel et al., 1992). Decreased function of midbrain dopamine systems has been associated with depressive states including anhedonia in rodents (Wise, 1982) and dysphoria in humans (Mizrahi et al., 2007). Thus one path to aversion appears to be reduced dopamine input to the NAc, which would reduce the stimulation of inhibitory dopamine D2-like receptors that seem critical for reward (Carlezon and Wise, 1996).

Other studies appear to confirm an important role of dopamine D2-like receptors in suppressing aversive responses. Microinjections of a dopamine D2-like antagonist into the NAc of opiate-dependent rats precipitates signs of somatic opiate withdrawal (Harris and Aston-Jones, 1994). Although the motivational effects were not measured in this study, treatments that precipitate opiate withdrawal often cause aversive states more potently than they cause somatic signs of withdrawal (Gracy et al., 2001; Chartoff et al., 2006). Interestingly, however, microinjections of a dopamine D1-like agonist into the NAc also produce somatic signs of withdrawal in opiate-dependent rats. The data demonstrate that another path to aversion is increased stimulation of excitatory dopamine D1-like receptors in rats with opiate-dependence induced neuroadaptations in the NAc. Perhaps not surprisingly, one consequence of D1-like receptor stimulation in opiate dependent rats is phosphorylation of GluR1 (Chartoff et al., 2006), which would lead to increased surface expression of AMPA receptors on the MSNs of the direct pathway.

B. Molecular evidence

Exposure to drugs of abuse (Turgeon et al., 1997) and stress (Pliakas et al., 2001) activate the transcription factor CREB in the NAc. Viral vector-induced elevation of CREB function in the NAc reduces the rewarding effects of drugs (Carlezon et al., 1998) and hypothalamic brain stimulation (Parsegian et al., 2006), indicating anhedonia-like effects. It also makes low doses of cocaine aversive (a putative sign of dysphoria), and increases immobility behavior in the forced swim test (a putative sign of "behavioral despair") (Pliakas et al., 2001). Many of these effects can be attributed to CREB-regulated increases in dynorphin function (Carlezon et al., 1998). Indeed, κ -opioid receptor-selective agonists have effects that are qualitatively similar to those produced by elevated CREB function in the NAc, producing signs of anhedonia and dysphoria in reward models and increased immobility in the forced swim test (Bals-Kubik et al., 1993; Carlezon et al., 1998; Pliakas et al., 2001; Mague et al., 2003; Carlezon et al., 2006). In contrast, κ -selective antagonists produce an antidepressant-like phenotype resembling that seen in animals with disrupted CREB function in the NAc (Pliakas et al., 2001; Newton et al., 2002; Mague et al., 2003). These findings suggest that one biologically important consequence of drug- or stress-induced activation of CREB within the NAc is

increased transcription of dynorphin, which triggers key signs of depression. Dynorphin effects are likely mediated via stimulation of κ -opioid receptors that act to inhibit neurotransmitter release from mesolimbic dopamine neurons, thereby reducing the activity VTA neurons, as explained above. This path to aversion appears to be reduced dopamine input to the NAc, which would produce reductions in the stimulation of inhibitory dopamine D2-like receptors that seem critical for reward (Carlezon and Wise, 1996). As explained below, there is also evidence that elevated expression of CREB in the NAc directly increases the excitability of MSNs (Dong et al., 2006) in addition to the loss of D2-regulated inhibition, raising the possibility that multiple effects contribute to the aversive responses.

Repeated exposure to drugs of abuse can elevate GluR1 expression in the NAc (Churchill et al., 1999). Viral vector-induced elevation of elevated GluR1 in the NAc increases drug aversion in place conditioning studies, an “atypical” type of drug sensitization (i.e., heightened sensitivity to the aversive rather than the rewarding aspects of cocaine). This treatment also increases ICSS thresholds (Todtenkopf et al., 2006), indicating anhedonia-like and dysphoria-like effects. Interestingly, these motivational effects are virtually identical to those caused by elevated CREB function in the NAc. These similarities raise the possibility that both effects are part of the same larger process. In one possible scenario, drug exposure might trigger changes in the expression of GluR1 in the NAc, which would lead to local increases in the surface expression of Ca^{2+} -permeable AMPA receptors, which would increase Ca^{2+} influx and activate CREB, leading to alterations in sodium channel expression that affect baseline and stimulated excitability of MSNs in the NAc (Carlezon and Nestler, 2002; Carlezon et al., 2005; Dong et al., 2006). Alternatively, early changes in CREB function might precede alterations in GluR1 expression. These relationships are currently under intensive study in several NIDA-funded laboratories, including our own.

C. Electrophysiological evidence

Although there has been little electrophysiological investigation of the hypothesis that widespread excitation of NAc neurons encodes information about aversive stimuli, the available data essentially mirror those for rewarding stimuli. First, two recent studies using aversive taste stimuli both indicate that three times as many NAc neurons respond to the stimuli with clear excitations as inhibitions (Roitman et al., 2005; Wheeler et al., 2008). Interestingly, these same studies find that units that respond to a sucrose or saccharin reward show the exact opposite profile: three times more cells with decreases in firing than those with increases. In addition, when an initially rewarding saccharin stimulus was made aversive by pairing it with the opportunity to self-administer cocaine, the predominant firing pattern of NAc units that responded to the stimulus shifted from inhibition to excitation (Wheeler et al., 2008). Thus, not only does this demonstrate that NAc may encode aversive states in firing increases, but that individual NAc neurons can track the hedonic valence of a stimulus by varying their firing-rate response to it.

Second, molecular genetic manipulations of synaptic and intrinsic membrane properties that increase the excitability of NAc neurons can shift the behavioral response of a stimulus from rewarding to aversive. For example, viral-mediated overexpression of CREB in NAc produces an increase in neuronal excitability in MSNs as indicated by an increase in the number of spikes in response to a given depolarizing current pulse (Dong et al. 2006). Under these conditions of enhanced NAc excitability, animals exhibit a conditioned place *aversion* to cocaine, rather than the place preference response that control animals show to the same dose (Pliakas et al., 2001). In addition, they exhibit increased depressive-like behaviors in forced swim test (Pliakas et al., 2001) and learned helplessness paradigm (Newton et al., 2002). Another molecular manipulation that produces a similar behavioral phenotype is the overexpression of the AMPAR subunit GluR1 in NAc (Kelz et al., 1999; Todtenkopf et al., 2006). Although it has

not yet been confirmed by electrophysiological study, this GluR1 overexpression is likely to produce an enhancement of synaptic excitability in NAc MSNs. Not only may this occur through the insertion of additional AMPARs in the membrane in general, but the abundance of GluR1 could potentially lead to the formation of GluR1 homomeric receptors, which are known to have a larger single-channel conductance (Swanson et al., 1997) and thus contribute even further to enhanced excitability.

Third, if NAc firing is elevated during aversive conditions, downstream targets should be suppressed via GABA release from MSNs during these conditions as well. Ventral pallidal unit recordings show very low firing rates following oral infusion of hypertonic saline—a taste stimulus that under normal physiological circumstances is aversive (Tindell, 2006). Although clearly more work with aversive stimuli of different modalities is needed to make any firm conclusions, the present data are consistent with the possibility that enhanced firing of NAc neurons during aversive conditions may suppress pallidal neuron firing as part of the process of encoding the unpleasant nature of a stimulus.

V. Testing the model

Based on the evidence described above, our working hypothesis is that rewarding stimuli reduce the activity of NAc MSNs, whereas aversive treatments increase the activity of these neurons. According to this model (Fig. 2), NAc neurons tonically inhibit reward-related processes. Under normal circumstances, excitatory influences mediated by glutamate actions at AMPA and NMDA receptors or dopamine actions at D1-like receptors are balanced by inhibitory dopamine actions at D2-like receptors. Treatments that would be expected to reduce activity in the NAc—including cocaine (Peoples et al., 2007), morphine (Olds et al., 1982), NMDA antagonists (Carlezon et al., 1996), L-type Ca²⁺ antagonists (Chartoff et al., 2006), palatable food (Wheeler et al., 2008) and expression of dominant-negative CREB (Dong et al., 2006)—have reward-related effects because they reduce the inhibitory influence of the NAc on downstream reward pathways. In contrast, treatments that activate the NAc by amplifying glutamatergic inputs (e.g., elevated expression of GluR1; Todtenkopf et al., 2006), altering ion channel function (e.g., elevated expression of CREB; Dong et al., 2006), reducing inhibitory dopamine inputs to D2-like cells (e.g., κ -opioid receptor agonists), or blocking inhibitory μ - or δ -opioid receptors (West and Wise, 1988; Weiss, 2004) are perceived as aversive because they increase the inhibitory influence of the NAc on downstream reward pathways. Interestingly, stimuli such as drugs of abuse may induce homeostatic (or allostatic) neuroadaptations that persist beyond the treatment and cause baseline shifts in mood. Such shifts may be useful in explaining co-morbidity of addiction and psychiatric illness (Kessler et al., 1997): repeated exposure to drugs that reduce the activity of NAc neurons might induce compensatory neuroadaptations that render the system more excitable during abstinence (leading to conditions characterized by anhedonia or dysphoria), whereas repeated exposure to stimuli (e.g., stress) that activate the NAc might induce compensatory neuroadaptations that render the system more susceptible to the inhibitory actions of drugs of abuse, increasing their appeal. This working hypothesis is testable through a variety of increasingly sophisticated approaches.

A. Testing the hypothesis with electrophysiology

One caveat to the inhibition/reward hypothesis is that widespread and prolonged inhibition of NAc firing, as in inactivation or lesion studies, does not appear to produce rewarding effects (e.g. Yun et al., 2004b). This raises the possibility that it is not inhibition of the NAc, per se, that encodes reward but rather the *transitions* from normal basal firing rates to lower rates that occur when rewarding stimuli are present. Prolonged inhibition may degrade the dynamic information normally encoded in the transient depressions of NAc firing.

Electrophysiology-based tests of the predictions of this hypothesis fall into two basic categories. The first category involves manipulating an animal's behavioral state to produce sustained changes in responsivity to rewarding stimuli followed by testing for electrophysiological correlates of this altered reward state. For example, the early withdrawal state from chronic exposure to psychostimulants is characterized by anhedonia and lack of responsiveness to natural rewarding stimuli. What would the inhibition/reward hypothesis predict about the electrophysiological status of NAc neurons during this state? The major prediction is that NAc neurons would exhibit decreases in the activity suppression normally produced by exposure to a rewarding stimulus (e.g. sucrose). To our knowledge, this has not yet been investigated. Possible mechanisms for such a decrease in inhibition, should it occur, might include overall increases in neuronal excitability produced by any combination of changes in intrinsic excitability (e.g. increased Na⁺ or Ca²⁺ currents, decreased K⁺ currents) or synaptic transmission (e.g. decreases in glutamatergic or increases in GABAergic transmission). On the other hand, the available data on NAc MSN excitability during early psychostimulant withdrawal suggest that it is actually decreased during this phase (Zhang et al., 1998; Hu et al., 2004; Dong et al., 2006; Kourrich et al., 2007). As noted above, it is possible that a prolonged depression in excitability may degrade reward-related information contained in transient firing inhibitions, perhaps by creating a "floor" effect and reducing the magnitude of these inhibitions. This possibility remains to be tested.

Considering the apparent link between NAc and ventral pallidum in reward encoding (see above), we would predict that any excitability changes produced by sustained modulation of an animal's reward state might be particularly evident in striatopallidal/D2 neurons. Although studying the detailed physiological properties of these neurons has been difficult in the past, the recent development of a line of BAC transgenic mice that expresses GFP in these neurons (Gong et al., 2003; Lobo et al., 2006) has made it possible to visualize them in *in vitro* slice preparations, greatly facilitating the potential for physiological characterization of D2 cells.

The second category of electrophysiology-based tests involves using genetic engineering (see below) to alter the functional expression of key components of the cellular machinery for excitability or excitability modulation in NAc neurons. In theory, this could enable modulation of the inhibitions or excitations associated with reward or aversion, respectively, in NAc neurons. With this in mind, perhaps the most useful target molecules would be those that participate in activity-dependent modulation of neuronal excitability, rather than in maintaining basal firing rates. These targets would likely provide a better opportunity to modulating stimuli responsiveness than more general targets (e.g. Na⁺ channel subunits), thus enabling the evaluation of the inhibition/reward hypothesis. For example, the firing frequency of active neurons can be controlled by various ionic conductances that produce spike after-hyperpolarizations (AHPs). By targeting NAc neurons with genetic (or possibly even pharmacologic) manipulation aimed at the channels that produce AHPs, it may be possible to decrease the magnitude of aversion-related excitatory responses in these neurons and thus to test whether this physiological change correlates with reduced behavioral indices of aversion.

B. Testing the hypothesis with behavioral pharmacology

One of the most obvious pharmacological tests would to determine if rats self-administer dopamine D2-like agonists directly into the NAc. Interestingly, previous work indicates that while rats self-administer combinations of D1-like and D2-like agonists into the NAc, they do not self-administer either drug component alone, at least at the doses tested (Ikemoto et al., 1997). While on the surface this finding might appear to invalidate our working hypothesis, electrophysiological evidence suggests that co-activation of D1 and D2 receptors on NAc neurons can, under some conditions, cause a reduction in their membrane excitability that is not seen in response to either agonist alone (O'Donnell and Grace, 1996). In addition, more

work is needed to study the behavioral effects of intra-NAc microinfusions of GABA agonists; historically, this work has been hindered by poor solubility of benzodiazepines—which are known to be addictive (Griffiths and Ator, 1980) despite their tendency to decrease dopamine function in the NAc (Wood, 1982; Finlay et al., 1992; Murai et al., 1994)—and the relatively small number of researchers who use brain microinjection procedures together with models of reward. Still other ways of testing our hypothesis would be to study the effects of manipulations in brain areas downstream of D2 receptor-containing MSNs. Again, early evidence suggests reward is encoded by activation of the ventral pallidum, a presumed consequence of inhibition of the MSNs of the indirect pathway (Tindell et al., 2006).

C. Testing the hypothesis with genetic engineering

The development of genetic engineering techniques that enable the direction of inducible or conditional mutations to specific brain areas will be an important tool with which to test our hypotheses. Mice with constitutive deletion of GluRA (an alternative nomenclature for GluR1) show many alterations in sensitivity to drugs of abuse (Vekovischeva et al., 2001; Dong et al., 2004; Mead et al., 2005, 2007), some of which are consistent with our working hypothesis and some of which are not. The loss of GluR1 early in development could dramatically alter responsiveness to numerous types of stimuli, including drugs of abuse. In addition, these GluR1-mutant mice lack the protein throughout the brain, whereas the research reviewed here focuses on mechanisms that occur within NAc. These points are especially important because loss of GluR1 in other brain regions would be expected to have dramatic, and sometimes very different, effects on drug abuse-related behaviors. As just one example, we have shown that modulation of GluR1 function in the VTA exerts the opposite effect on drug responses compared to modulation of GluR1 in the NAc (Carlezon et al., 1997; Kelz et al., 1999). The findings in GluR1-deficient mice are not inconsistent with the combined findings from the NAc and the VTA: constitutive GluR1 mutant mice are more sensitive to the stimulant effects of morphine (an effect that could be explained by the loss of GluR1 in the NAc), but they do not develop progressive increases in responsivity to morphine (an effect that could be explained by the loss of GluR1 in the VTA) testing occurs under conditions that promote sensitization and involve additional brain regions. Accordingly, one must be cautious in assigning spatial and temporal interpretations to data from constitutive knockout mice: the literature is becoming replete with examples of proteins that have dramatically different (and sometimes opposite) effects on behavior depending upon the brain regions under study (see Carlezon et al., 2005).

Preliminary studies from mice with inducible expression of a dominant-negative form of CREB—a manipulation which reduces the excitability of NAc MSNs—are hypersensitive to the rewarding effects of cocaine while being insensitive to the aversive effects of a κ -opioid agonist (DiNieri et al., 2006). Although these findings are consistent with our working hypothesis, further studies (e.g., electrophysiology) might help to characterize the physiological basis of these effects. Regardless, an increased capacity to spatially and temporally control the expression of genes that regulate the excitability of NAc MSNs will enable progressively more sophisticated tests of our working hypothesis.

D. Testing the hypothesis with brain imaging

Functional brain imaging has the potential to revolutionize our understanding of the biological basis of rewarding and aversive mood states in animal models and, ultimately, people. Preliminary data from imaging studies involving alert non-human primates are providing early evidence in support of the working hypothesis described above. Intravenous administration of high doses of the κ -opioid agonist U69,593—which belongs to a class of drugs known to cause aversion in animals (Bals-Kubik et al., 1993; Carlezon et al., 2006) and dysphoria in humans (Pfeiffer et al., 1986; Wadenberg, 2003)—causes profound increases in blood-oxygen level-dependent (BOLD) functional MRI responses in the NAc (Fig. 3: from M.J. Kaufman, B. deB.

Fredrick, S. S. Negus, unpublished observations; used with permission). To the extent that BOLD signal responses reflect synaptic activity, the positive BOLD response induced by U69,593 in the NAc is consistent with increased activity of MSNs, perhaps due to decreased dopamine input (DiChiara and Imperato, 1988; Carlezon et al., 2006). In contrast, positive BOLD signal responses are conspicuously absent in the NAc after treatment with an equipotent dose of fentanyl, a highly addictive μ -opioid agonist. While these fentanyl data do not indicate inhibition of the NAc per se, absence of BOLD activity in this region is not inconsistent with our working hypothesis. Clearly, additional pharmacological and electrophysiological studies are needed to characterize the meaning of these BOLD signal changes. The development of higher magnetic field strength systems is beginning to enable cutting-edge functional imaging and spectroscopy in rats and mice, opening the door to a more detailed understanding of BOLD signals and underlying brain function.

VI. Conclusions

We propose a simple model of mood in which reward is encoded by reduced activity of NAc MSNs, whereas aversion is encoded by elevated activity of these same cells. Our model is supported by a preponderance of evidence already in the literature, although more rigorous tests are needed. It is also consistent with clinical studies indicating reduced numbers of inhibitory dopamine D2-like receptors in the NAc of drug addicts, which may decrease sensitivity to natural rewards and exacerbate the addiction cycle (Volkow et al., 2007). The continued development of molecular and brain imaging techniques is establishing a research environment that is conducive to the design of studies that have the power to confirm or refute this model. Regardless, a better understanding of the molecular basis of these mood states is perpetually important and relevant, particularly as accumulated knowledge from decades of research is used to develop innovative approaches that might be used to treat and prevent addiction and other conditions (e.g., mood disorders) associated with dysregulation of motivation.

Acknowledgements

Funded by the National Institute on Drug Abuse (NIDA) grants DA012736 (to WAC) and DA019666 (to MJT) and a McKnight-Land Grant professorship (to MJT). We thank M.J. Kaufman, B. deB. Fredrick, and S.S. Negus for permission to cite unpublished data from their brain imaging studies in monkeys.

References

- Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 1989;12:366–75. [PubMed: 2479133]
- Bals-Kubik R, Ableitner A, Herz A, Shippenberg TS. Neuroanatomical sites mediating the motivational effects of opioids as mapped by the conditioned place preference paradigm in rats. *J Pharmacol Exp Ther* 1993;264:489–95. [PubMed: 8093731]
- Benavides DR, Quinn JJ, Zhong P, Hawasli AH, DiLeone RJ, Kansy JW, Olausson P, Yan Z, Taylor JR, Bibb JA. Cdk5 modulates cocaine reward, motivation, and striatal neuron excitability. *J Neurosci* 2007;27:12967–12976. [PubMed: 18032670]
- Bodnar RJ, Glass MJ, Ragnauth A, Cooper ML. General, mu and kappa opioid antagonists in the nucleus accumbens alter food intake under deprivation, glucoprivic and palatable conditions. *Brain Res* 1995;700:205–212. [PubMed: 8624711]
- Bozarth MA, Wise R. Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci* 1981;28:551–5. [PubMed: 7207031]
- Bozarth MA, Wise RA. Neural substrates of opiate reinforcement. *Prog Neuropsychopharmacol Biol Psychiatry* 1983;7:569–75. [PubMed: 6320300]

- Caine SB, Negus SS, Mello NK. Effects of dopamine D(1-like) and D(2-like) agonists on cocaine self-administration in rhesus monkeys: rapid assessment of cocaine dose-effect functions. *Psychopharmacol* 2000;148:41–51.
- Caine SB, Negus SS, Mello NK, Bergman J. Effects of dopamine D(1-like) and D(2-like) agonists in rats that self-administer cocaine. *J Pharmacol Exp Ther* 1999;291:353–60. [PubMed: 10490924]
- Carelli RM, Ijames SG, Crumling AJ. Evidence that separate neural circuits in the nucleus accumbens encode cocaine versus “natural” (water and food) reward. *J Neurosci* 2000;20:4255–4266. [PubMed: 10818162]
- Carlezon WA, Beguin C, DiNieri JA, Baumann MH, Richards MR, Todtenkopf MS, Rothman RB, Ma Z, Lee DY, Cohen BM. Depressive-like effects of the kappa-opioid receptor agonist salvinorin A on behavior and neurochemistry in rats. *J Pharmacol Exp Ther* 2006;316:440–7. [PubMed: 16223871]
- Carlezon WA Jr, Boundy VA, Haile CN, Lane SB, Kalb RG, Neve RL, Nestler EJ. Sensitization to morphine induced by viral-mediated gene transfer. *Science* 1997;277:812–4. [PubMed: 9242609]
- Carlezon WA, Devine DP, Wise RA. Habit-forming actions of nomifensine in nucleus accumbens. *Psychopharmacol* 1995;122:194–7.
- Carlezon WA, Duman RS, Nestler EJ. The many faces of CREB. *Trends Neurosci* 2005;28:436–45. [PubMed: 15982754]
- Carlezon WA, Nestler EJ. Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? *Trends Neurosci* 2002;25:610–5. [PubMed: 12446127]
- Carlezon WA, Thome J, Olson VG, Lane-Ladd SB, Brodtkin ES, Hiroi N, Duman RS, Neve RL, Nestler EJ. Regulation of cocaine reward by CREB. *Science* 1998;282:2272–5. [PubMed: 9856954]
- Carlezon WA Jr, Thome J, Olson VG, Lane-Ladd SB, Brodtkin ES, Hiroi N, Duman RS, Neve RL, Nestler EJ. Regulation of cocaine reward by CREB. *Science* 1998;282:2272–2275. [PubMed: 9856954]
- Carlezon WA, Wise RA. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. *J Neurosci* 1996;16:3112–22. [PubMed: 8622141]
- Chang JY, Zhang L, Janak PH, Woodward DJ. Neuronal responses in prefrontal cortex and nucleus accumbens during heroin self-administration in freely moving rats. *Brain Res* 1997;754:12–20. [PubMed: 9134954]
- Chao SZ, Ariano MA, Peterson DA, Wolf ME. D1 dopamine receptor stimulation increases GluR1 surface expression in nucleus accumbens neurons. *J Neurochem* 2002;83:704–712. [PubMed: 12390532]
- Chartoff EH, Mague SD, Barhight MF, Smith AM, Carlezon WA Jr. Behavioral and molecular effects of dopamine D1 receptor stimulation during naloxone-precipitated morphine withdrawal. *J Neurosci* 2006;26:6450–7. [PubMed: 16775132]
- Chartoff EH, Pliakas AM, Carlezon WA Jr. Microinjection of the L-type calcium channel antagonist diltiazem into the ventral nucleus accumbens shell facilitates cocaine-induced conditioned place preferences. *Biol Psychiatry* 2006;59:1236–9. [PubMed: 16458265]
- Chen MC, Parsegian A, Carlezon WA Jr. Effect of mesocorticolimbic microinjections of the kappa-opioid agonist U50,488 on intracranial self-stimulation in rats. *Soc Neurosci Abstr* 2008;34in press
- Childress, AR. What can human brain imaging tell us about the vulnerability to addiction and to relapse?. In: Miller, WR.; Carroll, KM., editors. *Rethinking Substance Abuse: What the science shows and what we should do about it*. New York: Guilford; 2006. p. 46-60.
- Churchill L, Swanson CJ, Urbina M, Kalivas PW. Repeated cocaine alters glutamate receptor subunit levels in the nucleus accumbens and ventral tegmental area of rats that develop behavioral sensitization. *J Neurochem* 1999;72:2397–403. [PubMed: 10349849]
- Cooper DC, White FJ. L-type calcium channels modulate glutamate-driven bursting activity in the nucleus accumbens in vivo. *Brain Res* 2000;880:212–8. [PubMed: 11033010]
- de Rover M, Lodder JC, Kits KS, Schoffelemeier AN, Brussaard AB. Cholinergic modulation of nucleus accumbens medium spiny neurons. *Eur J Neurosci* 2002;16:2279–2290. [PubMed: 12492422]
- Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A* 1988;85:5274–8. [PubMed: 2899326]
- DiNieri JA, Carle T, Nestler EJ, Carlezon WA Jr. Inducible disruption of CREB activity within nucleus accumbens alters sensitivity to rewarding and prodepressive drugs. *Soc Neurosci Abstr* 2006;32

- Dong Y, Saal D, Thomas M, Faust R, Bonci A, Robinson T, Malenka RC. Cocaine-induced potentiation of synaptic strength in dopamine neurons: behavioral correlates in GluRA(−/−) mice. *Proc Natl Acad Sci U S A* 2004;101:14282–14287. [PubMed: 15375209]
- Dong Y, Green T, Saal D, Marie H, Neve R, Nestler EJ, Malenka RC. CREB modulates excitability of nucleus accumbens neurons. *Nat Neurosci* 2006;9:475–7. [PubMed: 16520736]
- Donzanti BA, Althaus JS, Payson MM, Von Voigtlander PF. Kappa agonist-induced reduction in dopamine release: site of action and tolerance. *Res Commun Chem Pathol Pharmacol* 1992;78:193–210. [PubMed: 1282270]
- Dunn AJ. Stress-related activation of cerebral dopaminergic systems. *Ann N Y Acad Sci* 1988;537:188–205. [PubMed: 3202543]
- Elmer GI, Pieper JO, Levy J, Rubinstein M, Low MJ, Grandy DK, Wise RA. Brain stimulation and morphine reward deficits in dopamine D2 receptor-deficient mice. *Psychopharmacol* 2005;182:33–44.
- Fibiger HC, Nomikos GG, Pfau JG, Damsma G. Sexual behavior, eating and mesolimbic dopamine. *Clin Neuropharmacol* 15 Suppl 1992;1:566A–567A.
- Finlay JM, Damsma G, Fibiger HC. Benzodiazepine-induced decreases in extracellular concentrations of dopamine in the nucleus accumbens after acute and repeated administration. *Psychopharmacol* 1992;106:202–8.
- Franklin TR, Wang Z, Wang J, Sciortino N, Harper D, Li Y, Ehrman R, Kampman K, O'Brien CP, Detre JA, Childress AR. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. *Neuropsychopharmacol* 2007;32:2301–9.
- Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, Sibley DR. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* 1990;250:1429–32. [PubMed: 2147780]
- Goeders NE, Smith JE. Cortical dopaminergic involvement in cocaine reinforcement. *Science* 1983;221:773–5. [PubMed: 6879176]
- Gong S, Zheng C, Doughty ML, Losos K, Didkovsky N, Schambra UB, Nowak NJ, Joyner A, Leblanc G, Hatten ME, Heintz N. A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. *Nature* 2003;425:917–925. [PubMed: 14586460]
- Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends Neurosci* 2007;30:220–7. [PubMed: 17400299]
- Gracy KN, Dankiewicz LA, Koob GF. Opiate withdrawal-induced fos immunoreactivity in the rat extended amygdala parallels the development of conditioned place aversion. *Neuropsychopharmacol* 2001;24:152–60.
- Griffiths RR, Ator NA. Benzodiazepine self-administration in animals and humans: a comprehensive literature review. *NIDA Res Monogr* 1980;33:22–36. [PubMed: 6798448]
- Guix T, Hurd YL, Ungerstedt U. Amphetamine enhances extracellular concentrations of dopamine and acetylcholine in dorsolateral striatum and nucleus accumbens of freely moving rats. *Neurosci Lett* 1992;138:137–140. [PubMed: 1407652]
- Hakan RL, Henriksen SJ. Opiate influences on nucleus accumbens neuronal electrophysiology: dopamine and non-dopamine mechanisms. *J Neurosci* 1989;9:3538–3546. [PubMed: 2795139]
- Hallett PJ, Spoelgen R, Hyman BT, Standaert DG, Dunah AW. Dopamine D1 activation potentiates striatal NMDA receptors by tyrosine phosphorylation-dependent subunit trafficking. *J Neurosci* 2006;26:4690–700. [PubMed: 16641250]
- Harris GC, Aston-Jones G. Involvement of D2 dopamine receptors in the nucleus accumbens in the opiate withdrawal syndrome. *Nature* 1994;371:155–7. [PubMed: 7915401]
- Herman JP, Rivet JM, Abrous N, Le Moal M. Intracerebral dopaminergic transplants are not activated by electrical footshock stress activating in situ mesocorticolimbic neurons. *Neurosci Lett* 1988;90:83–8. [PubMed: 2901059]
- Hoebel BG, Monaco AP, Hernandez L, Aulisi EF, Stanley BG, Lenard L. Self-injection of amphetamine directly into the brain. *Psychopharmacol* 1983;81:158–63.
- Hollmann M, Hartley M, Heinemann S. Ca²⁺ permeability of KA-AMPA-gated glutamate receptor channels depends on subunit composition. *Science* 1991;252:851–3. [PubMed: 1709304]

- Hu XT, Basu S, White FJ. Repeated cocaine administration suppresses HVA-Ca²⁺ potentials and enhances activity of K⁺ channels in rat nucleus accumbens neurons. *J Neurophysiol* 2004;92:1597–1607. [PubMed: 15331648]
- Ikemoto I. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. *J Neurosci* 2003;23:9305–9311. [PubMed: 14561857]
- Ikemoto S, Glazier BS, Murphy JM, McBride WJ. Role of dopamine D1 and D2 receptors in the nucleus accumbens in mediating reward. *J Neurosci* 1997;17:8580–7. [PubMed: 9334429]
- Imperato A, Obinu MC, Demontis MV, Gessa GL. Cocaine releases limbic acetylcholine through endogenous dopamine action on D1 receptors. *Eur J Pharmacol* 1992;229:265–267. [PubMed: 1362707]
- Janak PH, Chang JY, Woodward DJ. Neuronal spike activity in the nucleus accumbens of behaving rats during ethanol self-administration. *Brain Res* 1999;817:172–184. [PubMed: 9889360]
- Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J Neurosci* 1992;12:483–8. [PubMed: 1346804]
- Kalivas PW, Duffy P. Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. *Biol Psychiatry* 1989;25:913–28. [PubMed: 2541803]
- Kelley AE, Bless EP, Swanson CJ. Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats. *J Pharmacol Exp Ther* 1996;278:1499–1507. [PubMed: 8819538]
- Kelley AE. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci Biobehav Rev* 2004;27:765–76. [PubMed: 15019426]
- Kelsey JE, Carlezon WA, Falls WA. Lesions of the nucleus accumbens in rats reduce opiate reward but do not alter context-specific opiate tolerance. *Behav Neurosci* 1989;103:1327–34. [PubMed: 2558677]
- Kelz MB, Chen J, Carlezon WA, Whisler K, Gilden L, Beckmann AM, Steffen C, Zhang YJ, Marotti L, Self DW, Tkatch T, Baranaukas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR, Nestler EJ. Expression of the transcription factor deltaFosB in the brain controls sensitivity to cocaine. *Nature* 1999;401:272–6. [PubMed: 10499584]
- Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord* 1997;45:19–30. [PubMed: 9268772]
- Kourrich S, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J Neurosci* 2007;27:7921–7928. [PubMed: 17652583]
- Leone P, Pocock D, Wise RA. Morphine-dopamine interaction: ventral tegmental morphine increases nucleus accumbens dopamine release. *Pharmacol Biochem Behav* 1991;39:469–72. [PubMed: 1946587]
- Liu ZH, Shin R, Ikemoto S. Dual Role of Medial A10 Dopamine Neurons in Affective Encoding. *Neuropsychopharmacol*. 2008in press
- Lobo MK, Karsten SL, Gray M, Geschwind DH, Yang XW. FACS-array profiling of striatal projection neuron subtypes in juvenile and adult mouse brains. *Nat Neurosci* 2006;9:443–452. [PubMed: 16491081]
- Mague SD, Pliakas AM, Todtenkopf MS, Tomasiewicz HC, Zhang Y, Stevens WC, Jones RM, Portoghese PS, Carlezon WA Jr. Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. *J Pharmacol Exp Ther* 2003;305:323–30. [PubMed: 12649385]
- Maldonado R, Saiardi A, Valverde O, Samad TA, Roques BP, Borrelli E. Absence of opiate rewarding effects in mice lacking dopamine D2 receptors. *Nature* 1997;388:586–9. [PubMed: 9252189]
- Malinow R, Malenka RC. AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* 2002;25:103–26. [PubMed: 12052905]
- Mangiavacchi S, Wolf ME. D1 dopamine receptor stimulation increases the rate of AMPA receptor insertion onto the surface of cultured nucleus accumbens neurons through a pathway dependent on protein kinase A. *J Neurochem* 2004;88:1261–1271. [PubMed: 15009682]
- Mansour A, Watson SJ, Akil H. Opioid receptors: past, present and future. *Trends Neurosci* 1995;18:69–70. [PubMed: 7537414]

- Mark GP, Rada P, Pothos E, Hoebel BG. Effects of feeding and drinking on acetylcholine release in the nucleus accumbens, striatum, and hippocampus of freely behaving rats. *J Neurochem* 1992;58:2269–2274. [PubMed: 1573406]
- Mead AN, Brown G, Le Merrer J, Stephens DN. Effects of deletion of *gria1* or *gria2* genes encoding glutamatergic AMPA-receptor subunits on place preference conditioning in mice. *Psychopharmacology (Berl)* 2005;179:164–171. [PubMed: 15619119]
- Mead AN, Zamanillo D, Becker N, Stephens DN. AMPA-receptor GluR1 subunits are involved in the control over behavior by cocaine-paired cues. *Neuropsychopharmacology* 2007;32:343–353. [PubMed: 16495937]
- McCarthy PS, Walker RJ, Woodruff GN. Depressant actions of enkephalins on neurones in the nucleus accumbens [proceedings]. *J Physiol* 1977;267:40P–41P.
- McFarland K, Davidge SB, Lapish CC, Kalivas PW. Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *J Neurosci* 2004;24:1551–60. [PubMed: 14973230]
- Meredith GE. The synaptic framework for chemical signaling in nucleus accumbens. *Ann N Y Acad Sci* 1999;877:140–56. [PubMed: 10415648]
- Mizrahi R, Rusjan P, Agid O, Graff A, Mamo DC, Zipursky RB, Kapur S. Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia. *Am J Psychiatry* 2007;164:630–637. [PubMed: 17403977]
- Murai T, Koshikawa N, Kanayama T, Takada K, Tomiyama K, Kobayashi M. Opposite effects of midazolam and beta-carboline-3-carboxylate ethyl ester on the release of dopamine from rat nucleus accumbens measured by in vivo microdialysis. *Eur J Pharmacol* 1994;261:65–71. [PubMed: 8001655]
- Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 2006;59:1151–9. [PubMed: 16566899]
- Newton SS, Thome J, Wallace TL, Shirayama Y, Schlesinger L, Sakai N, Chen J, Neve R, Nestler EJ, Duman RS. Inhibition of cAMP response element-binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. *J Neurosci* 2002;22:10883–90. [PubMed: 12486182]
- Nicola SM, Yun IA, Wakabayashi KT, Fields HL. Firing of nucleus accumbens neurons during the consummatory phase of a discriminative stimulus task depends on previous reward predictive cues. *J Neurophysiol* 2004;91:1866–1882. [PubMed: 14645378]
- O'Donnell P, Grace AA. Dopaminergic reduction of excitability in nucleus accumbens neurons recorded in vitro. *Neuropsychopharmacol* 1996;15:87–97.
- O'Donnell P, Grace AA. Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J Neurosci* 1995;15:3622–39. [PubMed: 7751934]
- Olds ME. Reinforcing effects of morphine in the nucleus accumbens. *Brain Res* 1982;237:429–40. [PubMed: 7083004]
- Parsegian A, Todtenkopf MS, Neve RL, Carlezon WA Jr. Viral vector-induced elevations of CREB expression in the nucleus accumbens produces anhedonia in the rat intracranial self-stimulation (ICSS) test. *Soc Neurosci Abstr* 2006;33in press
- Pennartz CM, Boeijinga PH, Lopes da Silva FH. Locally evoked potentials in slices of the rat nucleus accumbens: NMDA and non-NMDA receptor mediated components and modulation by GABA. *Brain Res* 1990;529:30–41. [PubMed: 1980846]
- Peoples LL, West MO. Phasic firing of single neurons in the rat nucleus accumbens correlated with the timing of intravenous cocaine self-administration. *J Neurosci* 1996;16:3459–3473. [PubMed: 8627379]
- Peoples LL, Kravitz AV, Guillem K. The role of accumbal hypoactivity in cocaine addiction. *ScientificWorldJournal* 2007;7:22–45. [PubMed: 17982574]
- Pfaus JG. Neurobiology of sexual behavior. *Curr Opin Neurobiol* 1999;9:751–8. [PubMed: 10607643]
- Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. *Science* 1986;233:774–6. [PubMed: 3016896]
- Phillips AG, LePiane G. Disruption of conditioned taste aversion in the rat by stimulation of amygdala: a conditioning effect, not amnesia. *J Comp Physiol Psychol* 1980;94:664–74. [PubMed: 7410628]

- Pliakas AM, Carlson RR, Neve RL, Konradi C, Nestler EJ, Carlezon WA Jr. Altered responsiveness to cocaine and increased immobility in the forced swim test associated with elevated cAMP response element-binding protein expression in nucleus accumbens. *J Neurosci* 2001;21:7397–403. [PubMed: 11549750]
- Rajadhyaksha A, Barczak A, Macías W, Leveque JC, Lewis SE, Konradi C. L-Type Ca^{2+} channels are essential for glutamate-mediated CREB phosphorylation and c-fos gene expression in striatal neurons. *J Neurosci* 1999;19:6348–59. [PubMed: 10414964]
- Roberts DC, Koob GF, Klonoff P, Fibiger HC. Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens. *Pharmacol Biochem Behav* 1980;12:781–7. [PubMed: 7393973]
- Roitman MF, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. *Neuron* 2005;45:587–97. [PubMed: 15721244]
- Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. *J Neurosci* 2007;27:1594–1605. [PubMed: 17301168]
- Snyder GL, Allen PB, Fienberg AA, Valle CG, Haganir RL, Nairn AC, Greengard P. Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and psychostimulants in vivo. *J Neurosci* 2000;20:4480–8. [PubMed: 10844017]
- Spanagel R, Herz A, Shippenberg TS. Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. *Proc Natl Acad Sci U S A* 1992;89:2046–50. [PubMed: 1347943]
- Stinus L, Le Moal M, Koob GF. Nucleus accumbens and amygdala are possible substrates for the aversive stimulus effects of opiate withdrawal. *Neuroscience* 1990;37:767–73. [PubMed: 2247222]
- Sun X, Milovanovic M, Zhao Y, Wolf ME. Acute and chronic dopamine receptor stimulation modulates AMPA receptor trafficking in nucleus accumbens neurons cocultured with prefrontal cortex neurons. *J Neurosci* 2008;28:4216–30. [PubMed: 18417701]
- Surmeier DJ, Ding J, Day M, Wang Z, Shen W. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci* 2007;30:228–35. [PubMed: 17408758]
- Svingos AL, Colago EE, Pickel VM. Cellular sites for dynorphin activation of kappa-opioid receptors in the rat nucleus accumbens shell. *J Neurosci* 1999;19:1804–13. [PubMed: 10024364]
- Swanson GT, Kamboj SK, Cull-Candy SG. Single-channel properties of recombinant AMPA receptors depend on RNA editing, splice variation, and subunit composition. *J Neurosci* 1997;17:58–69. [PubMed: 8987736]
- Taha SA, Fields HL. Encoding of palatability and appetitive behaviors by distinct neuronal populations in the nucleus accumbens. *J Neurosci* 2005;25:1193–1202. [PubMed: 15689556]
- Tindell AJ, Berridge KC, Aldridge JW. Ventral pallidal representation of pavlovian cues and reward: population and rate codes. *J Neurosci* 2004;24:1058–69. [PubMed: 14762124]
- Tindell AJ, Smith KS, Peciña S, Berridge KC, Aldridge JW. Ventral pallidum firing codes hedonic reward: when a bad taste turns good. *J Neurophysiol* 2006;96:2399–409. [PubMed: 16885520]
- Todtenkopf MS, Marcus JF, Portoghese PS, Carlezon WA Jr. Effects of kappa-opioid receptor ligands on intracranial self-stimulation in rats. *Psychopharmacol* 2004;172:463–70.
- Todtenkopf MS, Parsegian A, Naydenov A, Neve RL, Konradi C, Carlezon WA Jr. Brain reward regulated by AMPA receptor subunits in nucleus accumbens shell. *J Neurosci* 2006;26:11665–9. [PubMed: 17093088]
- Todtenkopf MS, Stellar JR. Assessment of tyrosine hydroxylase immunoreactive innervation in five subregions of the nucleus accumbens shell in rats treated with repeated cocaine. *Synapse* 2000;38:261–70. [PubMed: 11020229]
- Trujillo KA, Belluzzi JD, Stein L. Opiate antagonists and self-stimulation: extinction-like response patterns suggest selective reward deficit. *Brain Res* 1989;492:15–28. [PubMed: 2752295]
- Turgeon SM, Pollack AE, Fink JS. Enhanced CREB phosphorylation and changes in c-Fos and FRA expression in striatum accompany amphetamine sensitization. *Brain Res* 1997;749:120–6. [PubMed: 9070635]

- Uchimura N, Higashi H, Nishi S. Membrane properties and synaptic responses of the guinea pig nucleus accumbens neurons in vitro. *J Neurophysiol* 1989;61:769–779. [PubMed: 2723719]
- Vekovischeva OY, Zamanillo D, Echenko O, Seppälä T, Uusi-Oukari M, Honkanen A, Seeburg PH, Sprengel R, Korpi ER. Morphine-induced dependence and sensitization are altered in mice deficient in AMPA-type glutamate receptor-A subunits. *J Neurosci* 2001;21:4451–9. [PubMed: 11404432]
- Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol* 2007;64:1575–9. [PubMed: 17998440]
- Wadenberg ML. A review of the properties of spiradoline: a potent and selective kappa-opioid receptor agonist. *CNS Drug Rev* 2003;9:187–98. [PubMed: 12847558]
- Weiss RD. Adherence to pharmacotherapy in patients with alcohol and opioid dependence. *Addiction* 2004;99:1382–92. [PubMed: 15500591]
- Welter M, Vallone D, Samad TA, Meziane H, Usiello A, Borrelli E. Absence of dopamine D2 receptors unmasks an inhibitory control over the brain circuitries activated by cocaine. *Proc Natl Acad Sci U S A* 2007;104:6840–5. [PubMed: 17426149]
- West TE, Wise RA. Effects of naltrexone on nucleus accumbens, lateral hypothalamic and ventral tegmental self-stimulation rate-frequency functions. *Brain Res* 1988;462:126–33. [PubMed: 3179728]
- Wheeler RA, Twining RC, Jones JL, Slater JM, Grigson PS, Carelli RM. Behavioral and electrophysiological indices of negative affect predict cocaine self-administration. *Neuron* 2008;57:774–85. [PubMed: 18341996]
- Wise RA. Addictive drugs and brain stimulation reward. *Annu Rev Neurosci* 1996;19:319–40. [PubMed: 8833446]
- Wise RA. Neuroleptics and operant behavior: the anhedonia hypothesis. *Behav Brain Sci* 1982;5:39–87.
- Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol Rev* 1987;94:469–92. [PubMed: 3317472]
- Wise RA, Rompré PP. Brain dopamine and reward. *Annu Rev Psychol* 1989;40:191–225. [PubMed: 2648975]
- Wood PL. Actions of GABAergic agents on dopamine metabolism in the nigrostriatal pathway of the rat. *J Pharmacol Exp Ther* 1982;222:674–9. [PubMed: 6286931]
- Yun IA, Wakabayashi KT, Fields HL, Nicola SM. The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. *J Neurosci* 2004a;24:2923–2933. [PubMed: 15044531]
- Yun IA, Nicola SM, Fields HL. Contrasting effects of dopamine and glutamate receptor antagonist injection in the nucleus accumbens suggest a neural mechanism underlying cue-evoked goal-directed behavior. *Eur J Neurosci* 2004b;20:249–263. [PubMed: 15245497]
- Zahm DS. Functional-anatomical implications of the nucleus accumbens core and shell subterritories. *Ann N Y Acad Sci* 1999;877:113–28. [PubMed: 10415646]
- Zhang XF, Hu XT, White FJ. Whole-cell plasticity in cocaine withdrawal: reduced sodium currents in nucleus accumbens neurons. *J Neurosci* 1998;18:488–498. [PubMed: 9412525]

Fig. 1. Schematic illustrating the subunit composition of AMPA (glutamate) receptors. For simplicity, the receptors are depicted with 2 subunits. GluR2 contains a motif that blocks Ca^{2+} flux through the receptor, and thus heteromeric receptors that contain at least one GluR2 subunit are Ca^{2+} -impermeable. Conversely, high expression of GluR1 subunits favors formation of high conductance, Ca^{2+} -permeable AMPA receptors. Increased intracellular Ca^{2+} has important effects on neuronal functions such as depolarization, and has been implicated in neuroplasticity involving altered gene transcription.

Fig. 2.

Schematic depicting a simple working hypothesis of how the nucleus accumbens (NAc) may regulate rewarding and aversive states. **(a)** NAc neurons tonically inhibit reward-related processes. Under normal circumstances, there is a balance between cortical (PFC, AMG) excitatory (+) influences mediated by glutamate actions at AMPA and NMDA receptors, and midbrain (VTA) inhibitory (-) influences mediated by dopamine actions at D2-like receptors. NAc neurons have low baseline rates of firing, and depolarization-mediated influx of Ca^{2+} through NMDA receptors and calcium channels is not sufficient to alter gene expression. **(b)** Depolarization of NAc neurons containing D2-like receptors and enkephalin inhibits downstream areas implicated in reward (e.g., ventral pallidum) which is encoded as aversion. It also leads to elevated Ca^{2+} influx, which may trigger experience-dependent neuroadaptations (e.g., activation of CREB, elevated expression of GluR1) can produce feed-forward effects that dysregulate the system. AMG, amygdala; Ca, calcium channel; Ca^{2+} , calcium; CREB, cAMP response element binding protein; D2, dopamine D2-like receptor; DA, dopamine; ENK, enkephalin; G1/G2, AMPA glutamate receptor containing GluR1 and

GluR2; GABA, gamma-aminobutyric acid; GLU, glutamate; N, NMDA receptor; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area

Fig. 3.

Intravenous infusions of the μ -opioid agonist fentanyl and the κ -opioid agonist U69,593 induce overlapping but anatomically selective blood oxygen level dependent functional MRI (BOLD fMRI) responses in alert male cynomolgus monkeys (N=3). Results are from duplicate scans with each drug condition in each subject. Fentanyl induced positive BOLD fMRI responses in the caudate nucleus and bilaterally in putamen, amygdala, and insula. An equipotent dose of U69,593 induced positive BOLD fMRI responses in caudate nucleus and bilateral insula, but also induced positive responses in bilateral nucleus accumbens (NAc) and ventral striatum. Crosshairs are centered on the NAc. (From Kaufman, M.J., Frederick, B.deB., Negus, S.S., et al., in preparation; used with permission).