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Limbic and cortical information processing in the nucleus accumbens

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Abstract

The nucleus accumbens regulates goal-directed behaviors by integrating information from limbic structures and the prefrontal cortex. Here, we review recent studies in an attempt to provide an integrated view of the control of information processing in the nucleus accumbens in terms of the regulation of goal-directed behaviors and how disruption of these functions might underlie the pathological states in drug addiction and other psychiatric disorders. We propose a model that could account for the results of several studies investigating limbic-system interactions in the nucleus accumbens and their modulation by dopamine and provide testable hypotheses for how these might relate to the pathophysiology of major psychiatric disorders.

Introduction

The nucleus accumbens (NAcc) is a central component of the limbic system of the brain. This is based on its innervation by limbic structures, including excitatory afferents from the ventral hippocampus and the basolateral amygdala, and the medial prefrontal cortex (PFC) [1]. The NAcc integrates these limbic and cortical inputs and, in turn, projects to other basal ganglia nuclei including the ventral pallidum (VP) [1], which, in turn, sends feedback projections into the PFC via the mediodorsal nucleus of the thalamus [2]. This anatomical organization places the NAcc as a site for integration of emotional salience and contextual constraints processed in the amygdala and hippocampus, respectively, and executive/motor plans from the PFC, with the output positioned toward controlling goal-directed behavior [3]. Here, we discuss the mechanisms of limbic and cortical input integration in the NAcc and their modulation by dopamine (DA) in the regulation of goal-directed behavior, and how disruptions in these systems could underlie psychiatric disorders.

Functional importance of the NAcc

Involvement of the NAcc in diverse brain functions

The NAcc is thought to facilitate goal-directed behaviors by integrating information related to limbic drive and motor planning [3]. Nevertheless, the exact process by which the NAcc achieves this function is not yet clear, given that studies have revealed that the NAcc is involved in multiple distinct aspects of behavior. NAcc lesions cause disruptions of an array of cognitive and affective processes, including operant and emotional learning, response inhibition and behavioral flexibility [4–6]. Electrophysiological studies in awake animals also support a role

for the NAcc in these multiple functions [7,8]. Such a diverse array of functional involvements might derive from the integration of inputs from multiple brain regions within the distinct subdivisions that comprise the NAcc. Therefore, the balance of drives from limbic, thalamic and cortical inputs might determine how the output guides behaviors with respect to specific aspects of cognitive and affective functions. Such input interaction could be the basis of ensemble information processing [9] in the NAcc (Figure 1). Indeed, electrophysiological recordings from multiple neurons simultaneously in behaving animals has shown correlated spike firing in sets of neurons of the NAcc [7] that might reflect such ensemble-related activity.

The mechanisms of synaptic input integration

Anatomical and electrophysiological studies have shown that afferents from the PFC and limbic systems converge onto single NAcc projection neurons [10,11], indicating that limbic and cortical information integration is processed at the level of single neurons. *In vivo* intracellular recordings from NAcc projection neurons in anesthetized animals reveal that these neurons exhibit robust membrane-potential shifts between a hyperpolarized resting membrane potential (DOWN state) and periodical plateau depolarizations (UP states) [10,12]. UP states in NAcc neurons are driven by a barrage of excitatory synaptic inputs from the hippocampus, given that electrical stimulation of the hippocampal afferents within the fimbria-fornix can evoke transitions to the UP state, whereas inactivation of this fiber system eliminates UP transitions [10]. Moreover, population activity of the hippocampus is tightly correlated with NAcc membrane-potential dynamics, which are reflected as synchronization of UP transitions among a population of NAcc neurons, whereas synchronization between the NAcc membrane potentials and population activity in the PFC is comparatively weak [12,13]. These observations indicate that limbic and cortical inputs might contribute to distinct aspects of NAcc neuron activity.

Although UP-state transitions are large in magnitude, often >20 mV, neurons infrequently fire spikes during these UP states, with the majority of UP states remaining sub-threshold to spike firing [12]. This is primarily because the resting membrane potential of NAcc neurons is very hyperpolarized (approximately ranging from -75 to -85 mV) [10,12], demonstrating the crucial nature of UP-state transitions in facilitating spike activity. Therefore, NAcc neurons achieve supra-threshold spike firing only with strong excitatory drives, which require excitatory inputs from more than one afferent brain structure. Indeed, when electrical stimulation of the PFC is coincident with hippocampal-driven UP states, spike firing can be evoked in NAcc neurons [10]. Although these input-integration mechanisms are observed in anesthetized animals, which might be different from neural activity in the awake condition, it is, nonetheless, still likely that a similar mechanism has a strong role in modulating input integration and spike output in this region, especially given that a majority of striatal neurons in awake animals in baseline conditions remain quiescent or exhibit spike firing at low frequency (<1 Hz), which is comparable to that in anesthetized animals [14].

The role of synaptic plasticity in input integration

Synaptic plasticity is proposed to represent the cellular substrate of learning and memory. Given that the NAcc integrates inputs from multiple brain areas, the ability of synaptic plasticity to facilitate and attenuate synaptic inputs would have a substantial impact on how inputs are integrated within the NAcc. Synaptic plasticity has been assessed in the PFC–NAcc and the hippocampus–NAcc pathway by delivering high-frequency tetanic stimulation to the hippocampus and PFC while measuring evoked field potentials within the NAcc [15]. When tetanic stimulation was given in the hippocampus, long-term potentiation (LTP) was induced on hippocampus afferents simultaneously with induction of long-term depression (LTD) on PFC afferents. By contrast, when similar tetanic stimulation was given in the PFC, LTP was induced in PFC afferents, whereas LTD was induced simultaneously at hippocampus inputs.

These results indicate that hippocampus and PFC inputs compete with each other for control over the NAcc via induction of synaptic plasticity, with whichever pathway is most strongly activated, thereby 'winning' the competition. Indeed, a similar input competition between the amygdala and hippocampus that relies on the induction of synaptic plasticity has been reported [16], indicating that this synaptic-plasticity-based competition could be a common mechanism of input regulation within limbic and cortical systems. One of the consequences of this induction of synaptic plasticity could be that it would enable rapid facilitation of goal-directed behaviors mediated by specific sets of functionally related NAcc neurons when the organism requires behavioral expression of a well-learned response pattern.

Compartmentalization of NAcc functions

Several recent studies have revealed functional differences between the core and shell regions of the NAcc, with alterations in the core or shell producing unique deficits [4,17]. One way to account for this difference could be that the functional subdivisions of the NAcc mediate actions based on their complement of inputs. For example, the functional impact of NAcc disruption could depend on the site of origin or the differential balance of cortical and limbic inputs to these distinct NAcc subregions. Thus, the myriad of deficits associated with NAcc lesions might reflect disruption of information input originating in these afferent structures, rather than a specific function of the NAcc *per se*. The NAcc consists of two subregions, the core and shell, distinguished by differential expression of neuropeptides, morphology, membrane properties and synaptic inputs from afferent structures [18]. The core is suggested to play a part in guiding behavior toward a specific goal based on learning, whereas the shell seems to be crucial for unconditioned reward-seeking behaviors [4,17]. Such functional differences could be associated with distinct regulation of DA release between these subregions. Some studies have shown discrete patterns of DA release between the core and shell of the NAcc during reward-seeking behaviors [19,20]. However, even though clear differences exist between the core and shell, a recent study has also shown that neurons localized within the core or the shell have interactions via axon collaterals that extend between these regions [21], indicating that these subregions are not independent entities of information processing in the NAcc.

DA-system modulation of the NAcc

The NAcc receives a substantial DA innervation that arises from the ventral tegmental area (VTA) [22]. This mesolimbic DA input is essential for NAcc function, and compromises within this system are believed to underlie several psychiatric disorders [3,23,24]. The primary role of DA seems to be to modulate excitatory glutamatergic transmission [25], with a configuration of glutamatergic and DA terminals at close proximity on the top and neck of dendritic spines, respectively [26]. An intact DA innervation is important for some aspects of the function of the NAcc, given that DA depletion [27] and DA antagonists [28] injected into the NAcc impair some, but not all, of NAcc-dependent behaviors. Detailed mechanisms of the regulation of DA neuron activity and DA release in the NAcc are discussed elsewhere [29]; here, we focus on DA impact within the NAcc.

The role of DA in modulating input integration in the NAcc

The NAcc expresses DA receptors of both the D₁ and D₂ classes. These DA receptors seem to be expressed both postsynaptically on NAcc neurons [26,30] and on presynaptic terminals of limbic and cortical afferents innervating into the NAcc [31]. Activation of these pre- and postsynaptic DA receptors has been shown to affect excitability of NAcc neurons through interactions with ionotropic channels [32]. In addition, D₁ and D₂ receptors provide a specific and selective modulation of afferent transmission within the NAcc. When D₁ and D₂ agonists are applied to the NAcc via reverse microdialysis, there is a substantial impact on inputs arising

from limbic and cortical regions. Thus, D₁ agonists facilitate limbic (hippocampus) but not cortical (PFC) inputs, whereas D₁ antagonists have no effect on either the limbic or cortical input in anesthetized rats [33]. Conversely, administration of a D₂ agonist attenuates and D₂ antagonist facilitates cortical inputs without affecting limbic inputs [33], indicating that (i) limbic inputs are selectively modulated by D₁-receptor stimulation, (ii) cortical inputs are selectively modulated by D₂-receptor stimulation and (iii) low baseline concentration of DA tonically attenuates cortical input via D₂-receptor stimulation. This is consistent with DA-receptor-binding assays showing that D₂ receptors exhibit higher affinity for DA than do the D₁ receptors [34].

The impact of DA activation on synaptic integration is dependent on selective effects of tonic and phasic DA release [29]. Thus, pedunculopontine tegmentum (PPTg) activation, which promotes burst firing in VTA DA neurons, increases limbic-evoked responses without affecting cortical-evoked responses [33], indicating that phasic DA release selectively facilitates limbic inputs via D₁-receptor activation (Figure 2). By contrast, VP activation and inactivation, which decrease and increases tonic spike firing of DA neurons, causes attenuation and facilitation, respectively, of cortical inputs without altering limbic-evoked responses [33], indicating that tonic DA release selectively attenuates cortical inputs by D₂-receptor stimulation (Figure 2). When these systems function together, an increase in tonic and phasic DA stimulation would be expected to attenuate cortical input and potentiate limbic input. Thus, it seems that increases or decreases of DA release maintain the balance between limbic and cortical inputs into the NAcc.

The ability to induce synaptic plasticity in these pathways is differentially modulated by the DA system. Thus, synaptic plasticity induced by hippocampus stimulation was prevented by administration of a D₁ antagonist, indicating that hippocampal stimulation requires NAcc phasic DA release, which then stimulates D₁ receptors to facilitate LTP in the hippocampus–NAcc pathway. By contrast, synaptic plasticity induced by PFC stimulation was attenuated by local administration of a D₂ agonist, indicating that high-frequency PFC stimulation could act to reduce tonic D₂ stimulation to enable LTP to take place. An important consideration of these data relates to the functional importance of tonic baseline DA stimulation in *in vitro* slice studies, because tonic DA is present *in vivo* but would be strongly attenuated in the *in vitro* preparation owing to transection of DA fibers. Thus, previous studies that have examined the ability to induce LTP in the PFC–NAcc pathway *in vitro* [35] probably found this projection to be DA-independent owing to the attenuation of tonic D₂-receptor stimulation in this preparation.

DA-dependent regulation of goal-directed behavior: competition between behavioral flexibility and reward-dependent spatial learning

DA-neuron activity states determine the functional interactions between D₁ and D₂ receptors in the NAcc. A series of studies by has revealed that DA neuron spike firing seems to encode signals related to reward. Thus, DA neurons exhibit transient burst spike firing by presentation of unexpected rewards or sensory signals predicting such rewards [36]. By contrast, a transient suppression of tonic spike firing is induced by omission of expected reward presentation [36]. It is thought that these spike-firing patterns are used for reinforcement signals within the NAcc. Burst spike firing evoked by unexpected rewards should produce phasic DA release in the NAcc [37], which would selectively facilitate limbic drive of NAcc neurons via an action on D₁ receptors (Figure 3). By contrast, suppression of DA spike firing by omission of expected reward would be expected to induce a transient decrease in tonic DA stimulation of D₂ receptors in the NAcc; as a consequence, PFC inputs would be predicted to undergo facilitation (Figure 3).

Evidence indicates that behavioral drives exhibit competition within the NAcc and that the DA-neuron discharge pattern controls the outcome of this competition to most effectively guide behavioral outcomes. The role of reward signals and DA within the NAcc in guiding behavior has been examined using behavioral assessments and a disconnection model [33]. Behavioral assessments were performed using a cross-maze paradigm, in which animals were subjected to two tasks requiring allocentric (visual cue task) and egocentric (response-direction task) behavioral strategies to achieve a goal. An important component of the task is that once animals learned the correct response strategy in the first task, the task was altered in a way that required the animals to switch their response strategy. Disconnection of the hippocampus and NAcc by unilateral inactivation of the hippocampus combined with contralateral administration of a D₁ antagonist into the NAcc, eliminating DA facilitation of hippocampal afferents to the NAcc, impaired performance in both tasks, indicating that D₁-dependent hippocampus–NAcc interactions regulate the ability to acquire a learned response. Conversely, disconnection between the PFC and NAcc by unilateral inactivation of the PFC combined with administration of a D₂ agonist into the contralateral NAcc did not affect the initial learning process, but animals exhibited more perseveration when the task was switched, indicating that this pathway is important for behavioral flexibility. These observations indicate that reward signals of DA neurons caused by presentation of unexpected reward or sensory signals predicting rewards are used for learning response strategies via their modulation of hippocampus drive of NAcc neurons, whereas signals that result in an attenuation of DA release, such as the omission of expected rewards, are used for facilitation of PFC–NAcc interactions that are used for mediating behavioral flexibility (Figure 3).

Implications for psychiatric disorders

Disruptions of the DA system in the NAcc have been implicated in several psychiatric disorders. The involvement of the DA system in drug abuse has been a topic of substantial investigation. In addition, disruptions of the NAcc have also been suggested to occur in other psychiatric disorders such as schizophrenia [3], obsessive compulsive disorders [23] and attention deficit hyperactivity disorder [24].

Drug addiction

Several studies have examined the cellular basis of drug addiction, with a focus on DA-system regulation of synaptic plasticity within the NAcc, using animal models such as drug self-administration and sensitization [38]. Given the propensity for DA modulation of synaptic plasticity in these regions and the fact that repeated stimulation of DA receptors during drug-addiction processes alters the system states, it is likely that synaptic plasticity within these circuits plays a part in drug addiction. Indeed, a blockade of LTD induction on cortical afferents into the NAcc has been reported after drug sensitization in slice preparations [39,40]. Alterations of synaptic plasticity in the NAcc in drug self-administration have not been explored, although modulation of synaptic plasticity in this model is supported by indirect evidence from several studies showing augmentation of drug self-administration behaviors with activation of intracellular signaling molecules such as protein kinase A [41], inhibition of Cdk5 [42] and disruption of actin cycling [43], which are molecules known to be involved in synaptic plasticity [44,45].

Using the cocaine-sensitization model, rats were treated repeatedly with cocaine sufficient to induce behavioral sensitization and then subjected to electrophysiological examination [15]. In rats sensitized to cocaine, the ability to induce LTP in the hippocampus–NAcc pathway and LTD in the PFC–NAcc pathway by tetanic stimulation of the hippocampus was attenuated (i.e. the effects of hippocampus high-frequency stimulation were obscured by the cocaine sensitization process). By contrast, the ability of tetanic stimulation of the PFC to induce LTP at PFC afferents and LTD at hippocampus afferents was not altered. These data indicate that

the process of cocaine sensitization actually induced a state identical to that observed with hippocampus tetanization (i.e. a predominance of hippocampus inputs and attenuation of PFC inputs). Under such a condition, the imbalance induced in limbic and cortical inputs within the NAcc would be predicted to lead to disruption of normal goal-directed behavior. Thus, repeated cocaine-treated animals exhibited facilitation of spatial learning due to fewer regressive errors (consistent with hippocampal predominance) but increased perseveration when the task is switched (consistent with attenuation of PFC input), supporting this model. Therefore, it seems that there is a trade-off between learning and set shifting of response strategy with repeated treatment with DA agonists. Although speculative, such a perseveration could mimic the focus of drug-addicted individuals that have been locked into a behavioral state designed to obtain additional drug reinforcement while suppressing a drive to shift their behaviors to achieve more worthwhile goals.

Schizophrenia

Schizophrenia is a complex disorder that is likely to involve deficits in PFC [46] and limbic system circuits [47]. There is evidence that a circuit involving the PFC, NAcc and hippocampus and their modulation by DA could have central roles in this disorder. In particular, imaging studies show that schizophrenia patients exhibit abnormally high amphetamine-induced DA release in the limbic striatum [48], and antipsychotic drugs are believed to attenuate psychosis by an action in this region. Nevertheless, evidence for anatomical abnormalities within the striatum or the DA system itself is highly controversial in schizophrenia. Given that the NAcc receives synaptic inputs from the PFC and hippocampus, we propose that NAcc information processing is compromised secondary to dysfunctions within the PFC and hippocampus.

Schizophrenia patients reliably show impairments in using behavioral flexibility, exhibiting perseveration in tests that examine their ability to use executive function to switch response strategies such as in the Wisconsin card-sorting test (WCST) [49]. Indeed, deficits within the PFC in these patients are most likely to be responsible for such impairments [49], yet disruptions of DA-dependent information-processing mechanisms in the NAcc that we have described [33,50] might also take part in the dysfunction. Several studies have revealed that schizophrenia patients exhibit higher basal activity in the hippocampus than normal subjects, and this hyperactivity might be correlated with psychotic symptoms [51,52]. Consequently, an over-release of DA results in abnormally facilitated limbic–NAcc and attenuation of PFC–NAcc interactions, which produce disruption of behavioral flexibility in rodents [33]. Further evidence that augmented hippocampal activity disrupts behavioral flexibility comes from patients with temporal lobe epilepsy. These patients having hippocampus sclerosis often exhibit disruption of WCST performance with increased perseverative errors [53,54]. It is hypothesized that epileptic discharge in the hippocampus affects its afferent brain regions such as the PFC [55], resulting in deficits of cognitive functions such as behavioral flexibility that are suggested to be mediated by the PFC. However, given that the NAcc receives a massive hippocampus innervation that regulates DA release in this region [56], disruption in set shifting could also involve abnormal increases in DA release in the NAcc. Indeed, a similar over-activation of the hippocampus exists in the animal model of schizophrenia with prenatal treatment with the DNA methylating agent methylazoxymethanol acetate (MAM) [57]. This augmented hippocampal activity was found to increase DA-neuron tonic firing and, thereby, cause both pathologically augmented subcortical DA release and an abnormal attenuation of PFC inputs into this region. Although such over-activation of the hippocampus might seem at odds to other animal models of schizophrenia, such as the neonatal ventral hippocampal lesion [58], in actuality studies show that larger neonatal hippocampus lesions cause less pathology than smaller lesions [59]. Thus, it could be that neonatal ventral hippocampal lesions alter hippocampus function in the same way as that observed in MAM-treated rats: by disrupting organized hippocampus output in favor of disorganized rapid activity states.

Concluding remarks

Electrophysiological, neurochemical and behavioral studies in the NAcc have uncovered some important aspects of NAcc information processing because it relates to goal-directed behaviors. These studies have provided important insights into the mechanisms of information processing and associated behavioral functions within the NAcc and the unique role of the DA system in maintaining a balance between limbic and cortical drive within this region. Adaptive modifications in this balance are important for enabling the NAcc to shift between drives related to behaviors toward satisfying emotional or contextual salience (amygdala and hippocampus) and those that enable an organism to show behavioral flexibility to most effectively choose a response strategy (PFC).

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Figure 1.

A model of input integration within the NAcc. **(a)** When a novel situation is encountered, although excitatory inputs from sets of neurons (black circles) in regions 1, 2 and 3 (e.g. the hippocampus, amygdala and PFC) are recruited, the non-coincident inputs fail to bring NAcc neurons to threshold (gray circles) and, therefore, there is no spike firing in NAcc neurons and no output. **(b)** By contrast, when responding to a well-learned situation, a specific pattern of coincident inputs into the NAcc evokes spike firing in a set of neurons that codes for a previously learned behavioral response known to be effective at achieving a goal. **(c)** Under different behavioral conditions, a distinct pattern of coincident inputs produces a unique pattern of NAcc output leading to a different effective behavioral outcome.

Figure 2.

A schematic diagram illustrating how tonic and phasic DA release are proposed to modulate PFC and hippocampal glutamatergic inputs through D₂ receptors located presynaptically on PFC terminals and D₁ receptors located postsynaptically on NAcc neurons, respectively. Extracellular tonic DA levels are controlled by VP inputs that control DA-neuron population activity, whereas phasic DA release within the synaptic cleft is regulated by PPTg-mediated release of glutamate onto DA neurons in the VTA. Phasic DA release is then removed by reuptake into DA terminals via the DA transporter (DAT).

Figure 3.

DA regulation of limbic and cortical information processing in the NAcc. (a) Simplified anatomical organization of the hippocampal and PFC input integration and VTA DA afferents into the NAcc. (b) When animals encounter unexpected rewards or signals predicting rewards, phasic DA release is evoked, facilitating hippocampus drives into NAcc through D₁-receptor stimulation. In this condition, NAcc activity is facilitated, which, in turn, suppresses the VP. As a consequence, tonic inhibition of DA neurons is removed, thereby facilitating tonic DA release in the NAcc, which, in turn, attenuates PFC input via D₂-receptor stimulation. Therefore, information-irrelevant cortical inputs are filtered out and only highly salient information sent out from the PFC is capable of activating the thalamo-cortico-basal ganglia

loop; such feedback information from the thalamus to the PFC would then selectively reinforce this specific PFC–NAcc afferent drive. This process, therefore, mediates learning process of a response strategy for reward-seeking behavior. (c) By contrast, when animals encounter a situation that expected rewards are omitted, suppression of tonic firing of DA neurons and tonic release of DA in the NAcc occur, which strengthen PFC inputs into the NAcc via decreased stimulation of D₂ receptors. This PFC input facilitation mediates inhibition of reinforced reward-seeking behavior guided by hippocampus–NAcc information processing. Abbreviation: HPC, hippocampus.