Neurochemistry of the Nucleus Accumbens and its Relevance to Depression and Antidepressant Action in Rodents

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Abstract: There is accumulating evidence that the nucleus accumbens (NAc) plays an important role in the pathophysiology of depression. Given that clinical depression is marked by anhedonia (diminished interest or pleasure), dysfunction of the brain reward pathway has been suggested as contributing to the pathophysiology of depression.

Since the NAc is the center of reward and learning, it is hypothesized that anhedonia might be produced by hampering the function of the NAc. Indeed, it has been reported that stress, drug exposure and drug withdrawal, all of which produce a depressive-phenotype, alter various functions within the NAc, leading to inhibited dopaminergic activity in the NAc.

In this review, we describe various factors as possible candidates within the NAc for the initiation of depressive symptoms. First, we discuss the roles of several neurotransmitters and neuropeptides in the functioning of the NAc, including dopamine, glutamate, γ-aminobutyric acid (GABA), acetylcholine, serotonin, dynorphin, enkephaline, brain-derived neurotrophic factor (BDNF), cAMP response element-binding protein (CREB), melanin-concentrating hormone (MCH) and cocaine- and amphetamine-regulated transcript (CART). Second, based on previous studies, we propose hypothetical relationships among these substances and the shell and core subregions of the NAc.

Key Words: Depression, nucleus accumbens, glutamate, dopamine, γ-aminobutyric acid (GABA), acetylcholine, dynorphin, cAMP response element-binding protein (CREB).

INTRODUCTION

The nucleus accumbens (NAc), a part of the ventral striatum, is involved in motivation, reward, motor function and learning. Indeed, drugs of abuse increase locomotor activity, and preferentially and markedly increase dopamine release in the NAc. Recent studies have demonstrated that the NAc may play an important role in the etiology and pathophysiology of depression, although direct findings have never been reported. Exposure to chronic stress or withdrawal from long-term ingestion of drugs of abuse causes anhedonia (diminished interest or pleasure), a core symptom of major depressive disorder, in both humans and rodents [5,8,170]. Development of anhedonia has been ascribed to dysfunction of the reward pathway, in which the NAc plays a pivotal role [37,173]. Chronic stress or psychostimulant withdrawal has been reported to induce dramatic neurochemical alterations in the NAc, leading to depressive phenotypes [8,37,106,123].

In this review, we focus on several neurotransmitters and neuromodulators, which appear to play crucial roles in reward and regulation of mood in the NAc and describe alterations of these molecules in depressive states.

CLINICAL STUDIES

The involvement of the NAc in depression has been noted in the clinical studies although a direct indication has never been found in the NAc of depressed patients. Related study is that increased apathy is associated with lower volume of the NAc in patients infected with human immunodeficiency virus [122]. An fMRI study using cocaine-dependent subjects indicated that cocaine-induced activation in the NAc is correlated with behavioral measures of euphoria [20]. Neuropsychological study showed that recently depressed cases made faster decisions in the context of betting more of their available points in the decision-making test [85] and an fMRI study using healthy adults demonstrated that ventral striatum is activated in reward processes in the decision-making test [46]. Taken together, it is likely that the NAc of depressed patients is impaired in reward and decision- making. Furthermore, a recent study reported that immunolabeling of protein kinase A subunits was significantly decreased in the NAc of young suicide victims [117]. The previous studies indicated the involvement of NAc in cognition and response to aversive and rewarding stimulus in animal models of depression (shown in Table **1**).

THE NAC SHELL AND CORE SUBREGIONS

A recent study reported that selective lesions in the NAc core profoundly impaired the acquisition of drug-seeking behavior that was maintained by drug-associated conditioned reinforcers, but had only a minor effect on the acquisition of cocaine response under a schedule of continuous reinforcement, indicating that the NAc core is involved in the control of goal-directed behavior by associative processes, whereas the NAc shell controls the enhancing effects of drugs [70]. Thus, Pavlovian conditioned stimuli influence appetitive behavior such as drug-seeking. This drug-seeking behavior is characteristic of impulsivity, the mechanism of which is

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Table 1. The Functions of NAc in Animal Models of Depression

Function
Cognition
• Glutamate injected into the NAc decreased swimming in the forced swim test [134].
• Blockade of κ-opioid receptor in the NAc shell or core of learned helplessness rats improved behavioral deficits in the conditioned avoidance test [147].
• Blockade of CREB in the NAc of learned helplessness animals produced an antidepressant-like effect in the conditional avoidance test [111].
Under steady state
• Flinders sensitive line rats showed the decreased 5-HT turnover (5-HIAA/5-HT) and the increased DA turnover (DOPAC/DA) in the NAc [178,179].
• Chronic mild stress caused a decrease in dopamine D2 receptors in the NAc [118].
• Chronic mild stress did not affect basal dialysate DA in the NAc [37].
• Learned helplessness rats showed the decreased densities of dopamine D2 receptors in the NAc core [81].
• Learned helplessness rats showed increased expression of dynorphin A and B in the NAc shell and core [147].
• Cocaine withdrawal elevated basal levels of GABA, reduced basal levels of extracellular glutamate, and did not alter basal levels of DA in the NAc [172].
Response to aversive stress
• Chronic mild stress reversed the inhibitory response of DA transmission by the tail-pinch trial in the NAc shell [37].
• Forced swim stress failed to increase extracellular levels of DA in the NAc of Flinders sensitive line rats [173].
• In response to forced swim stress, Wistar-Kyoto rats exhibited a reduction in DA turnover (DOPAC/DA) and failed to increase 5-HIAA levels in the NAc [35].
Response to reward
• Chronic mild stress blunted the stimulatory response of DA transmission to food in the NAc shell [37].
• The increases in dopamine output observed in chronic stressed animals after cocaine administration were significantly lower than those observed in control rats [53].

thought to be controlled in the NAc centered neuronal networks [72]. Increased impulsivity is often observed in depression. Therefore, it is conceivable that the NAc is involved in problem-solving ability, as increased impulsivity must be assumed to have some effect on decision-making or suicide attempts. Another study demonstrated that habituation of dopamine responses to aversive stimuli was not observed in the NAc core, but was observed in the NAc shell, indicating that the NAc core handles generic motivational value whereas the NAc shell integrates the motivational valence and novelty [11]. In the field of psychiatry, resistant habituation reminds us of various symptoms such as recurrent luminescence, predicted anxiety or impulsive thinking. The recent study demonstrated that NAc core lesions retard instrumental learning with delayed reinforcement and increased sensitivity to differences in reinforcer magnitude, indicating that the NAc core is required for normal preference for a large, delayed reward over a small, immediate reward (self-controlled choice) [24].

CONNECTIVITY

The NAc contains small populations of γ-aminobutylic acid (GABA)-containing and cholinergic interneurons, in addition to a large number of efferent GABAergic medium spiny projecting neurons [102]. The activity of projecting medium spiny neurons is regulated by glutamatergic afferents arising from the prefrontal cortex, hippocampus and amygdala, by dopaminergic afferents from the ventral tegmental area [124], by serotonergic afferents from the raphe nucleus, and by noradrenergic afferents from the locus ceruleus. A schematic diagram is shown in Fig. **1**. These afferents converge primarily on GABA neurons, the main output cells of this region [102]. In addition, GABAergic projection neurons receive inhibitory input, primarily from a small population of GABAergic and cholinergic interneurons [75] but also through feedfoward inhibition [125] and axon collaterals of neighboring medium spiny neurons [29].

Medium spiny neurons project to a restricted part of the globus pallidus and the substantia nigra from the core, whereas from the shell, they project not only to the subcommissural part of the ventral pallidum and the ventral tegmental area but also to widespread areas in the hypothalamus and extended amygdala [102]. NAc output is regulated by numerous systems including glutamatergic afferent from the medial prefrontal cortex and hippocampus, both of which differentially regulate activities in the shell and core subregions (Fig. **2**). Furthermore, various systems such as glutamate, dopamine, GABA, acetylcholine, serotonin and so on regulate each other through pre- and post- receptors (Fig. **3**). A schematic diagram about the relationships among typical

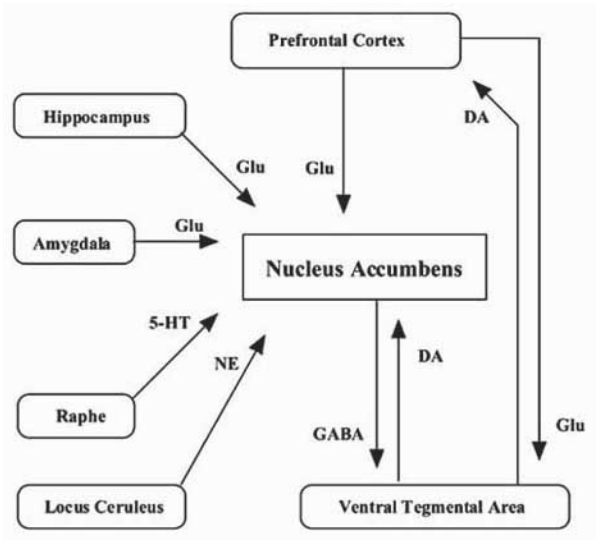

Fig. (1). Connectivity of the NAc with other brain regions such as prefrontal cortex, ventral tegmental area (VTA). Activity of the NAc is mainly regulated by dopaminergic (from VTA) and glutamatergic afferents (from frontal cortex, amygdala and hippocampus). In addition, inputs of GABAergic, serotonergic (from raphe) and adrenergic afferents (from locus ceruleus) as well as cholinergic interneuons (within the NAc) also modified activity of the NAc.

receptors is shown in Fig. **3**. Recently, an emerging body of evidence suggests that the activities of medium spiny projecting neurons, as well as these afferents neurons, are regulated locally by several neuropeptides and transcriptional factors, which are expressed in the NAc, and which are up- or down-regulated by various stressful situations [110].

DOPAMINE

The dopamine system is distributed to restricted brain regions known as the mesocortical, mesolimbic, and nigrostriatal dopamine projections. The mesocortical dopamine system supplies projections to the medial prefrontal and cingulate cortex, whereas the mesolimbic dopamine system innervates the NAc as well as the amygdala and septum. The dopaminergic system has been implicated in depression, and accumbal dopamine has been of particular interest, as dopamine in the NAc has been shown to be associated with motivation, reward, and hedonia [79]. Dopaminergic abnormalities within the limbic areas of the brain were observed in several animal models of depression [42,81,178]. Disruption of dopaminergic function within the NAc causes anhedonia, a cardinal symptom of depression in human as well as in rodents [5,170].

It is well known that withdrawal from long-term use of drugs of abuse such as phencyclidine, amphetamine and nicotine precipitates withdrawal syndromes characterized by affective symptoms including anhedonia [8], and reduces extracellular dopamine concentrations within the NAc [123]. Similarly, subchronic treatment with cocaine induces changes in tyrosine hydroxylase activity in the NAc [13,164]. Moreover, the mesolimbic dopamine system appears to be highly susceptible to stress. Thus, it has been reported that acute exposure to different forms of stress increases dopamine release in the NAc [73,163]. In contrast, long-term exposure to various unavoidable stress factors decreases dopamine release in the NAc shell [37,38,143]. Furthermore, it has also been reported that mice exposed to escapable foot shock show an increase in dopamine release in the NAc, while those exposed to inescapable foot shock show a decrease in dopamine release in the NAc [22]. In addition, prolonged exposure to the forced swimming test, an animal model of depression, promotes a reduction of dopamine release in the NAc [138]. Both homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) contents were reported to decrease in the NAc after forced swimming stress, and this reduction lasts for a longer time in animal models of depression, using Flinders Sensitive Line rats [173] and Wistar-Kyoto rats [35]. Furthermore, chronic stress was reported to reduce the cocaine-induced increase in dopamine output in the NAc shell [53], indicating an im-

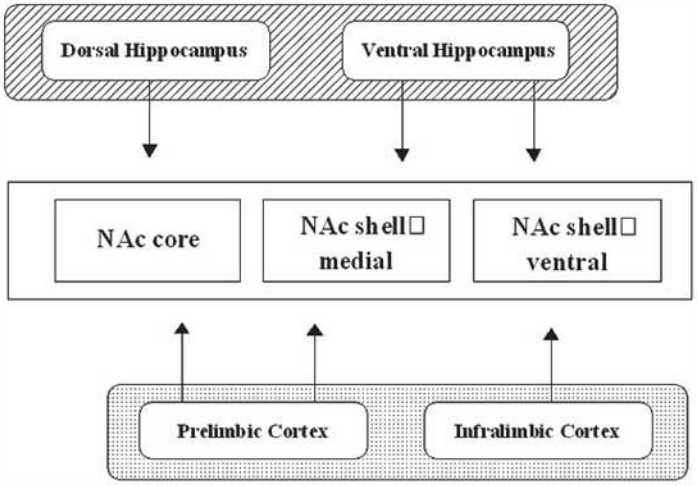

Fig. (2). Schematic illustration of connections of the NAc shell and core regions with subregions of hippocampus and prefrontal cortex. Please note that three portions of the NAc could be affected efficiently by two regions of hippocampus and prefrontal cortex.

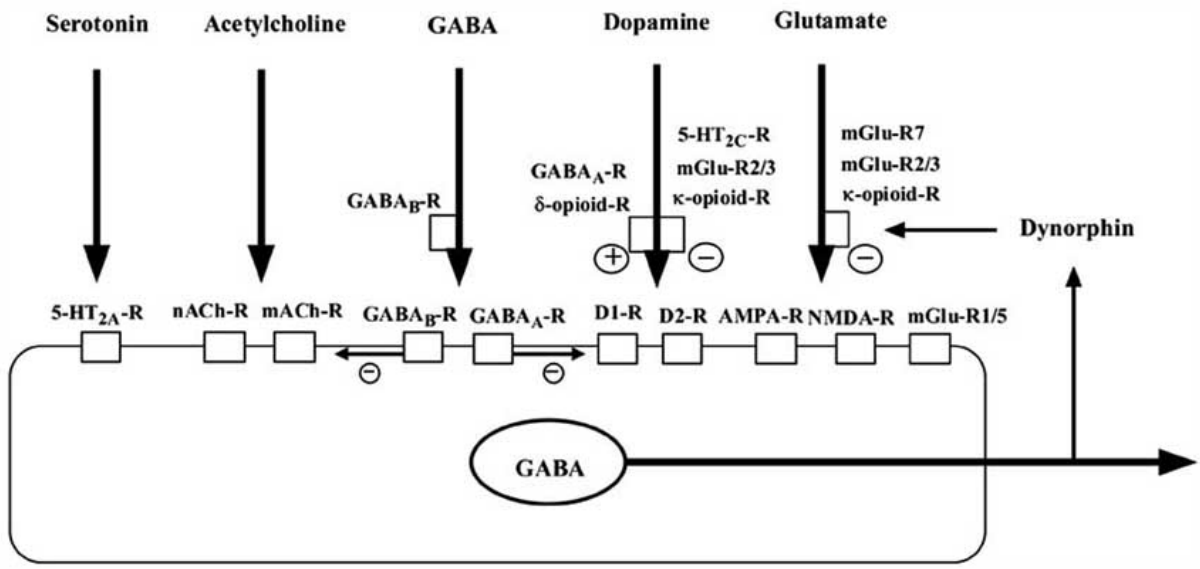

Fig. (3). Schema of regulation of GABAergic medium spiny projecting neurons and the relationships among dopamine, glutamate, GABA, acetylcholine, enkephaline, dynorphin and their receptors in the NAc. Activity of GABAergic medium spiny neurons in the NAc is heavily regulated by dopaminergic (from ventral tegmental area) and glutamatergic afferents (from frontal cortex, amygdala and hippocampus) as well as GABAergic and cholinergic interneuons. Dopaminergic and glutamatergic activity in the NAc is also regulated by neuropeptides such as dynorphin and enkephalin. Regulation by other neurotransmitters such as serotonin and neuropeptides such as MCH and CART peptides may be involved.

pairment of responsiveness to both aversive and pleasurable stimulus. In contrast, it has been demonstrated that chronic administration of the antidepressant imipramine increases both basal extracellular dopamine levels and a dopamine agonist amphetamine-induced extracellular dopamine levels in the NAc [69]. However, another study reported that chronic administration with antidepressants such as imipramine and fluoxetine prevented an NMDA receptor antagonist phencyclidine-increased dopamine turnover (DOPAC/dopamine ratio) in the NAc [36]. These reports support the proposed relationship between depressive behavior and dopaminergic activity in the NAc.

This hypothesis is supported by reports describing how dopaminergic agents such as dopamine reuptake inhibitors, presumably by increasing synaptic available dopamine concentration, have been successful in treating major depression [54,181]. Consistent with these findings, it has been demonstrated that pramipexole, a D2 dopamine receptor agonist, reverses anhedonia induced by chronic exposure to mild unpredictable stress [171], and a D2/D3 dopamine receptor agonist exhibits antidepressant-like effects in numerous depression models including learned helplessness paradigm and chronic mild stress model [104]. Moreover, it has been reported that stimulation of D2/3 dopamine receptors, but not of the D4 dopamine receptor, exhibits an antidepressant-like effect in the forced swimming test [12]. However, it should be noted that these dopamine agonists do not necessarily act within the NAc, and that other regions such as the prefrontal cortex, amygdala and ventral tegmetal area should be taken into account.

Both the shell and core of NAc receive a dense afferent dopaminergic innervation from the ventral mesencephalon [102]. The psychotomimetic drug phencyclidine, a noncompetitive NMDA receptor antagonist, elevated extracellular dopamine levels in the NAc shell but not in the core [95]. Phencyclidine, when injected directly into the shell, but not into the core, results in reward activity [26]. These results suggest that dopaminergic (and glutamateregic) input to the shell region of NAc may be more involved in the reward effect than similar input to the core region.

Dopaminergic activity in the NAc is regulated by numerous substances including glutamate, serotonin, GABA, acetylcholine, and neuropeptides. Terminal dopamine release in the NAc is under tonic GABAergic inhibition mediated mainly by $GABA_A$ (and possibly by $GABA_B$) receptors (see GABA section; Fig. **3**). Serotonin regulates dopamine release in this region both positively and negatively (see serotonin section; Fig. **3**). Endgenous opioid peptides, dynorphin and enkephalin, negatively and positively regulate dopamine release, respectively (see dynorphin and enkephalin sections; Fig. **3**).

It has been reported that dopamine directly modulates a number of postsynaptic conductances in the NAc [113], as did reward-predictive cues [114]. Indeed, inactivating dopamine neurons reduces excitation in the NAc induced by reward-predictive cues [176]. A recent study reported that D1 receptors in the NAc may act as a determinant in reward and participate in reward prediction and spatial learning [165]. It has been reported that dopamine inhibits both glutamate and GABA release in the region [124]. It has been suggested that

dopamine preferentially inhibits GABA release in the NAc, producing a net excitatory effect on projecting medium spiny neurons [64], and this may explain how dopamine can excite medium spiny neurons, while dopamine inhibits glutamate release.

Another recent study reported that chronically stressed rats showed a decrease in the number of dopamine transporter (DAT) binding sites, and an increase in the number of D1 binding sites in the NAc shell [143]. In contrast, chronic treatment with antidepressants increased expression of dopamine receptors, including the D2 and D3 types, in the NAc shell [2,86]. Likewise, electroconvulsive shock treatment increased D3 dopamine receptor mRNA and binding in the NAc shell [86]. In contrast, it has been reported that chronic mild stress decreased the number of D2 dopamine receptors binding in the NAc, which are reversed by chronic treatment with imipramine [118]. Interestingly, reduced D2 dopamine receptor expression due to chronic mild stress was observed in both the NAc shell and core, although antidepressant treatment (imipramine and fluoxetine) countered the decreased D2 dopamine receptor mRNA in the shell, but not in the core [44], suggesting that a stress-induced change in the number of D2 dopamine receptor in the NAc shell is more reversible than similar changes in the NAc core.

GLUTAMATE

Glutamate, a major excitatory neurotransmitter in the brain, is involved in several physiological and pathological conditions. Dysfunction of excitatory amino acid transmission may play a role in the etiology and pathophysiology of depression [121]. In clinical studies, it has been reported that elevated glutamate levels were observed in plasma and cerebrospinal fluid of depressed patients [4,87,98], and the administration of antidepressants has been shown to decrease plasma glutamate levels significantly in patients diagnosed with depression [89]. Furthermore, it has been reported that a single intravenous dose of ketamine (a non-competitive NMDA receptor antagonist) had antidepressant effects in depressed patients [14]. Several lines of preclinical evidence indicate that manipulation of glutamatergic transmission is effective in treating depressive behavior. For example, it has been reported that various types of compounds such as NMDA receptor antagonists [119,150], mGluR5 antagonists [160], AMPA potentiators [88], and mGluR2/3 antagonists [28] show antidepressant-like activity in a variety of animal models.

A previous study reported that withdrawal from repeated cocaine use reduced the extracellular content of glutamate in the NAc core [130], and that microinjection of AMPA into the NAc increased motor activity in cocaine sensitized rats, which was blocked by the microinjection of non-NMDA antagonists into the NAc core [130]. Moreover, a recent study has reported that the injection of NMDA receptor antagonists MK-801 or AP-5 into the NAc results in antidepressant-like behavior in forced swimming tests [134]. Since non-competitive NMDA receptor antagonists have been shown to increase glutamate release in the NAc [1], some antidepressant effects of NMDA antagonists could be mediated through increased glutamate release [142]. The possible mechanism may be that the blockade of NMDA receptor on GABA neurons reduces GABA release, which in turn reduces the inhibition of glutamate neurons, with released glutamate acting on the AMPA receptor. Although this hypothesis remains to be proven, it may help to explain the seemingly paradoxical antidepressant effects of AMPA receptor potentiators and mGluR2/3 antagonists. Given that blockade of mGluR2/3 (presynaptic autoreceptor) increases glutamate release and that stimulation of postsynaptic AMPA receptor is involved in the anti-anhedonic action of mGluR2 antagonists [77], increased glutamate transmission in the NAc (possibly mediated through postsynaptic AMPA receptor) might be involved in this antidepressant action. It was also reported that injection of mGluR2/3 antagonists into the NAc increased dopamine release [68]. Of note, recent studies with KO mice lacking mGluR2 showed enhanced place preference associated with cocaine and increased dopamine release in the NAc, and showed reduced immobility time in the forced swimming test [107]. Likewise, it has been reported that KO mice lacking mGluR7, which also functions as a presynaptic autoreceptor, exhibit antidepressant-like activity [33]. These results indicate the respective roles of dopamine and glutamate in the NAc (Fig. **3**). In support of these findings, it has been reported that transcranial magnetic stimulation, an effective treatment for major depression, increases the release of dopamine and glutamate in the NAc [177].

In contrast, it was reported that injection of glutamate into the NAc produces depressive behavior [134]. These reports also indicated that enhanced glutamate release by forced swimming on the second day coincides with decreased swimming [134]. Therefore, these data suggest the implication of increased glutamate activity in the NAc in depressive behavior. In the context of the hypothesis discussed above, increased glutamate appears to act on NMDA receptors of GABAergic neurons, which results in an increase of inhibitory tone.

Of note, local NMDA receptor blockade in the NAc core impaired spatial learning, while similar manipulation in the NAc shell had no effect [156]. AMPA receptor blockade in the NAc core impaired working memory [92]. A recent study reported that spatial memory consolidation required co-activation of glutamate and dopamine receptors within the NAc [49]. Furthermore, a previous study showed that NMDA receptors in the NAc are are involved in consolidation of spatial information, whereas AMPA receptors in the NAc are important for spatial discrimination [139]. Another recent study showed that NMDA and AMPA receptors in the NAc core play a critical role in invigorating response during instrumental learning, but are less important in guiding response according to reward-predictive cues [57]. NMDA receptor antagonism in the NAc impairs response-reinforcement learning to obtain food [76]. This appetitive instrumental learning requires coincident activation of NMDA and dopamine D1 receptors within the NAc core [157]. It is now believed that these types of information on learning and memory are weakly related with depression. However, given that reward sometimes requires learning and that the loss of pleasure observed in depression may reflect an inability to obtain reward, it is possible that enhancement of the learning

and memory of new experiences could interfere with the memory of the stressful experience and thereby result in an antidepressant effect [146].

These reports indicate that glutamate in the NAc is involved in the production of behavioral depression. It is conceivable that the antidepressant role of glutamate might be ascribed to the blockade of NMDA receptors and activation of AMPA receptors, although the precise mechanism remains to be proven.

GABA

γ-Aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the mammalian brain, where it is widely distributed. It has recently been suggested that major depressive disorder is associated with dysfunction of GABAergic transmission [19,83]. Reports have indicated that plasma and cerebrospinal fluid GABA levels were reduced in depressed patients [127,128]. In contrast, antidepressant treatments with selective serotonin reuptake inhibitors (SSRIs), mood stabilizers or electroconvulsive therapy appear to eliminate the deficit in GABA levels associated with major depressive disorder [83]. Likewise, reduced GABA transmission has been reported in animal models of depression such as the forced swimming test [18] and learned helplessness model [129]. A recent study reported that pretreatment $GABA_B$ receptor agonist baclofen antagonizes cocaine- and morphine-induced dopamine release in the NAc, indicating the involvement of $GABA_B$ receptros in the NAc in reward processes [47].

In the NAc, GABA has been recognized as playing a paramount role in fast transmission. GABA is utilized by common, spiny projection neurons and by one category of aspiny interneurons [102]. The flow of information through the NAc is dependent upon the activity of the neuron: a GABAergic, medium-sized spiny projection cell, which contributes to the excitability of the nucleus and forms an important substrate for neuromodulation. There are two major receptor subtypes for GABA: ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors, both of which are expressed in the NAc [97]. Of these, $GABA_A$ receptors consist mostly of postsynaptic receptors, whereas $GABA_B$ receptors are localized presynaptically and postsynaptically (Fig. **3**). Functional differences of $GABA_A$ and $GABA_B$ receptors in the NAc are suggested. It has been reported that $GABA_A$ receptors exert inhibitory control on dopamine release within the NAc, although the role of $GABA_B$ receptors is less prominent [136].

Psychostimulant withdrawal is thought to be as a model of depression [8]. Withdrawal from repeated cocaine administration increased the extracellular content of GABA in the NAc core, which might be a result of the functional desensitization of $GABA_B$ presynatic autoreceptor [172]. The extracellular GABA provides inhibitory tone on $GABA_B$ presynaptic autoreceptors to regulate GABA release [172] (Fig. **3**). Within the NAc, activation of either $GABA_A$ or $GABA_B$ receptors inhibits acetylcholine release, although tonic GABA inhibition appears mainly under the influence of $GABA_A$ receptors [133]. A recent study using the unilateral injection technique has indicated that $GABA_A$ receptors in the NAc shell exert inhibitory control on dopamine-mediated turning behavior, whereas $GABA_B$ receptors in the NAc shell exert inhibitory control over acetylcholine-mediated turning behavior [3] (Fig. **3**). Because cholinergic interneurons perform excitatory regulation of dopamine release in the NAc (presumably through nicotinic receptor), the inhibitory effects of GABA on acetylcholine release inhibit dopamine release. It has been suggested that reduced dopamine release in the NAc may cause anhedonia. Therefore, direct or indirect regulation of dopaminergic activity by GABAergic neurons within the NAc may be responsible for the etiology of depression, although the significance of each receptor subtype ($GABA_A$ and $GABA_B$) within the NAc has yet to be fully elucidated.

A recent study showed that infusion of allopregnanolone into the NAc produced antidepressant-like effects in ovariectomized rats [105]. Allopregnanolone is a neurosteroid, which is known to be an agonist for $GABA_A$ receptors. In human beings, cerebrospinal fluid concentrations of allopregnanolone were reduced in depressed patients and recovered after antidepressant treatments [137,166]. However, allopregnanolone works in other regions such as the prefrontal cortex and hippocampus where $GABA_A$ receptors are widely distributed. Further study will be required to gain an understanding of the role of allopregnanolone in the NAc.

ACETYLCHOLINE

The central cholinergic system may play a role in depressive disorders. Stimulation of the central cholinergic system with cholinomimetics or cholinesterase inhibitors causes depressive phenotypes such as depressed mood, dysphoria and anhedonia [39]. Depressed human subjects are supersensitive to cholinergic challenge relative to controls [39]. Moreover, anti-muscarinic agents have been reported to have antidepressant-like activity in rodents [30]. The implication of hypercholinergic activity in depressive behavior was further supported by the fact that the Flinders Sensitive Line rats, which display depressive phenotypes, were developed by selective breeding for increased sensitivity to the cholinesterase inhibitor [115]. This genetic animal model of depression showed depressive behavior such as enhanced immobility in the forced swim test [116].

The NAc contains aspiny cholinergic interneurons, which interact with dopaminergic input, glutamatergic input as well as with the GABAergic medium spiny projection neurons [102]. Acetylcholine and dopamine have the opposite effects on the NAc. It should be noted that acetylcholine enhancement in the NAc is reported to prevent addictive behavior with cocaine and morphine [63]. The cholinergic neurons are more densely distributed in the shell than in the core [102]. The cholinergic interneurons control the excitability and membrane properties of these output neurons mainly by stimulating post-synaptic muscarinic receptors [102]. Thus, the cholinergic interneurons appear to be well suited for controlling the transmission of limbic information to the accumbens target nuclei. It has been reported that acetylcholine release in the NAc increases response to an aversively conditioned taste stimulus [96] or during withdrawal from drugs

of abuse [135], indicating the implication of the accumbal cholinergic system in reward, emotion or depression.

It has been reported that injection of the M1-muscarinic receptor antagonist pirenzepine into the NAc exhibits an antidepressant effect in the forced swimming test without changing locomotor activity [30]. In contrast, local injection of the M2-muscarinic receptor antagonist gallamine results in depressive-like behaviors in the same paradigm and an increase in acetylcholine release in the NAc [30]. Increased acetylcholine may stimulate post-synaptic M1-muscarinic receptor to cause depressive behavior.

Injection of nicotine into the NAc increases dopamine release in the NAc [103]. In this context, the mechanism of nicotine is similar to that of drugs of substance abuse. Withdrawal symptoms from either nicotine or substances of abuse can be considered from the point of view of dopamine release in the NAc. Therefore, it is unsurprising that nicotine and nicotine receptor ($\alpha4\beta2$) agonist showed antidepressant-like activity in rodents [48,144]. However, some contradictory reports indicate that nicotine receptor antagonism may mediate antidepressant-like activity [148,152]. Indeed, it has also been reported that antidepressants inhibit nicotine receptors [51,60] and that nicotine receptor antagonist enhances the antidepressant effect of imipramine and citalopram [132]. This discrepancy may stem from the differential expression of nicotine receptor subunits or differential selectivity of the compound for the subunits. The role of nicotine receptors in the NAc in depression remains to be verified.

SEROTONIN

Serotonin (5-HT) is known to be involved in depression, aggression, and suicidality. As it has been demonstrated that SSRIs serve as effective medication for major depressive disorder, much attention has been focused on the serotonergic system of the brain. Serotonergic responsivity was reported to be dulled in a subgroup of young depressed patients [94].

It has been postulated that serotonergic neurons in the NAc play an important role in motivation, reward and certain forms of stress [100,108], and short duration immobilization stress has been shown to alter 5-HT levels in the shell of the NAc [100]. Finders Sensitive Line rats, a genetic model of depression, showed a decrease in 5-HT turnover (5-HIAA/5-HT ratio) in the NAc [180]. Wistar-Kyoto rats, which are prone to develop stress-induced depression, exhibited significantly lower tissue levels in 5-HT and 5-HIAA in the NAc in stress conditions in spite of the fact that normal control rats exhibit a significant increase of 5-HIAA in response to stress [35], indicating the dulled serotonergic responsivity in the NAc in depression. Similarly, another model of depression, the olfactory bulbectomized rat displayed blunted serotonergic response to a challenge with a metabolic stressor lipopolysaccharide [32]. Other model of depression, chronically stressed rats, also showed a reduced 5-HT response, but not the basal levels, in the NAc shell after cocaine administration [93], indicating the dulled pleasure stimulation.

It has been reported that serotonergic transmission regulates dopamine release within the NAc, both positively and negatively, while local application of serotonin into the NAc has been reported to stimulate dopamine release [120]. It is considered that the mal-regulation of dopaminergic activity in the NAc by 5-HT may be involved in a depressive phenotype [40]. In support of this hypothesis, an increased inhibitory effect of 5-HT_{2C} receptors on accumbal dopamine release was observed in Flinders Sensitive Line rats, an animal model of depression [42], and chronic antidepressant treatment normalized the serotonin-dopamine interaction as well as depressive behavior in the forced swimming test [178]. Serotonin-induced alterations in dopamine release involve the interaction of other types of serotonin receptors. Activation of 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 receptors induces dopamine release in the NAc [23,120,174] while activation of 5-HT_{2C} receptors reduces dopamine release in the NAc [42].

It has been reported that local injection of serotonin into the NAc increased the release of β-endorphin in the region, which is enhanced by co-infusion of fluoxetine [179]. Since β-endorphin in the NAc has rewarding and reinforcing effects [78], this interaction has been postulated to be involved in depression.

Both core and shell subregions of the NAc received a dense serotonergic innervation from the raphe nucleus [167], while 5-HT-labeled axon terminals in the shell are more numerous and more frequently formed synaptic contacts of the symmetric variety relative to the 5-HT-labeled axon terminals in the core region [168]. In the NAc shell, 5-HT-containing axon terminals form mainly symmetric, inhibitory-type, synapses with GABAergic neurons and their targets, indicating a neuromodulatory role (largely inhibition) for 5-HT on GABAergic neurons in the NAc shell [167]. The authors demonstrated that 5-HT- and GABA-labeled axons were also frequently apposed, suggesting other presynaptic sites for modulatory interactions in the NAc shell. Moreover, a relatively high incidence of convergence between serotonergic and GABAergic terminals on common dendrites, presumably of cholinergic neurons, has been observed [167], suggesting that 5-HT afferents may have direct effects on cholinergic neurons (inhibition) and indirect effects of excitation involving inhibition of inhibitory GABAergic neurons.

DYNORPHIN/κ OPIOID RECEPTOR

It has been reported that κ opioid receptor agonists increases immobility time in the rat forced swimming test without effects on locomotor activity [90], suggesting that activation of κ opioid receptor produces depressive phenotypes. To support this hypothesis, it has been reported that a κ opioid receptor antagonist as well as gene disruption of prodynorphin attenuate increased immobility following exposure to repeated forced swim stress [101].

The NAc is a brain region critically involved in aversive behaviors associated with dynorphin and its receptor (κ-opioid receptor) agonists. Indeed, microinjection of κ-opioid receptor agonists into the NAc causes conditioned place aversions that likely reflect dysphoric states [6]. It has also been reported that exposure to various stressors such as immobilization, forced swimming, and inescapable shock markedly increase dynorphin immunoreactivity in both the shell and core of NAc [147]. Given that depression in humans is often

precipitated or worsened by physical or psychological stress, and stress is reported to produce depression [106], increased dynorphin expression in the NAc by stress could play an important role in formation of depression. Furthermore, there are several lines of evidence showing that blockade of κ opioid receptor produces antidepressant-like activity in animal models. Thus, intracerebroventricular or intraaccumbal injection of norBNI, a κ opioid receptor antagonist, decreases immobility in the forced swimming test [90] or reduces escape failure in the learned helplessness test [111,147].

Kappa opioid receptors have been reported to mediate aversion by regulating mesolimbic dopaminergic activity in the NAc [62]. Indeed, both systemic and intraaccumbal injection of the κ opioid receptor agonist reduce dopamine release in the NAc, while both systemic and intraaccumbal injection of the κ opioid receptor antagonist norBNI increase dopamine release [91,159]. Furthermore, injection of D1 receptor antagonists into the NAc attenuated the conditioned place aversion by the κ opioid receptor agonist [145], consistent with the supposition that κ opioid-mediated aversion is due to the inhibition of dopamine release in the NAc. It was reported that chronic cocaine administration increased κ opioid receptors in the NAc [31]. Thus, given that the dopamine system in the NAc plays a major role in motivation and reward and could contribute to the anhedonia observed in depressed patients, it is suggested that a decrease in dopaminergic activity in the NAc by increased dynorphin expression due to exposure to stress might be responsible for the formation of depression.

The GABAergic spiny neurons in the NAc shell receive glutamatergic input from the prefrontal cortex, amygdala, and hippocampus, in addition to dopaminergic input from the ventral tegmental area. Interestingly, it was demonstrated that κ opioid receptor is present on the presynaptic terminals of the presumed excitatory synapses as well as on the dendrites of the medium spiny neurons [161], which raises the possibility that some of the effects mediated by κ opioid receptor may be attributable to the regulation of glutamatergic excitatory transmission. Indeed, it has been reported that the κ opioid receptor agonist decreases glutamate release in the NAc shell [65] and it is hypothesized that the behaviors induced by a κ opioid receptor agonists in the NAc shell are partially dependent on modulation of glutamatergic input to medium spiny neurons [65].

ENKEPHALIN/δ OPIOID RECEPTOR

A recent study reported that endogenous enkephalin modulates the basal hedonic state in pro-enkephalin knockout mice [151]. It has been reported that the enkephalin catabolism inhibitor exhibited antidepressant-like activity in learned helplessness and that this effect was reversed by the δ opioid receptor antagonist naltrindole [162]. Consistent with this hypothesis, δ opioid receptor agonists have been reported to display antidepressant-like activity in the forced swimming test [21,141], while KO mice lacking δ opioid receptor display a depressive-like phenotype in the forced swimming test [50].

It has been reported that chronic treatment with antidepressants increases [Met5]enkephalin-like immunoreactivity in the NAc [34]. Likewise, repeated electroconvulsive shocks cause an increase in [Met5]enkephalin content in the NAc [66]. In contrast, in another study chronic treatment with antidepressants was reported to decrease [Met]enkephaline content in the NAc [84]. Antidepressants seem to alter the peptide in the NAc, in spite of some conflicting results in previous reports.

The NAc contains δ opioid receptors, which are supposed to be located in the presynapse of dopaminergic terminals because local administration of δ opioid receptor agonists increase dopamine release in the NAc [158] (Fig. **3**). Several lines of evidence have suggested the implication of enkephalin/δ opioid receptor in the NAc in depression. An increase in [Met5]enkephalin release in the NAc by exposure to a congener was curbed after chronic mild stress procedure [15], and the level of [Met5]enkephalin was reduced in the NAc in chronic mild stress model [43], suggesting that the activity of the enkephalinergic system in the NAc could be reduced in a stress-induced model of anhedonia. Indeed, δ opioid receptor agonists, when infused into the NAc, increase dopamine release in the NAc [52], which may explain the antidepressant-like action of δ opioid receptor agonists. Although the precise mechanism mediated by antidepressant effects of δ opioid receptor remains to be determined, the interaction between δ opioid receptor and dopaminergic system in the NAc has been suggested as a possibility.

BDNF

BDNF is now recognized not only for its impact on neurons, but also for its implications in learning, motivation and regulation of mood. A recent study reported that serum BDNF levels were significantly reduced in antidepressant-free patients with depression, and were negatively correlated with the severity of depression [74]. Another study demonstrated that decreased serum BDNF levels in antidepressant-naïve patients recovered to normal levels associated with lower severity of depression after antidepressant medication [149].

Repeated stress decreases BDNF expression in the hippocampus [153], while antidepressant treatment as well as electroconvulsive seizure increases BDNF levels in the hippocampus [112]. Moreover, it has been reported that administration of BDNF into the hippocampus causes antidepressant-like effects in the forced swimming test and learned helplessness test [146]. These findings are in good agreement with the decreased serum BDNF levels in patients with depression, and strongly suggest that a decreased BDNF level in the hippocampus causes a depressive phenotype.

However, in contrast to the hippocampus, it has been reported that BDNF in the NAc is involved in the development of a depression-like phenotype. Thus, intra-NAc injection of adenoviral vector encoding truncated tyrosine kinase receptor B (TrkB) (which can act as a dominant-negative receptor) exhibits an antidepressant-like phenotype [45]. Moreover, it has been reported that chronic exposure to or withdrawal from drugs of abuse, conditions in which an anhedonic state can be produced, induces an increase in BDNF levels in the NAc [58]. In contrast, it has been reported that increased BDNF or stimulation of TrkB in the NAc enhance

dopamine release and dopamine-related behaviors [109], and intra-NAc BDNF infusions enhances drug reward mechanisms [67]. These events contradict the finding that increased dopamine function and reward lead to antidepressant-like activity. The mechanism underlying the action of BDNF in the NAc remains to be elucidated.

CREB

CREB is a constitutively expressed transcription factor activated by phosphorylation through cAMP pathway and other intracellular signaling cascades [99]. Transgenic mice overexpressing CREB display depressive behavior in the learned helplessness test (increased escape failure), whereas mice overexpressing dominant-negative mutant CREB (mCREB) or rats with viral-expressed mCREB in the NAc showed a decrease in escape failure, an antidepressant-like effect [111]. Furthermore, mCREB expression decreased the expression of prodynorphin in NAc medium spiny neurons [111]. Thus, increased CREB (perphaps taken together with increased dynorphin) in the NAc could produce a depressive phenotype in animal models of depression.

It has been reported that elevated transcription of CREB in the NAc is associated with increased immobility in the forced swim test, while decreased CREB expression in the NAc exhibits the opposite effect, i.e., an antidepressant-like effect [131]. Acute and chronic stresses as well as chronic exposure to drugs of abuse have shown to activate CREB in the NAc [10,131]. It has been reported that increased CREB function in the NAc decreases reward responses to drugs of abuse, whereas decreased CREB function has the opposite effect [25,131]. Thus, rats expressing dominant-negative CREB spent more time in an environment associated with cocaine in a place conditioning study, while rats overexpressing CREB exhibited increased cocaine aversion [131].

Moreover, CREB activity in the NAc shell appears to control gating of behavioral responses to emotional stimuli [10], such that the increase in CREB function in the NAc shell following stress or drug exposure may contribute to symptoms of emotional numbing or anhedonia. This is interesting because cessation of drugs of abuse induces a withdrawal syndrome that is manifestly similar to the symptoms of major depressive disorder in humans [8]. Likewise, in rodents, withdrawal from drugs of abuse elevated the brain stimulation reward threshold in intracranial self-stimulation [59] and reduced motivation to obtain a sucrose solution under a progressive ratio schedule of reinforcement [9], both of which reflect anhedonia. Moreover, it has been shown that extracelluar dopamine level in the NAc is reduced during cocaine withdrawal [169]; thus it is presumed that increased CREB function in the NAc may inhibit dopaminergic activity.

In the NAc, prodynorphin has been identified as a target of CREB, and is induced by activation of cAMP-CREB cascade [110]. It has been reported that viral-mediated elevations of CREB in the NAc shell elevate local dynorphin mRNA, while overexpression of dominant-negative CREB in the NAc shell decreases dynorphin mRNA [25]. Consistent with this finding, it has been reported that injection of a κ opioid receptor antagonist into the NAc leads to the display of antidepressant effects in rodent models of depression [111,147]. Therefore, one plausible explanation of dysphoric and depressive phenotype by increased CREB in the NAc is that CREB-mediated increase in dynorphin within the NAc decreases local dopamine tone *via* actions at the κ opioid receptor on the terminals of mesolimbic dopamine neurons.

MCH

Melanin-concentrating hormone (MCH) is produced predominantly by neurons in the lateral hypothalamus and the zona incerta with extensive projections throughout the brain [16]. MCH has two receptor subtypes, designated MCH1R and MCH2R, both of which are G protein-coupled receptors [56]. An emerging body of evidence suggests that MCH1R plays an important role in the regulation of mood and stress.

MCH1R is highly expressed in the NAc shell [16,17,61, 140]. Moreover, it has recently been reported that MCH1R is co-expressed in dynorphin-positive medium spiny neurons in this region [55], and that injection of MCH into the NAc shell causes depressive behavior in the forced swimming test [55], suggesting that MCH may exert its depressive-like effects through interaction with MCH1R in the NAc shell.

Recently, it has been reported that MCH1R null mice exhibit upregulation of mesolimbic dopamine receptors with increased expression of dopamine D1- and D2-like receptors in the NAc shell, and that they show supersensitivity to D-amphetamine and dopamine D1 receptor agonist-induced locomotor hyperactivity [155]. Moreover, intracerebroventricular injection of MCH decreases DOPAC levels in the NAc [175]. These results indicate that MCH1R negatively modulates dopaminergic function in the NAc. Considering the co-expression of MCH1R with dynorphin, it is presumed that MCH inhibits dopaminergic activity in the NAc by positively regulating dynorphin expression or release, which may in turn inhibit dopamine release in the region; this mechanism may be involved, at least in part, in the depressive phenotype caused by MCH. Moreover, MCH has been reported to inhibit dopamine D1 receptor agonist-induced phosphorylation of Ser^{845} of the AMPA receptor subunit GluR1 in the NAc slices, the event, which leads to reduced AMPA transmission [55]. Thus, MCH1R may possibly negatively regulate AMPA transmission *via* D1 receptor in the NAc. This effect is of interest because it has been reported that AMPA potentiators have antidepressant effects in behavioral despair models such as the forced swim and tail suspension test [88], and this mechanism might also be involved in the depressive phenotype produced by MCH.

In accordance with the above findings, it has recently been reported that nonpeptidic MCH1R antagonists, when administered systemically, exhibit antidepressant effects in forced swimming test [17,27]. Moreover, injection of MCH1R antagonists to the NAc shell resulted in antidepressant effects in the forced swimming test [55]. Future studies remain to be investigated whether MCH or MCH1R expression in the NAc is increased following stress exposure or withdrawal from drugs of abuse.

CART

Cocaine- and amphetamine-regulated transcript (CART) was identified as a mRNA acutely upregulated in the NAc after administration of cocaine or amphetamine in rats [41]. To date, several CART peptide fragments have been identified, and among them, two CART peptide fragments, CART-(55-102) and CART-(62-102), were found to be biologically active [7,82].

High levels of CART peptide immunoreactivity were found in both the shell and core of the NAc in rats [80] and monkeys [154] with more abundant expression in the shell region. In the shell, CART was found to be highly concentrated in medium spiny projection neurons that contain GABA [154], suggesting that CART peptide may be a co-transmitter with GABA in a subpopulation of projection neurons in the shell.

Moreover, it has been reported that CART peptide-immunoreactive dendrites were found to be in contact with tyrosine hydroxylase-positive terminals that displayed the ultrastructural features of dopamine containing boutons, indicating that CART peptide-immunoreactive neurons receive direct synaptic input from dopaminergic afferents [154]. In contrast, CART mRNA-containing cell bodies or CART-immunoreactive cell bodies were not found in the VTA, whereas CART-containing axons and nerve terminals were found. Thus, CART might well be a region-specific chemical in the NAc and striatum.

It has been reported that injection of CART peptide into the NAc inhibits cocaine-induced hyperlocomotion [71], suggesting the implication of CART peptide in the reward pathway. CART is likely to act at least partly on GABA-containing neurons. In the NAc, CART may possibly inhibit GABA output *via* receptors (although unidentified) on GABA ergic neurons. Although the relationship between CART and depression has yet to be demonstrated, based on the implication of CART in the reward pathway through modulation of the GABA-dopamine interaction, it is highly likely that CART peptide in the NAc plays an important role in the pathophysiology of depression.

CONCLUDING REMARKS

Dysfunction of dopaminergic activity in the NAc may be deeply involved in the pathophysiology of depression. Reduced dopaminergic activity in the NAc was also observed in animal models of depression as well as after chronic mild stress. In this context, dopamine receptor agonists should provide beneficial effects in treating impaired NAc-related functions such as reward, motivation, and learning. Indeed, dopaminergic agents such as dopamine reuptake inhibitors have been reported to be effective in the treatment of patients with major depressive disorder [54,181]. Further studies are required to elucidate the importance of dopamine in the NAc in depression and the effectiveness of dopamine-related agents for the treatment of depression.

Dopaminergic activity in the NAc is regulated by numerous substances. These include dynorphin, MCH, and CART, which are postulated to negatively modulate dopamine release in the NAc. Interestingly, it has been reported that expression of dynorphin in the NAc is increased in animal models of depression, learned helplessness and psychostimulant withdrawal. Thus, the reduced dopaminergic activity seen in depression could be ascribed to increased expression of negative modulators of the dopamine system, including dynorphin, in the NAc under stressful conditions. Here, it should be noted that dopaminergic agents, by acting outside the NAc, generate not only beneficial effects in the treatment of depressive mood but also a number of adverse side effects. In this case, neuropeptides such as dynorphin, MCH, and CART might be ideal targets for therapeutic agents with fewer unwanted effects.

It is well recognized that GABAergic neurons function as the main neurons in the NAc, and that the flow of information through the NAc is dependent on the activity of GABAergic spiny projecting neurons. Moreover, it has also been recognized that the glutamatergic corticolimbic pathway plays an important role in the balance of activity between the cortical and subcortical regions. However, in spite of the crucial roles of these amino acids in the NAc, studies on the involvement of these amino acids in the NAc in depression have been hampered by the fact that they are abundantly and ubiquitously distributed throughout the brain; moreover, findings on local injection of agonists/antagonists for these amino acid receptors into the NAc are currently limited. Likewise, the role of cholinergic systems in the NAc in depression must be clarified, although here it is interesting to note that cholinergic neurons in the NAc are interneurons, but not projecting neurons. Although currently prescribed antidepressants exert their effects through the serotonin or norepinephrine systems, these neurotransmitters do not appear to be involved in the main functions within the NAc.

Depression may affect various brain regions, and different symptoms seen in subjects with depression may be attributed to different magnitudes of impairments among the affected brain regions. Accumulating evidence has clearly indicated the importance of the NAc in pathophysiology of depression, and the roles of several neurotransmitters, neuropeptides, and transcriptional factors in this region in depression have been investigated. Further studies are required to delineate the interaction among these molecules in the NAc, and to elucidate their implications in depressive disorder.

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Received: June 30, 2005 Revised: September 06, 2005 Accepted: February 08, 2006