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Cocaine-induced Homeostatic Regulation and Dysregulation of Nucleus Accumbens Neurons

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Abstract

Homeostatic response is an endowed self-correcting/maintaining property for living units, ranging from subcellular domains, single cells, and organs to the whole organism. Homeostatic responses maintain stable function through the ever-changing internal and external environments. In central neurons, several forms of homeostatic regulation have been identified, all of which tend to stabilize the functional output of neurons toward their prior “set-point.” Medium spiny neurons (MSNs) within the forebrain region of the nucleus accumbens (NAc) play a central role in gating/regulating emotional and motivational behaviors including craving and seeking drugs of abuse. Exposure to highly salient stimuli such as cocaine administration not only acutely activates a certain population of NAc MSNs, but also induces long-lasting changes in these neurons. It is these long-lasting cellular alterations that are speculated to mediate the increasingly strong cocaine-craving and cocaine-seeking behaviors. Why do the potentially powerful homeostatic mechanisms fail to correct or compensate for these drug-induced maladaptations in neurons? Based on recent experimental results, this review proposes a hypothesis of homeostatic dysregulation induced by exposure to cocaine. Specifically, we hypothesize that exposure to cocaine generates false molecular signals which mislead the homeostatic regulation process, resulting in maladaptive changes in NAc MSNs. Thus, many molecular and cellular alterations observed in the addicted brain may indeed result from homeostatic dysregulation. This review is among the first to introduce the concept of homeostatic neuroplasticity to understanding the molecular and cellular maladaptations following exposure to drugs of abuse.

1. Introduction

Homeostasis is central for living organisms (Cannon, 1963). With appropriate homeostatic responses, individual cells, tissues, organs and organisms are able to maintain relatively stable functional output throughout the ongoing internal and external challenges (Cannon, 1963). For central neurons, homeostatic plasticity is a powerful endogenous mechanism that functions to maintain stable neuronal function. Thus far, several forms of homeostatic neuroplasticity have been characterized in different brain regions, all of which act to stabilize the overall functional output of the neurons toward their prior “set-point” (Turrigiano and Nelson, 2004). With homeostatic plasticity, neurons mobilize available resources to restore or functionally

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compensate for the altered cellular components throughout developmental regulations, metabolic turnovers, and even pathological insults.

A stable function of nucleus accumbens (NAc) medium spiny neurons (MSNs) is essential for proper behavioral outputs of emotional and motivational drives. When measured at the cellular level, natural rewards or modest incentive stimuli rarely produce long-lasting biochemical and biophysical changes in the NAc (Hyman et al., 2006). However, following exposure to drugs of abuse, a large number of adaptive changes occur, affecting presynaptic terminals, postsynaptic receptors, voltage-gated ion channels on the membrane, and neuromodulators, resulting in profound alterations in NAc MSNs (Hyman et al., 2006). Apparently, normal function of NAc MSNs fails to be restored in drug-exposed animals because of, hypothetically, either a shift of the homeostatic “set point” or malfunctional homeostatic mechanisms.

Dysregulation of the reward system characterized by a chronic deviation of reward set point is termed allostasis (Koob and Le Moal, 2001). It is a process of maintaining apparent stability around a new set point through changes, but at a price (Sterling, 1988). From a reductionist point of view, allostasis results from inadequate local and global feedback regulations. Although it is more complex than homeostasis as it typically involves the whole brain and body instead of simply local feedbacks, it is mediated by the same molecular and cellular mechanisms that underlie homeostasis, or rather, malfunctional homeostasis.

This review summarizes several forms of homeostatic neuroplasticity and their potential roles in cocaine-induced cellular alterations of NAc MSNs. Based on these observations, we hypothesize that the key signaling substrates controlling homeostatic plasticity are altered by exposure to cocaine, and the consequent false signals mislead homeostatic plasticity. Thus, a large number of molecular and cellular alterations observed in NAc MSNs from cocaine-exposed animals are results of homeostatic dysregulation.

2. Concept of homeostatic neuroplasticity

2.1 Regulated versus homeostatic plasticity

Depending on the induction mechanism, expression specificity/pattern, and functional roles, neuroplasticity can be categorized as regulated or homeostatic neuroplasticity (Fig. 1). Regulated neuroplasticity, also called experience- or activity-dependent plasticity, refers to a large category of plasticity that occurs upon specific/contingent stimulations. Two well-characterized forms of regulated plasticity are long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmissions. The two defining properties of regulated neuroplasticity are contingency and specificity (Malenka and Nicoll, 1999). For example, a successful induction of LTP at excitatory synapses within the CA1 region of the hippocampus requires a contingent pre- and post-synaptic activation (thus, pre- and post-synaptic contingency), and expression of LTP occurs exclusively within the activated projection afferent (thus, afferent-specificity). Accordingly, regulated plasticity has been proposed as a cellular mechanism mediating the formation of contingent memory following learning processes (Lomo, 2003; Malenka and Nicoll, 1999). In general, regulated neuroplasticity follows positive feedback loops which shift the neuron from its original functional state to a new functional state in order to gain new, or modified, behavioral outputs.

Homeostatic plasticity often occurs “spontaneously” upon persistent internal or external drive. It follows negative feedback loops to restrain neural activity within a normal operating range, a range so narrow that it typically becomes a “set point.” Homeostatic plasticity is one of the few important mechanisms that function to maintain the stability of neurons and neural circuits. One form of homeostatic neuroplasticity that has been well characterized is homeostatic synaptic compensation at the neuromuscular junction. It functions to maintain stable synaptic

transmission against pre- or post-synaptic alterations. For example, when the sensitivity of postsynaptic neurotransmitter receptors was chronically decreased, presynaptic neurotransmitter release is gradually and persistently increased, such that the synaptic depolarization of muscle is restored to precisely the levels observed in the absence of the perturbation (Davis and Bezprozvanny, 2001; Davis, 2006). As such, the altered synaptic transmission can be fully restored through homeostatic mechanisms. Although not clearly defined, it appears that contingency and specificity are not the two essential properties for homeostatic plasticity. Indeed, several lines of evidence support a notion that homeostatic plasticity is triggered by non-coincidental events, and is more likely a non-specific, global effect (Turrigiano and Nelson, 2004).

Functionally, the key difference between regulated and homeostatic plasticity is that regulated plasticity tends to drive the functional output of a neuron away from the prior “set-point,” whereas homeostatic plasticity tends to maintain the overall functional output of a neuron around the “set-point.” Thus, regulated and homeostatic plasticity functionally oppose and complement each other. Without regulated plasticity, new forms of neural activity, new memories, and behavioral patterns may not be formed, whereas without homeostatic plasticity, neural activity may eventually run out of control, and behavioral output may become highly unpredictable.

2.2 Different forms of homeostatic plasticity

The functional output of a neuron is defined by its action potential firing. Two major factors that determine in vivo action potential firings are integrated synaptic input and intrinsic membrane excitability. Synaptic input drives the membrane potential toward, or away from, the threshold for action potential firing. The intrinsic membrane excitability not only sets the action potential threshold, but also determines how often to fire action potentials once the membrane potential moves beyond the threshold. It has been recognized that homeostatic plasticity plays a role in regulating both synaptic transmission and membrane excitability, as well as the interaction of the two. These different forms of homeostatic plasticity may play a profound role in stabilizing the functional output of neurons.

2.2.1 Two-way homeostatic regulation of synaptic transmission—Homeostatic plasticity at synapses has been demonstrated in several preparations as a two-way communication between the pre- and postsynaptic sites. The most clear-cut results are from studies of the neuromuscular junction, in which alterations of presynaptic release cause opposing changes on postsynaptic acetylcholine receptors, such that the postsynaptic responsiveness is altered to functionally compensate for the presynaptic changes (Axelsson and Thesleff, 1959; Davis and Goodman, 1998; Sandrock et al., 1997). On the other hand, a reduction in the number and/or function of postsynaptic receptors induces a compensatory increase in presynaptic release (Berg and Hall, 1975; Davis and Goodman, 1998; Paradis et al., 2001). Such two-way homeostatic trans-synaptic crosstalks appear to also exist in central neurons. In cultured cortical, hippocampal, or spinal neurons, a decrease in network (presumably synaptic) activity induces a global increase in excitatory synaptic strength, whereas an increase in the network activity, achieved by partial inhibition of inhibitory synaptic input, results in a homeostatic decrease in excitatory synaptic strength (Burrone et al., 2002; Lissin et al., 1998; O’Brien et al., 1998; Ramakers et al., 1990; Turrigiano et al., 1998; Van Den Pol et al., 1996; Watt et al., 2000). Thus, synaptic homeostasis is achieved, at least in part, by intra-synaptic homeostatic signaling.

2.2.2 Homeostatic membrane plasticity—Homeostatic mechanisms also exist around somatic membrane to gauge and stabilize the intrinsic membrane excitability of neurons in response to changes in membrane activity. In cortical neuronal cultures, chronic prevention of

action potential firing induces an increase in the density of voltage-gated sodium channels and a decrease in potassium channels, effects that collectively function to compensate for the decreased membrane activity (Desai et al., 1999a; Desai et al., 1999b). In dorsal root ganglion neurons, chronic membrane excitation (achieved by chronic electrical stimulation) induces a gradual decrease in voltage-gated calcium conductances, a change that tends to dampen membrane excitability (Li et al., 1996). Thus, membrane-residing voltage-gated ion channels may be selectively targeted as the local functional domains for homeostatic regulation.

2.2.3 Homeostatic synapse-membrane crosstalk—It is now evident that homeostatic mechanisms not only exist locally within relatively independent subcellular domains (i.e., synapses or somatic membrane), but often function between subcellular domains, such as between synapses and the non-synaptic membrane. This synapse-membrane crosstalk may occur to contribute critically to whole-cell homeostasis. Some of the first evidence for synapse-membrane crosstalk was demonstrated in stomatogastric ganglion (STG) neurons from the spiny lobster *Panulirus* and the crab *Cancer*. STG neurons *in vivo* fire in bursts, which is driven by rhythmic excitatory synaptic input. When the synaptic input is pharmacologically inhibited or anatomically removed, STG neurons become silent but over time (~70 hr) regain the rhythmic firing patterns (Turrigiano et al., 1994). Further evidence shows that this homeostatic recovery is mediated by expression and rearrangement of a set of voltage-gated ion channels (Turrigiano et al., 1994). Thus, synaptic alteration (loss of synaptic innervations) is sensed and transferred to a regulatory mechanism related to ion channels on the somatic membrane, which results in a restoration of the functional output of STG neurons.

In the mammalian CNS, it has been observed similarly in the visual cortex that lowering visual drive from the retina induces a compensatory increase in the intrinsic membrane excitability, several synapses away, in layer 2/3 pyramidal neurons (Maffei and Turrigiano, 2008). In addition, the reverse is also true; changes at the somatic membrane can be sensed and transferred to synapses to induce global scaling of synaptic strength (so-called synaptic scaling). In cultured cortical neurons, selective inhibition of postsynaptic action potential firing by locally blocking voltage-gated sodium channel at the soma is sufficient to increase synaptic glutamatergic receptors through the dendrite (Ibata et al., 2008). Furthermore, changes in the membrane activity (action potential firing) are capable of inducing homeostatic regulations of presynaptic release mechanisms, as has been shown at the neuromuscular junction (Davis and Bezprozvanny, 2001) and in cultured cortical neurons (Wierenga et al., 2006).

Of particular interest is a phenomenon observed in the rat NAc MANs, which is phenotypically identical to the above-mentioned restoration of oscillating behaviors in cultured STG. A common *in vivo* physiological property of many types of central neurons is the rhythmic oscillation of the membrane potential between a hyperpolarized downstate potential (e.g., -75 mV) and a relatively depolarized upstate potential (e.g., -55 mV) (O'Donnell and Grace, 1995; Wilson and Kawaguchi, 1996). The upstate is the functionally active state for most of the oscillating neurons to fire action potentials (O'Donnell and Grace, 1995; Wilson and Groves, 1981; Wilson and Kawaguchi, 1996). This upstate-downstate oscillation is well exemplified in the dorsal striatal and NAc MSNs *in vivo* (Mahon et al., 2006; O'Donnell and Grace, 1993; O'Donnell and Grace, 1995; Wilson and Kawaguchi, 1996). It is driven by rhythmically synchronous activation of excitatory synaptic input (Huang et al., 2008; Plenz and Kitai, 1996; Plenz and Kitai, 1998). When NAc slices are acutely prepared, however, the cell bodies of most glutamatergic projections are removed, and upstate events become rare in NAc MSNs. However, after ~24 hrs of "recovery" *in vitro*, ~50% of NAc MSNs regain the upstate-downstate cyclings and fire action potentials during the upstate (Lee et al., 2008). In contrast to STG neurons (Turrigiano et al., 1994), recovery of upstate-downstate cycling is not mediated by postsynaptic ion channels. Instead, it is likely mediated by the recovery of synchronous activity of existing glutamatergic terminals, as the spontaneous presynaptic

release, but not the efficacy of individual excitatory synapses, was significantly upregulated during the course of slice culture (Lee et al., 2008). Although it remains to be determined how those glutamatergic terminals severed from the soma achieve synchronous activity, it is clear that under different conditions, very different cellular resources are utilized by different cell types to achieve a common biological purpose, to homeostatically regain the lost function. Nonetheless, the self-governing homeostatic mechanisms must exist 1) to “remember” the set-point, 2) to continuously compare the current functional output with the set-point so as to detect the altered functional output, 3) to trigger appropriate molecular cascades once a change is detected, and 4) to suspend the homeostatic responses once the functional output is modified close to the set-point. Thus, homeostatic responses are not random events; they are highly organized and sophisticated self-ruling cascades including several levels of regulatory substrates. As such, tweaking the critical components within the homeostatic cascade can be a way for either pathogenic insults to twist the functional output of neurons or therapeutic approaches to enhance homeostatic recovery of the neuronal function.

3. Homeostatic plasticity in NAc

A large portion of drug-induced adaptive cellular changes are likely homeostatic (Kalivas, 2005; Nestler, 1992). However, understanding homeostatic plasticity and its role in addiction is still in its infant phase. Thus far, only a small number of studies directly address this issue in addiction-related brain regions including the NAc.

3.1 Synaptic scaling, in vitro studies

Synaptic scaling is a relatively well-defined form of homeostatic synaptic plasticity, expressed as global scaling of synaptic weights up or down to compensate for altered neural activity. It can be induced globally or locally, and is mediated by adjustments of presynaptic release and/or postsynaptic responsiveness (Turrigiano and Nelson, 2004).

The involvement of synaptic scaling in drug-induced cellular adaptations was first proposed in NAc MSNs as a potential mechanism mediating cocaine withdrawal-induced upregulation of synaptic AMPA receptors (AMPA) (Boudreau and Wolf, 2005). The rationale was that following repeated cocaine exposure, the NAc and its source of glutamatergic innervations from the medial prefrontal cortex (PFC) both become metabolically hypoactive (Goldstein and Volkow, 2002; Porrino et al., 2002; Porrino et al., 2007). The decreased activity in NAc MSNs is hypothesized to trigger synaptic scaling at excitatory synapses to increase the postsynaptic responsiveness (Boudreau and Wolf, 2005; Boudreau et al., 2007). The ability of NAc MSNs to undergo synaptic scaling was subsequently demonstrated in vitro. In these studies, NAc MSNs, which are GABAergic neurons, are co-cultured with PFC glutamatergic neurons to restore excitatory synapses (Sun et al., 2005; Sun and Wolf, 2009). It was shown then that prolonged (1–3 days) pharmacological blockade of glutamate AMPARs causes an increase in the number of surface and synaptic AMPARs. Reciprocally, blocking GABAergic transmission leads to a decrease in the surface and synaptic AMPARs (Sun and Wolf, 2009). Furthermore, the increased synaptic AMPARs appear to be GluR1/2-containing AMPARs, as the surface and total levels of GluR1 and GluR2, but not GluR3, are bi-directionally regulated as MSNs undergo synaptic scaling (Sun et al., 2008; Sun and Wolf, 2009). Interestingly, repeated pretreatment with dopamine, which acutely increases the surface level of GluR1 and GluR2 subunits of AMPARs, occludes the homeostatic up-regulation of postsynaptic AMPARs in NAc MSNs (Sun and Wolf, 2009). Because a common acute pharmacological effect of drugs of abuse is to increase the level of dopamine in the NAc, this occlusion effect suggests that dopamine may be one substrate for cocaine exposure to trigger homeostatic scaling of AMPARs in NAc neurons. It is worth noting that unlike the effect of dopamine (Sun and Wolf, 2009), repeated exposure to cocaine does not significantly alter the surface levels of GluR1 and GluR2 are not altered when measured during short-term withdrawal

(Boudreau and Wolf, 2005; Boudreau et al., 2007). This seemingly discrepant results may reflect the impact of the short-term withdrawal even it is short (i.e., 1 day), the difference between in vitro and in vivo conditions, or the difference between acute and homeostatic effects of dopamine and cocaine.

3.2 Homeostatic synapse-driven membrane plasticity

More recently, we demonstrated a novel form of homeostatic crosstalk in NAc MSNs between excitatory synapses and membrane excitability, so-called homeostatic synapse-driven membrane plasticity (hSMP; Fig. 2) (Ishikawa et al., 2009). hSMP is triggered by a chronic increase or decrease in the strength of excitatory synaptic transmission and is expressed as a persistent decrease or increase in membrane excitability (Ishikawa et al., 2009). Given that the functional output of a central neuron is largely determined by the integration of synaptic input and membrane excitability, hSMP functions to stabilize the output of NAc MSNs by offsetting the impact of altered synaptic activity on action potential firing. Furthermore, hSMP also exists in hippocampal neurons (Schlüter et al., unpublished data), suggesting that hSMP is not limited to NAc MSNs and may be a general regulatory mechanism for central neurons.

In theory, hSMP requires a sensor to gauge the intensity of synaptic activity, an executive component to translate the sensed information into the regulation of membrane component, and a set of ion channels to express hSMP. Our results suggest that synaptic NMDA receptors (NMDARs) may act as sensors because manipulations of synaptic NMDARs alone are sufficient to induce bi-directional modulations of membrane excitability of NAc MSNs (Ishikawa et al., 2009). Synaptic NMDARs have long been known to function as coincidence detectors for regulated synaptic plasticity (Malenka and Nicoll, 1999), where the NMDAR subunit compositions as well as the level of activity drive synaptic transmission toward different destinies, LTP or LTD, depending on specific experimental conditions (Barria and Malinow, 2005; Berberich et al., 2005; Liu et al., 2004; Massey et al., 2004; Morishita et al., 2007). Our results show that in addition to be co-incidence detectors, synaptic NMDARs may also function to detect the overall activity level of excitatory synapses (Ishikawa et al., 2009). Identification of synaptic NMDARs as the trigger for hSMP provides significant insight in identifying the potentially coordinative and cooperative subcellular network that carries out homeostatic regulation. Using a pharmacological approach, our preliminary studies show that NR2A- and NR2B-containing NMDARs may differentiate their roles in mediating bi-directional regulation of membrane excitability via hSMP. More specifically, persistent activation of NR2B-, but not NR2A-containing, NMDARs induces a homeostatic decrease in membrane excitability of NAc MSNs (unpublished data). Given that NR2A- and NR2B-containing NMDARs are coupled to different sets of intracellular signaling cascades or to the same signaling cascades but with different intensity (Barria and Malinow, 2005; Berberich et al., 2005; Berberich et al., 2007; Cull-Candy and Leszkiewicz, 2004; Leonard et al., 1999; Liu et al., 2004; Massey et al., 2004; Strack et al., 2000; Vicini et al., 1998), targeting NMDAR subunits and their differentially coupled intracellular signaling cascades may be a feasible starting point to tackle the cellular logic underlying hSMP.

The expression of hSMP-based decrease in the membrane excitability of NAc shell MSNs is mediated by regulation of calcium-activated SK type potassium channels; an increase in the activity of synaptic NMDARs induces a gradual up-regulation of SK channel-mediated afterhyperpolarization (AHP), resulting in dampening of the membrane excitability (Ishikawa et al., 2009). This result is intriguing because SK channel activity is otherwise not typically detectable by electrophysiology in NAc shell neurons (Ishikawa et al., 2009). As such, hSMP may initiate certain protein expression and/or delivery mechanisms de novo to achieve the overall balancing act. On the other hand, hSMP-mediated increase in the membrane excitability of NAc MSNs does not involve SK channels (Ishikawa et al., 2009). Thus, other unidentified

substrates are employed for the expression of hSMP-mediated increase in membrane excitability. Taken together, the available results suggest that although the intrinsic membrane excitability is the final target of hSMP, different repertoires of membrane-located ion channels are involved in different directions of hSMP-based modulations.

4. Homeostatic regulation and dysregulation in NAc following exposure to cocaine

Following exposure to cocaine, both excitatory synaptic input and membrane excitability of NAc MSNs undergo substantial changes. These changes are dependent on the timing (e.g., exposure vs. withdrawal, short-term vs. long-term withdrawal, and withdrawal vs. re-exposure), and the specific procedures (e.g., self-administration vs. i.p. injection by experimenter). Two key questions this review considers are whether these cocaine-induced cellular changes are homeostatically linked, and whether homeostatic plasticity acts to maintain the functional stability of NAc MSNs in cocaine-treated animals.

4.1 Short-term withdrawal

4.1.1 Repeated i.p. injections of cocaine—Most results describing cocaine-induced cellular adaptations are obtained using the sensitization procedure (e.g., i.p. injection of cocaine for 5 – 10 days, 10 – 20 mg/kg/day). During short-term withdrawal (on withdrawal day 1–3), results about the strength of excitatory synapses in NAc MSNs come from biochemical measurements of surface receptor protein levels and electrophysiological recordings of excitatory transmissions onto NAc neurons. Using a cross-linking technique to label surface AMPAR subunits, Wolf and colleagues demonstrated that surface AMPARs, mostly enriched at synapses of NAc MSNs, remain unchanged at this time point (Boudreau and Wolf, 2005; Boudreau et al., 2007). Nevertheless, Thomas and colleagues measured AMPAR- and NMDAR-mediated excitatory postsynaptic currents (EPSCs) in NAc shell MSNs and found that the ratio of AMPAR EPSCs to NMDAR EPSCs (AMPA/NMDAR ratio) is decreased at this withdrawal time point (Kourrich et al., 2007). Although the decrease was initially interpreted as a down-regulation of synaptic AMPARs and no change in NMDARs, more recent evidence suggests that new NMDARs, especially NR2B-containing NMDARs, are inserted into postsynaptic locations, resulting in generation of nascent, NMDAR-only synapses in NAc MSNs (Huang et al., 2009). As such, the overall synaptic level of NMDARs is up-regulated at this withdrawal time point and thus may present a coherent explanation for a lack of change in surface AMPARs (Boudreau and Wolf, 2005; Boudreau et al., 2007) and a decrease in AMPAR/NMDAR ratio (Kourrich et al., 2007) during this short-term withdrawal time point.

Approximately in parallel to synaptic alterations mentioned above, the intrinsic membrane excitability is decreased in NAc shell MSNs at the same withdrawal time point, as measured by action potential firing upon somatic current injections (Dong et al., 2006; Ishikawa et al., 2009; Kourrich and Thomas, 2009; Mu et al., 2010). The decreased membrane excitability is likely mediated by a combination of changes in voltage-gated sodium channels (Zhang et al., 1998), calcium channels (Hu et al., 2004; Zhang et al., 2002), and potassium channels (Hu et al., 2004; Kourrich and Thomas, 2009), as well as calcium-activated SK type potassium channels (Ishikawa et al., 2009). These cocaine-induced membrane adaptations, among others, may act in sync to reduce the responsiveness of MSNs to synaptic excitation. Indeed, in vivo recordings from NAc MSNs revealed that their action potential firings upon iontophoretically-applied glutamate is decreased during short-term withdrawal from repeated exposure to cocaine (White et al., 1995).

What may be the underlying homeostatic regulations at this withdrawal time point? Apparently, AMPAR-mediated synaptic scaling has not yet kicked in to play (Boudreau and Wolf, 2005;

Boudreau et al., 2007). This may be surprising given that NAc MSNs undergo synaptic scaling relatively quickly (within 3 days) when overall activity level drops or when repeated exposure to dopamine occurs (Wolf and Ferrario, 2010). The lack of synaptic scaling after 5 days of cocaine exposure may suggest the process being suppressed or temporarily suspended. On the other hand, it is relatively clear that homeostatic crosstalk between excitatory synapses and membrane excitability is involved in cocaine-induced membrane adaptations at this withdrawal time point. As described in 3.2, in NAc MSNs, hSMP functions to increase or decrease the intrinsic membrane excitability in response to a decrease or increase in excitatory synaptic activity, respectively. Furthermore, synaptic NMDARs act as the sensor for the activity level of excitatory synapses (Ishikawa et al., 2009). As such, even surface or synaptic AMPARs do not appear to be altered; an increased overall activity of synaptic NMDARs may trigger the hSMP system with a false signal (described in 3.2) and initiate a homeostatic decrease in the membrane excitability of MSNs. Indeed, our preliminary results suggest that up-regulation of synaptic NR2B-containing NMDARs, which mediates generation of silent synapses at this stage (Huang et al., 2009), induces a homeostatic decrease in membrane excitability of NAc MSNs (unpublished data). In addition, hSMP-triggered decrease in membrane excitability of NAc MSNs is mediated in part by the functional expression of SK channels, and inhibition of SK channels partially restores the intrinsic membrane excitability of NAc MSNs following exposure to cocaine (Ishikawa et al., 2009). Thus, during short-term withdrawal, hSMP as an effective synapse → membrane homeostatic mechanism may be usurped by drugs of abuse to produce homeostatic dysregulation in NAc.

4.1.2 Repeated self-administration of cocaine—After short-term (1 d) withdrawal from repeated self-administration of cocaine, a slight but significant decrease in the surface level of AMPARs in NAc MSNs is detected (Conrad et al., 2008), whereas the overall synaptic NMDARs are likely to be up-regulated due to generation of silent synapses (Lee and Dong, unpublished data). At a similar withdrawal time point, the intrinsic membrane excitability is decreased (Mu et al., 2010). Similar to what happens following i.p. injections of cocaine, hSMP may contribute to the decreased membrane excitability of NAc MSNs as a result of increased NMDAR-signaling at this withdrawal time point.

4.2 Long-term withdrawal

4.2.1. Repeated i.p. injections of cocaine—After 7–21 days of withdrawal from repeated i.p. injections of cocaine, excitatory synapses onto NAc MSNs appear to be strengthened. On the presynaptic side, glutamate release is presumably increased by reduced presynaptic group 2/3 metabotropic glutamate receptor (mGluR2/3) signaling (Moran et al., 2005). mGluR2/3 located on the presynaptic terminals normally sense the extrasynaptic level of glutamate and inhibit presynaptic release upon activation (Niswender and Conn, 2010). Following long-term withdrawal, the basal level of non-synaptic, extracellular glutamate is reduced (Baker et al., 2003; Hotsenpiller et al., 2001; McFarland et al., 2003; Miguens et al., 2008a; Pierce et al., 1996), presumably due to decreased activity of cystine-glutamate exchanger (Baker et al., 2003) and glutamate transporter-1 (GLT-1) on the glial cell membrane (Knackstedt et al., 2010), which together decrease presynaptic mGluR2/3 activation (Moran et al., 2005). Meanwhile, mGluR2/3 receptors and the downstream signaling are also down-regulated (Xi et al., 2002). Both alterations in mGluR2/3 activation and signaling result in disinhibition of presynaptic glutamate release (Kalivas, 2009). On the postsynaptic side, AMPARs are upregulated at both protein and functional levels (Boudreau and Wolf, 2005; Boudreau et al., 2007; Kourrich et al., 2007). Specifically, GluR1/2-containing AMPARs are upregulated at excitatory synapses onto NAc MSNs (Boudreau and Wolf, 2005; Boudreau et al., 2007). In addition, an increase in the number and size of the dendritic spines is also observed at this time point (Lee et al., 2006; Robinson and Kolb, 1999), suggesting a coordinated remodeling process that functions to strengthen the excitatory transmission onto NAc MSNs.

In parallel to increased excitatory synaptic transmission, the intrinsic membrane excitability of NAc shell MSNs is decreased during long-term withdrawal from repeated i.p. injections of cocaine (Dong et al., 2006; Ishikawa et al., 2009; Kourrich and Thomas, 2009; Mu et al., 2010). Thus, it appears that the decreased membrane excitability of NAc MSNs is a consequence of increased excitatory synaptic strength via hSMP. Consistent with this notion, SK type calcium-activated potassium channels, which are one of the key expression substrates for hSMP, continue to be up-regulated in NAc MSNs at this withdrawal time point (Ishikawa et al., 2009; Mu et al., 2010); Selective inhibition of SK channels partially restores the membrane excitability of NAc MSNs in cocaine-pretreated rats (Ishikawa et al., 2009). Nonetheless, the reverse could also be true, that the decrease in membrane excitation leads to a homeostatic compensatory increase in the postsynaptic responsiveness, namely synaptic scaling. This may occur especially since a decrease in the membrane excitability already exists during short-term withdrawal, in the absence of changes in synaptic strength. The causal relationships between these two sets of changes during exposure or withdrawal remain to be determined.

The homeostatic regulations underlying the above-mentioned changes include glutamate exchanger- and transporter-mediated glutamate homeostasis (Kalivas, 2004), mGluR-mediated modulation of presynaptic release, AMPAR-mediated postsynaptic scaling, and potentially, hSMP. Alterations in NAc at this stage can be triggered by reduced upstream (e.g., mPFC) activity. However, although enhanced transmission efficacy may partially compensate for the reduced presynaptic activity, it also increases the dynamic range upon which subsequent cocaine exposure could exert its effect; decreased membrane excitability of NAc MSNs may reduce the basal firings and, in effect, enhances the signal-to-noise ratio when cocaine challenge occurs (see 4.3 re-exposure). Therefore, the above-mentioned homeostatic regulations in NAc may have been taken advantage of by addictive drugs following long-term withdrawal to refine cocaine-related signal transmission/processing in NAc.

Other potential homeostatic mechanisms regulating synaptic transmission in NAc include endocannabinoid-mediated regulation of glutamate release. Activity in NAc MSNs induces tonic release of endocannabinoids, which activates presynaptic CB1 receptors and inhibits presynaptic release of glutamate (Heifets and Castillo, 2009). Decreased postsynaptic responsiveness and thus decreased postsynaptic activity may induce lower levels of CB1-mediated inhibition of presynaptic release. As such, the retrograde CB1-signaling may function as a homeostatic mechanism balancing presynaptic release and postsynaptic responsiveness. This potential homeostatic mechanism appears to be disrupted by cocaine exposure, as one i.p. injection of cocaine completely abolishes CB1 receptor-mediated synaptic modulation in NAc MSNs (Fourgeaud et al., 2004). Thus, CB1-signaling as a potential homeostatic regulator for pre- vs. postsynaptic coordination (Kim and Alger, 2010) can be targeted by drugs of abuse to induce homeostatic dysregulation. Another set of potential molecular candidates mediating homeostatic regulation between pre- and postsynaptic responses in NAc MSNs is neurexins and neuroligins. Neurexins and neuroligins are expressed pre- and post-synaptically, respectively. They bind to each other and their interactions affect both presynaptic release and postsynaptic responsiveness (Craig and Kang, 2007; Dean and Dresbach, 2006). An increasing body of evidence suggests that neurexin-neuroligin complex is subject to dynamic regulation following exposure to drugs of abuse (Hishimoto et al., 2007; Kelai et al., 2008; Novak et al., 2009; Tiruchinapalli et al., 2008). Though lacking specific results, it is speculated that the neurexin-neuroligin complex is tweaked by exposure to drugs of abuse, disrupting the pre- and postsynaptic homeostasis.

4.2.2 Repeated self-administration of cocaine—AMPA-mediated synaptic transmission in the NAc is enhanced after long-term withdrawal from extended access to cocaine self-administration, and this enhancement is achieved by synaptic incorporation of

calcium-permeable, GluR2-lacking AMPA receptors (CP-AMPA receptors) (Conrad et al., 2008). It remains a controversy whether such synaptic recruitment of these atypical AMPARs also occurs during long-term withdrawal from repeated i.p. injections of cocaine; one lab shows rectification of AMPAR EPSCs during long-term withdrawal (Mameli et al., 2009), suggesting the recruitment of CP-AMPA receptors at synapses, whereas others do not detect such a change (Boudreau et al., 2007; Kourrich et al., 2007). Nonetheless, CP-AMPA receptors are different from the “regularly” expressed GluR2-containing AMPARs in that CP-AMPA receptors have higher single channel conductance and a higher permeability to calcium ions (Cull-Candy and Leszkiewicz, 2004; Liu and Zukin, 2007). As such, synaptic expression of CP-AMPA receptors not only increases the overall AMPAR-mediated transmission (synaptic strength), but also activates calcium-based signals. Collectively, the overall strength of excitatory synapses at NAc MSNs is up-regulated during long-term withdrawal from cocaine self-administration.

Similar to repeated i.p. injections of cocaine, cocaine self-administration also reduces cystine-glutamate exchange and thus decreases the extracellular glutamate level in NAc during long-term withdrawal (Baker et al., 2002; Baker et al., 2003; Miguens et al., 2008b). The potential homeostatic regulations among decreased extracellular glutamate, potentially up-regulated presynaptic release of glutamate, and increased postsynaptic responsiveness are discussed in the previous section.

Unlike what follows repeated i.p. injections of cocaine, following cocaine self-administration, the membrane excitability of NAc MSNs returns to the baseline level during long-term withdrawal (Mu et al., 2010). The increased excitatory synaptic strength and the lack of change in membrane excitability of NAc MSNs taken together raise the question of why hSMP and/or synaptic scaling lose their efficacy under this withdrawal condition. As summarized above, the only known difference in the increased excitatory synaptic strength between i.p. injections and self-administration of cocaine is, arguably, the increase in CP-AMPA receptors in self-administering animals. For hSMP, postsynaptic NMDARs act as the detector of synaptic strength and initiate the first step of signaling (calcium influx) toward regulation of membrane excitability (Ishikawa et al., 2009). CP-AMPA receptors are similar to NMDARs in that they also conduct calcium ions and thus may augment calcium-based signaling in hSMP-based regulation. However, it has been known that calcium-based signaling is also under stringent compartmentational regulation; a calcium wave generated from one signaling cascade may not functionally diffuse into other calcium-mediated signaling cascades (Petersen, 2002; Zaccolo et al., 2002). In MSNs (in either NAc or dorsal striatum), calcium-signaling, depending on its source, differentially regulates voltage-gated ion channels and thus exerts different impact on the membrane excitability of these neurons (Hernandez-Lopez et al., 1997; Hernandez-Lopez et al., 2000; Hu et al., 2005; Shen et al., 2005). Furthermore, in addition to conducting calcium ions, CP-AMPA receptors are also permeable to zinc ions, which are co-released with glutamate from presynaptic terminals and, in turn, trigger zinc-dependent intracellular signaling cascades that are not activated by the NMDAR-calcium pathway (Jia et al., 2002; Redman et al., 2009; Sensi et al., 1999). Nonetheless, the physiological consequences of Ca^{2+} signalings following Ca^{2+} influx from NMDARs and CP-AMPA receptors can be different. If NMDARs and CP-AMPA receptors play opposite roles in hSMP, the lack of membrane alteration in rats withdrawn from cocaine self-administration may be explained as a cancellation of these two effects. At the theoretical level, if CP-AMPA receptors play a role opposite to that of NMDARs, it once again suggests that the detector/sensor of homeostatic mechanisms is targeted by drugs of abuse and the resulting false signal induces homeostatic dysregulation.

4.3. Re-exposure

4.3.1 Following long-term withdrawal from repeated i.p. injections—Twenty-four hours after a single re-exposure to cocaine or cocaine-related cues during long-term withdrawal

from repeated i.p. cocaine injections, the surface levels of AMPARs are substantially decreased to a degree comparable to or lower than that in naïve or saline-treated animals (Boudreau et al., 2007). In addition, re-exposure to cocaine substantially increases the level of non-synaptic, extracellular glutamate in NAc (Baker et al., 2003). On the other hand, re-exposure to cocaine from long-term withdrawal brings the decreased membrane excitability of NAc MSNs back to “normal” (as in saline-treated control rats) (Mu et al., 2010). To some extent, re-exposure can be regarded as an acute stimulation. It is likely that effects observed after re-exposure are a combination of regulated and homeostatic processes.

4.3.2 Following long-term withdrawal from repeated self-administration of cocaine—Thus far, no results are available about regulation of excitatory synaptic strength of NAc MSNs upon re-exposure to cocaine during long-term withdrawal from cocaine self-administration, but one study provides a hint suggesting that the function of synaptic AMPARs may be up-regulated (Anderson et al., 2008). Similar to that following i.p. injections of cocaine, re-exposure to cocaine during long-term withdrawal from cocaine self-administration also abruptly increases extracellular glutamate (Miguens et al., 2008a), which may lead to a decrease in presynaptic release of glutamate onto NAc MSNs. On the other hand, upon re-exposure, the intrinsic membrane excitability of NAc MSNs becomes higher than that in saline-treated control rats (Mu et al., 2010). Again, although there may be homeostatic links among the putative increased postsynaptic responsiveness, decreased presynaptic release, and increased membrane excitability of NAc MSNs upon re-exposure to cocaine, regulated plasticity that acutely occurs upon re-exposure must be taken into consideration for these effects.

5. A hypothesis of homeostatic dysregulation following exposure to cocaine

We have summarized cocaine-induced alterations in presynaptic release of glutamate, postsynaptic responsiveness, and intrinsic membrane excitability of NAc MSNs (Table 1). Using the two basic forms of homeostatic plasticity, one between pre- and postsynaptic activities, and the other between synaptic input and membrane excitability as a conceptual basis, we attempt to provide a homeostatic point of view in understanding cocaine-induced subcellular alterations in NAc MSNs (Fig. 3).

Homeostatic plasticity expresses in multiple forms, which together with other homeostatic responses normally are sufficient to maintain normal functional output of neurons against a variety of internal/external environmental changes, developmental/metabolic turnover, and even pathogenic insults. However, in drug-exposed animals, the brain reward system continuously drifts away from the previously-set homeostatic point (so-called allostasis), resulting in addiction-related behavioral alterations. The functional output of neurons in addiction-associated brain regions (e.g., the NAc) is substantially altered, raising the key question of why homeostatic mechanisms fail in drug-exposed animals. Based on the results from cocaine-treated animals (summarized in the early sections of this manuscript), we hypothesize that the key components determining homeostatic plasticity/responses are targeted by drugs of abuse to produce false signals, resulting in homeostatic dysregulation. This notion is exemplified in the potential hSMP-mediated regulation of membrane excitability of NAc MSNs in cocaine-exposed rats. During short-term withdrawal from repeated i.p. injections of cocaine, although the excitatory synaptic strength (synaptic AMPARs) of NAc MSNs appears not to be changed, synaptic NMDARs as the sensors of hSMP are up-regulated. This projects a false image that excitatory synaptic strength is increased; the membrane excitability of NAc MSNs may thus be decreased via hSMP.

Whereas this hypothesis is formulated mainly based on results from cocaine-treated animals, we speculate that homeostatic regulation and dysregulation are common phenomena occurring upon other drugs of abuse as well, although the specific molecular and cellular machinery

mediating these homeostatic responses may differ. Nonetheless, this hypothesis suggests that despite the enormous number of drug-induced cellular and sub-cellular alterations, the key substrates of homeostatic responses should be focused on with emphasis because alterations of these key homeostatic substrates may be the primary targets for drugs of abuse to trigger cascades of secondary changes. This hypothesis also suggests a homeostatic point of view in correcting/restoring drug-induced neuronal alterations. Studies using gene chip or high throughput screening indicate that more than twenty thousand molecules in the brain are altered during exposure to drugs of abuse, and even more during withdrawal from chronic exposure (McClung and Nestler, 2003; McClung et al., 2005; McClung and Nestler, 2007). Apparently, individual correction of all these identified and possibly even more unidentified drug-induced alterations is not a feasible clinical approach for treating addiction. Instead of focusing on individual targets, an alternative approach is to manipulate a small number of key homeostatic molecules, to tweak the endogenous homeostatic mechanisms, and thus to restore the normal functions of the associated brain regions at the functional level. This homeostasis-based approach is not uncommon in medical practice, especially for treating mental disorders. For example, for most of the antidepressants to achieve therapeutic efficacy, it takes a long latent period during which cascades of homeostatic regulations occur. The monoamine system that these antidepressants interact with is related but not likely to be the direct substrates mediating depression, whereas the homeostatic responses triggered by monoamine-antidepressant interaction might.

6. Concluding Remarks

In summary, based on cocaine-induced cellular alterations, we propose a homeostatic plasticity-based viewpoint in understanding addiction-related homeostatic regulation and dysregulation. This viewpoint brings both opportunities and challenges to the behavioral studies of drug abuse. On one hand, complex drug-taking/seeking behaviors often involve complex molecular and cellular processes. The viewpoint of homeostatic regulation/dysregulation may provide a logic link that brings together individual molecules as a homeostatic network in understanding behavioral alterations. On the other hand, with this viewpoint in mind, behavioral alterations induced by manipulation of a single molecule may not be readily interpreted as an independent effect of this molecule; molecular and cellular homeostatic responses secondary to the manipulation of this molecule must also be considered.

It is also important to note that this viewpoint does not explain all drug-induced molecular and cellular adaptations. An important but not fully discussed topic in this manuscript is drug-induced regulated plasticity, such as LTP and LTD of excitatory synaptic transmission. Indeed, we believe that it is the interaction between homeostatic and regulated plasticity that produces the multiplicity of cellular and molecular alterations observed in the addicted brain. To understand the neuronal basis underlying drug addiction, future studies must differentiate as well as relate regulated plasticity and homeostatic plasticity upon exposure to drugs of abuse.

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Figure 1.

Using synaptic plasticity as an example, the diagram shows the differences between regulated and homeostatic plasticity. **A** A postsynaptic neuron receives multiple presynaptic inputs (1, 2, and 3). These presynaptic terminals may project from different neurons and thus may also represent synapses from different pathways. **B** Regulated synaptic plasticity exhibits two defining properties, contingency and specificity. A successful induction of regulated synaptic plasticity requires a contingent activation of pre- and postsynaptic terminals (diagrammed as action potential firing at both presynaptic and postsynaptic terminals at synapse 2; affected synapse is in shade), and is only expressed in the affected pathway (e.g., only synapse 2 is potentiated by enhanced postsynaptic responsiveness). Other synapses (1 and 3), although located on the same postsynaptic neuron, are not altered because they are not within the contingently activated pathway. **C** Homeostatic synaptic plasticity is induced and expressed "globally". Chronic decrease of postsynaptic receptor sensitivity induces a global increase in presynaptic release such that the action potential firing of postsynaptic neurons is restored.

Figure 2.

A schematic view of homeostatic synapse-driven membrane plasticity in NAc neurons. On the postsynaptic membrane, AMPARs mediate most of postsynaptic current, and NMDARs are also activated during synaptic transmission. The activity of synaptic NMDARs is positively correlated with the activity level of excitatory synapses. As such, the constitutively active NMDAR-coupled intracellular signaling (e.g., the CaMKII-mediated signaling) can be up- or down-regulated accordingly on a real-time base, which in turn modulates ion channels (e.g., SK channels) located on the somatic membrane.

Figure 3.

Summary of synaptic and membrane alterations in NAc neurons following non-contingent exposure to cocaine. A typical non-contingent cocaine procedure is to treat the animal with 5-day i.p. injections of cocaine (15–20 mg/kg/day), followed by different withdrawal periods. An important synaptic alteration in NAc neurons during the late phase of cocaine exposure and short-term withdrawal is the appearance of silent synapses enriched in NR2B-containing NMDARs. These silent synapses decrease over time during long-term withdrawal. Synaptic/surface AMPARs in NAc neurons are altered minimally if any (i.e., a slight decrease) during short-term withdrawal, but are greatly up-regulated during long-term withdrawal. The intrinsic membrane excitability of NAc neurons is decreased throughout short- and long-term withdrawal. Based on the timing of these cocaine-induced synaptic and membrane alterations, we hypothesize that these cellular alterations are homeostatically linked. For example, although synaptic AMPARs are not up-regulated during short-term withdrawal, the increased NMDAR-mediated activity may create a false signal of increased synaptic strength to trigger hSMP, resulting in observed decrease in membrane excitability (?1). Furthermore, newly generated silent synapses provide extra synaptic lots that may facilitate synaptic recruitment of new AMPARs during long-term withdrawal (?2). The synaptic recruitment of AMPARs during long-term withdrawal may result from regulated or homeostatic plasticity. For homeostatic plasticity, a potential mechanism is that the decreased membrane excitability may trigger another round of membrane-to-synapse homeostatic response, resulting in an increase in excitatory synaptic strength in NAc neurons (?3).

Summary of cocaine-induced alterations at excitatory synapses and intrinsic membrane excitability of NAc neurons.

Table 1

Cocaine Procedures	Short-term Withdrawal		Long-term Withdrawal		Re-exposure	
	Contingent	Non-contingent	Contingent	Non-contingent	Contingent	Non-contingent
Synaptic Strength	↓ ¹	↔ ^{2,3} or ↓ ^{4,5}	↑ ¹	↑ ^{2,3,6,7,8;}	↑ ⁹	↓ ^{2,10}
Membrane Excitability	↓ ¹¹	↓ ^{5,11,12,13,14,15}	↔ ¹¹	↓ ^{11,13,15}	↑ ^{11,16,17}	↔ ¹¹

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