Nucleus Accumbens and Dopamine-Mediated Turning Behavior of the Rat: Role of Accumbal Non-dopaminergic Receptors

Hiroko Ikeda1,2,*, Junzo Kamei2, Noriaki Koshikawa1,3, and Alexander R. Cools4

1Department of Pharmacology, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
2Department of Pathophysiology and Therapeutics, Hoshi University School of Pharmacy and Pharmaceutical Sciences, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan
3Division of Oral and Craniomaxillofacial Research, Dental Research Center, Nihon University School of Dentistry, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8310, Japan
4Radboud University Medical Centre Nijmegen, Donders Institute for Brain, Cognition and Behavior: Psychoneuropharmacology, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Received March 26, 2012; Accepted August 20, 2012

Abstract. Accumbal dopamine plays an important role in physiological responses and diseases such as schizophrenia, Parkinson’s disease, and depression. Since the nucleus accumbens contains different neurotransmitters, it is important to know how they interact with dopaminergic function: this is because modifying accumbal dopamine has far-reaching consequences for the treatment of diseases in which accumbal dopamine is involved. This review provides a summary of these interactions, and our current knowledge about them are as follows: A) AMPA receptors are required for dopamine-dependent behavior and vice versa; NMDA receptors modulate the activity at the level of AMPA and/or dopamine D1 receptors. B) GABA_A receptors, but not GABA_B receptors inhibit dopamine-dependent behavior. C) Nicotinic receptors are required for dopamine-dependent behavior, whereas muscarinic receptors inhibit dopamine-dependent behavior. D) α-Adrenoceptors inhibit dopamine-dependent behavior in contrast to β-adrenoceptors, which potentiate this behavior. E) μ- and δ_2-opioid receptors elicit behavior that requires an intact dopaminergic function and δ_2-opioid receptors modulate dopamine-dependent behavior. F) Orexin 2 receptors play an important, modifying role in dopamine-dependent behavior. G) Somatostatin receptors potentiate dopamine-dependent behavior. It is suggested that modulation of the above-mentioned non-dopaminergic receptors provide new tools to control physiological functions as well as diseases mediated by accumbal dopamine.

Keywords: dopamine, nucleus accumbens, turning behavior

1. Introduction

Dopamine in the central nervous system plays an important role not only in behavior and physiological responses, but also in many diseases (review: 1; depression: 2; drug addiction: 3 – 5; attention deficit hyperactivity disorder (ADHD): 6, 7; schizophrenia: 8, 9; Parkinson’s disease, review: 10). The nucleus accumbens (Nacc), which is a terminal area of the mesolimbic dopaminergic neurons, is known to be one of the main structures controlling physiological responses, behavior, and diseases (1). The Nacc is a heterogeneous structure and is divided anatomically into at least two structures, that is, the shell and the core (11 – 14). There are many differences between these two structures. For instance, the dopamine plexus is richer in the shell than in the core (13), and the concentration of dopamine is higher in the shell than in the core (12). Furthermore, the dopamine D1 binding in the rostral areas of the Nacc appears to be higher in the shell than in the core, whereas the dopamine D2 binding...
appears to be lower in the shell than in the core (11). Thus, it is not remarkable that dopamine functions vary across the core and the shell (15, 16). The shell is thought to play a pivotal role in dopamine-mediated functions because it contains the largest amount of dopaminergic terminals and the highest concentration of dopamine (12, 13).

Unilateral activation of the Nacc has been shown to elicit two characteristic types of turning behavior, namely circling and pivoting (16, 17). Circling is marked by normal hindlimb stepping, normal forelimb stepping, turns of large diameter (> 30 cm), and running, whereas pivoting is marked by abnormal hindlimb stepping, turns of small diameter (< 20 cm), and spinning around one hindlimb (17). More specifically, we have provided pharmacological evidence that unilateral stimulation of dopamine D1/D2 receptors in the Nacc shell, but not the Nacc core, elicits contraversive pivoting, whereas unilateral stimulation of acetylcholine receptors in the Nacc shell elicits contraversive circling (15, 16). Since the contraversive pivoting induced by unilateral stimulation of dopamine D1/D2 receptors in the Nacc shell is a characteristic feature of the function of accumbal dopamine in the Nacc shell and the contraversive circling induced by unilateral stimulation of acetylcholine receptors in the Nacc shell is a characteristic feature of the function of accumbal acetylcholine in the Nacc shell, these behaviors are very useful tools for studies on analysis of interactions between various accumbal, neuroactive compounds as well as for studies on analysis of the involved output stations of the Nacc. We have provided evidence that the shell-specific, dopaminergic pivoting is mediated via a substrate that differs from that involved in the shell-specific, cholinergic circling (16, 18 – 21).

The Nacc receives not only dopaminergic projections from the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), but also many other neuronal projections releasing other neurotransmitters and neuropeptides (see below). It is important to know to what extent these neuroactive compounds direct the function of accumbal dopamine: this is because accumbal dopamine has important therapeutic consequences for the treatment of diseases in which accumbal dopamine is involved. This review provides a summary of these interactions. Since a single neurotransmitter or neuropeptide can act at distinct receptors, this review focuses on the involved receptors.

2. Interaction with dopamine in the Nacc

Because the Nacc receives a variety of neuronal projections, each releasing their own neurotransmitter and/or neuropeptide, it is not surprising that mutual interactions between dopamine and neurotransmitters such as glutamate, γ-aminobutyric acid (GABA), acetylcholine, noradrenaline, serotonin, and neuropeptides such as enkephalin, orexin, and somatostatin occur in the Nacc (see below). These interactions as revealed by studying how compounds that selectively interact with one of the various accumbal, non-dopaminergic receptors influence the shell-specific, dopaminergic pivoting, are discussed below. Recently, heterodimerization of dopamine receptors has been shown for both the D1/D5- and D2/D3/D4-receptor families, which couple positively and negatively, respectively, to adenylyl cyclase (for reviews: 22, 23; see also: 24). Notably, heterodimers are formed by D1 and adenosine A1 receptors, D2 or D3 and adenosine A2 receptors, D2 and somatostatin SST5 receptors, and D2 and cannabinoid CB1 receptors. Further, D1s, D2s, and D3 receptors physically assemble into functional D1/D2, D1/D3, and D2/D3 heterodimers possessing binding and coupling profiles distinct from the respective monomers. By using different experimental approaches various groups have, in fact, demonstrated the existence of dopamine heterodimers in both transfected cell systems and the striatum with peculiar pharmacological, signaling, and functional properties. The putative role of these heteromers in the physiological regulation of accumbal function is yet unknown. For that reason, the role of these heteromers will not be discussed, although future research may show that these have a functional and therapeutic significance.

2.1. Glutamate

The Nacc receives glutamatergic inputs from several brain areas including the prefrontal cortex, amygdala, and hippocampus (25 – 27). Anatomical evidence indicates that there are interactions between dopaminergic and glutamatergic inputs in the Nacc (28, 29). The ionotropic glutamate receptors are classified into three types, that is, N-methyl-D-aspartic acid (NMDA), α-amino-3-hydro-5-methyl-4-isoxazolpropionic acid (AMPA), and kainate receptors (30). Glutamatergic agonists have been found to enhance dopamine release in the Nacc, possibly via non-NMDA receptors (31), whereas accumbal dopamine has been found to increase extracellular glutamate levels in the Nacc (32). In behavioral studies, agonists of the glutamatergic ionotropic receptors, AMPA and NMDA receptors, have been found to stimulate locomotor activity when injected into the Nacc, and drugs that inhibit dopaminergic neurotransmission have been found to inhibit these effects (33, 34). Thus, both accumbal glutamate and accumbal dopamine regulate motor function.

To analyze in more detail the functional interaction between glutamate and dopamine in the Nacc shell, we have examined the role of glutamate receptors in eliciting
the shell-specific, dopaminergic pivoting. Unilateral injection of AMPA into the Nacc shell elicited contraversive pivoting and this effect was inhibited by the AMPA-receptor antagonist NBQX (1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide), indicating that unilateral stimulation of AMPA receptors in the Nacc shell elicits contraversive pivoting, which pattern is identical to that induced by unilateral stimulation of dopamine receptors in the Nacc shell (35). The contraversive pivoting induced by stimulation of AMPA receptors in the Nacc shell was inhibited by the dopamine D₁/D₂-receptor antagonist Z(-)(cis)-flupenthixol injected into the same area (35), indicating that the contraversive pivoting elicited by the stimulation of AMPA receptors in the Nacc shell requires intact dopaminergic neurotransmission in this brain region. Since AMPA-receptor stimulation has been found to enhance extracellular levels of dopamine in the Nacc (31), it has been suggested that stimulation of presynaptic AMPA receptors on dopaminergic terminals elicits contraversive pivoting (31, 35). In this context, it has to be stated that the stimulatory effects of AMPA receptors on dopamine release in the Nacc are not necessarily due to direct actions of this excitatory amino acid on dopaminergic terminals: indirect actions through intrinsic neurons or feedback loops cannot be excluded (36).

Stimulation or inhibition of NMDA receptors in the Nacc shell does not elicit turning behavior (35). The notion that NMDA receptors are not involved in this respect fits in with the finding that there is no functional interaction between accumbal NMDA receptors and accumbal dopamine receptors. In fact, evidence is available that local application of NMDA does not affect dopamine release from the Nacc (31). However, the NMDA-receptor antagonist MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,b]cyclohepten-5,10-imine] has been found to inhibit dose-dependently the shell-specific, AMPA-induced pivoting when co-administered with AMPA into the Nacc shell (35), suggesting that NMDA receptors in the Nacc shell play a modulatory role in pivoting induced by unilateral injection of AMPA into the Nacc shell.

Contraversive pivoting induced by unilateral injection of a mixture of the dopamine D₁-receptor agonist SKF 38393 and D₂-receptor agonist quinpirole in the Nacc shell is inhibited by both MK-801 (Fig. 1A) and NBQX (Fig. 1B) injected into the same region (35). Thus, it has been concluded that the shell-specific, dopaminergic pivoting requires intact glutamatergic neurotransmission in the same region (35). This conclusion complements the earlier reported finding that locomotor activity produced by cocaine or dopamine D₁/D₂-receptor agonists are antagonized by intra-accumbens administration of AMPA- or NMDA-receptor antagonists (37, 38).

It has been suggested that stimulation of presynaptic dopaminergic receptors on glutamatergic terminals elicits contraversive pivoting identical to that elicited by stimulation of AMPA receptors in the Nacc shell (32, 35) because accumbal dopamine is known to increase the release of accumbal glutamate (32).

Recently, it has been reported that NMDA receptors
are localized on the neurons that contain dopamine D_{1} receptors in the Nacc shell (39). Moreover, stimulation of dopamine D_{1} receptors in the Nacc shell phosphorylates AMPA receptors, thereby strengthening the function of AMPA receptors (40). Therefore, an alternative explanation concerning the above-mentioned results is that NMDA and AMPA receptors postsynaptically modulate the dopamine function, possibly via D_{1} receptors.

The above-mentioned results indicate that 1) accumbal AMPA receptors direct the shell-specific, dopaminergic pivoting, 2) accumbal, dopamine D_{1}/D_{2} receptors direct shell-specific, AMPA-mediated pivoting, and 3) accumbal NMDA receptors at best modulate the activity at the level of the involved accumbal AMPA and/or dopamine D_{1} receptors.

2.2. GABA

The Nacc contains two types of GABA receptors, namely GABA_{A} and GABA_{B} receptors (41). GABA_{A} receptors have been found to inhibit accumbal dopamine release, although GABA_{B} receptors are not devoid of a modulatory role in this respect (42).

There is a close relationship between GABAergic and dopaminergic systems in the Nacc in terms of regulating locomotor behavior. For example, GABA_{A}-receptor agonists reduce the hyperlocomotion induced by the dopamine D_{1}/D_{2}-receptor agonist apomorphine (43, 44), whereas the GABA_{A}-receptor antagonist picrotoxin enhances locomotor stimulant effects of dopamine-receptor agonists (43, 45). Recently, we have found that intra-shell injection of muscimol, but not bicuculline, inhibits the contraversive pivoting induced by a mixture of SKF 38393 and quinpirol into the Nacc shell (Fig. 1C) and that this effect of muscimol is antagonized by bicuculline (46), indicating that this inhibitory effect of muscimol on the shell-specific, dopaminergic pivoting is GABA_{A}-receptor specific. On the other hand, the shell-specific, dopaminergic pivoting is also inhibited by baclofen, but this effect of baclofen is not prevented by 2-hydroxysaclofen (46), suggesting that the dopamine D_{1}/D_{2} receptor–mediated pivoting is not mediated by GABA_{B} receptors. Since stimulation of GABA_{A} receptors inhibits the dopamine release in the Nacc (42), the effect of muscimol is elicited via inhibition of endogenous dopamine release, which causes insufficient stimulation of dopamine D_{1}/D_{2} receptors. Previously it has been shown that stimulation of D_{1} receptors (one of the D_{2}-like receptors) reduces GABA_{A}-receptor current through a phospho-dependent endocytosis mechanism in the Nacc (47). If the reduction of GABA_{A}-receptor current induced by the stimulation of D_{1} receptors contributes to eliciting the shell-specific, dopaminergic pivoting, muscimol might strengthen the GABA_{A}-receptor current and inhibit the shell-specific, dopaminergic pivoting.

In conclusion, GABA_{A}, but not GABA_{B}, receptors in the Nacc shell exert an inhibitory control upon the shell-specific, dopaminergic pivoting (46).

2.3. Acetylcholine

As stated in the Introduction, unilateral activation of acetylcholine receptors in the Nacc shell predominantly elicits contraversive circling, whereas unilateral activation of dopamine D_{1}/D_{2} receptors in the Nacc shell predominantly elicits contraversive pivoting (15, 16). Thus, these results have indicated that both acetylcholine and dopamine receptors in the Nacc play a crucial role in eliciting locomotor activity, but that there are subtle differences.

The available literature reveals that there is an interaction between cholinergic and dopaminergic systems in the Nacc. For instance, stimulation of dopamine D_{1} receptors has been found to increase acetylcholine release in the Nacc, whereas stimulation of dopamine D_{2} receptors has been found to inhibit acetylcholine release in the Nacc (48, 49). These data suggest that dopamine D_{1} receptors exert an excitatory control on the cholinergic neurons in contrast to dopamine D_{2} receptors that exert an inhibitory control on these neurons. On the other hand, a muscarinic acetylcholine–receptor antagonist has been found to increase dopamine release in the Nacc, whereas a muscarinic acetylcholine–receptor agonist has been found to inhibit the increase of dopamine release induced by amphetamine (50) or by electric stimulation (51), suggesting that muscarinic acetylcholine receptors exert an inhibitory control on the dopaminergic neurons in the Nacc. Moreover, a nicotinic acetylcholine–receptor agonist has been found to increase dopamine release in the Nacc (52), suggesting that nicotinic acetylcholine receptors exert an excitatory control on the dopaminergic neurons.

In line with the above-mentioned neurochemical findings, it has been found that the nicotinic acetylcholine–receptor antagonist mecamylamine significantly suppresses the contraversive pivoting induced by the mixture of SKF 38393 and quinpirol into the Nacc shell (Fig. 1D) (29), suggesting that accumbal, nicotinic acetylcholine receptors indeed exert an excitatory control on shell-specific, dopaminergic-dependent behavior as suggested by the above-mentioned neurochemical studies. Since nicotinic acetylcholine receptors are both presynaptically and postsynaptically localized in the Nacc (53), it cannot be excluded that the effect of mecamylamine is just mediated via an enhanced dopamine release. Recently, nicotinic acetylcholine receptors in the Nacc shell have been reported to form complexes with presynaptic dopamine D_{2} receptors; stimulation of these nicotinic
receptors has been found to increase dopamine level (54). In contrast, postsynaptic, nicotinic acetylcholine receptors are known to facilitate the GABA-mediated inhibition of the output neurons from the Nacc (53). There is evidence that the contraversive pivoting induced by the stimulation of dopamine D₁/D₂ receptors in the Nacc shell is funneled via GABAergic neurons innervating the SNc (15, 18, 21) and that GABAergic neurons from the Nacc to the SNc are inhibited by the stimulation of dopamine D₁/D₂ receptors in the Nacc shell (15). On the basis of these data, it has been suggested that the mecamylamine’s inhibitory effects on dopaminergic function are at least partly induced by disinhibition of the GABAergic output neurons from the Nacc shell (53, 55).

The muscarinic acetylcholine–receptor antagonist methylscopolamine significantly increases the contraversive pivoting induced by a mixture of SKF 38393 and quinpirole injected into the Nacc shell (Fig. 2A) (55), suggesting that the muscarinic acetylcholine receptors indeed exert an inhibitory control on the shell-specific, dopamine-dependent behavior as suggested by the above-mentioned neurochemical studies. Given the findings that a muscarinic acetylcholine–receptor antagonist increases dopamine release in the Nacc (50) and muscarinic acetylcholine receptors inhibit dopamine D₁-receptor signaling in Nacc (56), it has been hypothesized that methylscopolamine potentiates the dopaminergic pivoting by 1) a methylscopolamine-mediated enhancement of dopamine release in the Nacc shell, and by 2) a methylscopolamine-mediated disinhibition of dopamine D₁-receptor signaling in the Nacc shell (50, 55, 56).

In contrast to the cholinergic influence on the shell-specific, dopamine-dependent behavior, dopamine D₁/D₂ receptors appear to exert no influence on accumbal, acetylcholine-dependent behavior. Thus, it has been found that inhibition of dopamine D₁ and/or D₂ receptors does not affect the contraversive circling elicited by unilateral administration of the acetylcholine-receptor agonist carbachol into the Nacc shell (55). To what extent these data really indicate that there is no influence of dopamine receptors on the function mediated by cholinergic receptors remains open for discussion because the above-mentioned neurochemical studies have revealed that dopamine D₁ and D₂ receptors exert an excitatory and inhibitory control on the cholinergic neurons, respectively.

The available information has led to the conclusion that stimulation of nicotinic acetylcholine receptors in the Nacc shell is required for the shell-specific, dopamine-dependent behavior and that, in contrast, muscarinic acetylcholine receptors in the Nacc shell inhibit the production of the shell-specific, dopamine-dependent behavior (55).

2.4. Noradrenaline

The Nacc shell receives noradrenergic projections mainly from the nucleus tractus solitaries and the locus coeruleus (57). Previous studies have revealed that noradrenaline can functionally influence dopamine in the Nacc (58; for review: 59, 60). For example, stimulation of α-adrenoceptors has been found to decrease dopamine release in the Nacc, whereas stimulation of
β-adrenoceptors has been found to increase dopamine release in the Nacc (58, 61). Thus, these results suggest that α- and β-adrenoceptors exert an inhibitory and an excitatory control on dopamine release in the Nacc, respectively.

To determine the functional interaction between adrenergic and dopaminergic receptors in the Nacc shell, we have analyzed the role of α- and β-adrenoceptors in the Nacc shell in rat turning behavior. The local administration of neither α- nor β-adrenoceptor agonists and antagonists elicits turning behavior (62). As described above, although a β-adrenoceptor agonist increases dopamine release in the Nacc (58, 61), it cannot elicit turning behavior. Another possibility is the localization of receptors in the Nacc shell. We have already reported that there are at least two distinct pathways involved in the production of pivoting, namely the shell-ventral pallidum pathway that mediates locomotor activity and the accumbens–nigra–striatum pathway that mediates asymmetry (15, 17, 21). If other neurotransmitters affect just one dopaminergic pathway, they cannot elicit turning behavior.

Unilateral injection of the α-adrenoceptor agonist phenylephrine into the Nacc shell dose-dependently inhibited contraversive pivoting induced by a mixture of SKF 38393 and quinpirole into the Nacc shell (Fig. 1E) (62). This effect of phenylephrine was antagonized by phentolamine, which alone did not affect the dopaminergic pivoting. Therefore, it can be concluded that the inhibitory effect of phenylephrine on the dopaminergic pivoting is α-adrenoceptor-specific within the Nacc shell. The fact that α-adrenoceptors inhibit dopaminergic pivoting might be explained by presynaptic and/or postsynaptic mechanisms. As mentioned above, stimulation of α-adrenoceptors inhibits dopamine release in the Nacc (58, 60). This outcome implies that stimulation of accumbal dopamine D_{1}/D_{2} receptors by means of SKF 38393 and quinpirole elicits pivoting only when the baseline tonus at one or both subtypes of these dopamine receptors is already high. Since stimulation of dopamine D_{1} receptors by means of endogenous dopamine has been found to be necessary for the display of behavior elicited by stimulation of dopamine D_{2} receptors (63), it is thought that the baseline tonus is high, especially at the level of the dopamine D_{1} receptors. Accordingly, it is attractive to postulate that accumbal α-adrenoceptors control at least accumbal dopamine D_{1} receptors.

We have shown that the β-adrenoceptor agonist isoprenaline injected into the Nacc shell dose-dependently potentiated the contraversive pivoting induced by a mixture of SKF 38393 and quinpirole injected into the Nacc shell (Fig. 2B) (62); the effect of isoprenaline was antagonized by a dose of propranolol that per se had no effect on this pivoting, indicating that the potentiating effect of isoprenaline is β-adrenoceptor-specific (62). These data agree with the findings from neurochemical studies showing that stimulation of β-adrenoceptors increases dopamine release in the Nacc shell (62). All these data indicate that α-adrenoceptors in the Nacc shell exert an inhibitory effect on the shell-specific, dopaminergic pivoting in contrast to β-adrenoceptors in the Nacc shell, which exert a stimulatory effect on shell-specific dopaminergic pivoting (for references, see above).

2.5. Serotonin

Serotonin (5-HT) receptors are widely distributed in the brain (64). There are many reports indicating that the serotonergic system modulates dopamine function in the brain. However, most reports focused on the interaction between 5-HT and dopamine in the VTA, since serotonin neurons project from the dorsal and medial raphe nuclei to the VTA (65). In fact, injection of 5-HT into the VTA increases dopamine level in the Nacc (66). The interaction between 5-HT and dopamine in the Nacc has also been reported. The 5-HT_{1B}-receptor agonist increases dopamine level in the Nacc (67). Moreover, 5-HT_{2C}-receptor antagonists inhibit cocaine-induced dopamine release in the Nacc (68). In the behavioral studies, the injection of 5-HT_{3}-receptor agonist potentiates cocaine-induced behavior (69). More specifically, injection of 5-HT_{1B}-receptor agonist and antagonist into the Nacc shell potentiates and inhibits cocaine-induced locomotor activity, respectively, whereas the same drug injected into the Nacc core is without effect (70). Since the reports examining the role of the serotonergic system in the Nacc shell and core are limited and there are many subtypes of 5-HT receptors, further studies are needed to clarify the role of the serotonergic system in modulating accumbal dopamine functions.

2.6. Opioid

Opioid receptors (i.e., μ-, δ-, and κ-opioid receptors) have been reported to regulate mesolimbic dopaminergic neuronal activities. For example, activation of μ-opioid receptors by intra-cerebral administration of the agonists fentanyl and [d-Ala^{2},N-Me-Phe^{4},Gly^{2}-ol]-enkephalin (DAMGO) (VTA: 71, Nacc: 72) and δ-opioid receptors by means of the agonists deltorphin II and [d-Pen^{25}]-enkephalin (DPDPE) given into the Nacc (72, 73) enhances extracellular dopamine concentration in the Nacc.
whereas activation of \(\kappa\)-opioid receptors by means of the agonist U69593 given into the Nacc decreases dopamine concentration in the Nacc (74). The involved receptors are thought to be located in the VTA (for \(\mu\)-opioid receptors) and the Nacc (for \(\delta\)- and \(\kappa\)-opioid receptors).

Stimulation of \(\mu\)-opioid receptors in the VTA has been found to increase locomotor activity (75, 76). This effect is considered to be dopamine-dependent because it does not occur in 6-hydroxydopamine (6-OHDA)-lesioned animals (76). In contrast, hyperlocomotion induced by \(\mu\)-opioid receptor stimulation in the Nacc is unaffected by dopamine depletion (75, 77). A similar hyperlocomotion induced by \(\delta\)-opioid receptor stimulation in the Nacc is also unaffected by dopamine depletion (73, 77). Therefore, the enhanced locomotor activity induced by injections of \(\mu\)- and \(\delta\)-opioid receptor agonists into the Nacc is thought to be dopamine-independent. However, because 6-OHDA-lesioned animals were used in the latter studies, compensatory changes in the Nacc may have affected the results. This probably explains why these behavioral results are contradictory to the results of the above-mentioned neurochemical studies.

We have examined the role of opioid receptors in the Nacc shell in eliciting dopamine-dependent behavior. Unilateral injections of DAMGO and deltorphin II, but not DPDPE, into the Nacc shell significantly elicited contraversive pivoting (78). The pivoting induced by DAMGO and deltorphin II was receptor-specific because each behavioral response was significantly inhibited by the \(\mu\)-opioid receptor antagonist \(\delta\)-Phe-Cys-Tyr-d-Trp-Orn-Thr-Phe-Thr-NH\(_2\) (CTOP) and the \(\delta\)-opioid receptor antagonist nalttriben (NTB), respectively (78). The phenotype of this contraversive pivoting was similar to that elicited by unilateral injection of a mixture of SKF 38393 and quinpirole into the Nacc shell (see also 15, 16, 21). In fact, the contraversive pivoting elicited by stimulation of \(\mu\)- or \(\delta\)-opioid receptors in the Nacc shell was significantly inhibited by \(\text{cis}-(Z)\)-flupenthixol injected into the Nacc shell (78). These results allow the conclusion that the \(\mu\)- and \(\delta\)-opioid receptor-mediated effects require an intact dopaminergic system. This fits in with our earlier published data that local applications of these opioid receptor agonists (i.e., DAMGO and deltorphin II) enhance extracellular levels of dopamine in the Nacc (72). Thus, it is likely that both \(\mu\)- and \(\delta\)-opioid receptors are presynaptically localized on dopaminergic neurons that mediate the dopaminergic pivoting.

Despite the fact that stimulation of \(\delta\)-opioid receptors, like stimulation of \(\mu\)- and \(\delta\)-opioid receptors, enhances the release of accumbal dopamine (72), such stimulation did not elicit pivoting (78). A possible explanation for this finding is that the \(\delta\)-opioid receptors, in contrast to the \(\mu\)- and \(\delta\)-opioid receptors, are localized on dopaminergic terminals that are not involved in the production of pivoting. Indeed, there are at least two distinct neuronal pathways involved in the production of pivoting, namely the shell–ventral pallidum pathway that mediates locomotor activity and the accumbens–nigra–striatum pathway that mediates asymmetry (17; see also 16, 21). In view of these considerations, it has been hypothesized that a) \(\mu\)- and \(\delta\)-opioid receptors are presynaptically localized on dopaminergic neurons that impinge on both the shell–ventral pallidum pathway and the accumbens–nigra–striatum pathway, and that b) \(\delta\)-opioid receptors are at best presynaptically localized on dopaminergic neurons that impinge just on the accumbens–nigra–striatum pathway (72, 73, 78). An alternative explanation for the ineffectiveness of the \(\delta\)-opioid receptor agonist might be that the DPDPE-induced increase of extracellular dopamine is due not to stimulation of \(\delta\)-opioid receptors, but to stimulation of opioid-independent mechanisms.

It has been found that contraversive pivoting induced by a mixture of SKF 38393 and quinpirole into the Nacc shell is also inhibited by NTB (Fig. 1F), but not by CTOP or the \(\delta\)-opioid receptor antagonist \((E)\)-7-benzylidenenaltrexone (BNTX) (78). These results therefore suggest that \(\delta\)-, but not \(\mu\)- and \(\delta\)-, opioid receptors interact with postsynaptically localized dopamine D\(_1/D_2\)-receptor mechanisms involved in the production of pivoting.

These results demonstrate that unilateral stimulations of \(\mu\)- or \(\delta\)-opioid receptors, but not \(\delta\)-opioid receptors, in the Nacc shell elicit contraversive pivoting that requires intact dopamine D\(_1/D_2\)-receptor mechanisms in the Nacc shell. Moreover, it has been shown that the shell-specific, dopaminergic pivoting is modulated by \(\delta\)-, but not \(\mu\)- and \(\delta\)-, opioid receptors.

2.7. Orexin

Orexins (orexin A and B) are peptides, which were originally isolated from rat hypothalamus (79). Because the hypothalamus is the regulatory center for autonomic and endocrine homeostatic systems, orexins are thought to regulate such systems including feeding behavior, arousal activity, and arterial pressure (79 – 81). Orexin neurons and orexin receptors are not only present in the hypothalamus, but also extensively distributed across various brain areas (82, 83). This may imply that these peptides play an important role in several physiological functions.

Previously, it has been reported that orexin neurons originating in the lateral hypothalamus impinge upon dopaminergic cells in the VTA (84 – 86). Orexins injected into the VTA activate dopaminergic neurons (86). These results indicate that stimulation of orexin receptors in the VTA activates dopamine neurons and, accordingly,
increases dopamine release in the Nacc (86), and, subsequently, increases locomotor activity.

Since the Nacc has been found to contain mRNA for both orexin 1 receptors and orexin 2 receptors (83), we examined the role of orexin receptors in dopamine-dependent behavior. Orexin A injected into the Nacc shell significantly potentiated the contraversive pivoting induced by a mixture of SKF 38393 and quinpirole injected unilaterally into the Nacc shell (Fig. 2C) (87). The potentiating effect of orexin A was not antagonized by the orexin 1-receptor antagonist SB 334867, which alone did not significantly modify the contraversive pivoting induced by the mixture of SKF 38393 and quinpirole injected unilaterally into the Nacc shell (87). Our result indicates that the effect of orexin A was not mediated via orexin 1 receptors in the Nacc shell. Since orexin A is equipotent at orexin 1 and 2 receptors, we have examined the role of orexin 2 receptors in dopaminergic pivoting. The orexin 2 receptor–selective agonist orexin B injected into the Nacc shell significantly potentiated the contraversive pivoting induced by the mixture of SKF 38393 and quinpirole injected unilaterally into the Nacc shell (Fig. 2D) (87). This result shows that orexin 2 receptors play an important, modifying role in eliciting the shell-specific, dopaminergic pivoting. This conclusion is supported by the recent report that orexin B and dopamine synergistically increases the firing rate of neurons in the Nacc shell (88).

Previous reports have indicated that the cell bodies of dopaminergic neurons in the VTA are innervated by orexin neurons originating in the lateral hypothalamus and that stimulation of orexin receptors in the VTA activates dopamine neurons (84 – 86). Since the injection of orexin A into the VTA is reported to be more effective in eliciting hyperlocomotion than that of orexin B (85, 86), it has been suggested that orexin 1 receptors, but not orexin 2 receptors, in the VTA stimulate dopaminergic neurons. Our results demonstrate that orexin 2 receptors in the Nacc shell, which is the terminal area of dopamine neurons originating in the VTA, also modulate the function mediated by accumbal dopamine. These data are in line with the previously reported finding that the expression of orexin 2-receptor mRNA in the Nacc is greater than that of orexin 1-receptor mRNA in the Nacc (83). Thus, different subtypes of orexin receptors, that is, orexin 1 and 2 receptors, modulate dopaminergic function in the VTA and the Nacc, respectively.

2.8. Somatostatin

Somatostatin is a tetradecapeptide that was originally isolated from mammalian hypothalamus and characterized as a potent physiological inhibitor of growth hormone secretion from the anterior pituitary (89). Somatostatin and its receptors are not only present in the hypothalamus, but also widely distributed across the central nervous system (90, 91). Since the striatum and Nacc are reported to contain both somatostatin and its receptors (90, 92), it is possible that somatostatin regulates dopaminergic function in these brain areas.

Many neurochemical and behavioral studies on the functional role of somatostatin in the striatum have been reported. In neurochemical studies, systemic or intra-striatal injection of somatostatin or a somatostatin-receptor agonist increases dopamine release in the striatum (93). These results indicate that somatostatin positively regulates dopamine release in the striatum. Conversely, dopamine also regulates somatostatin level in the striatum (94, 95). For example, dopamine-receptor antagonists such as haloperidol reduce somatostatin-like immunoreactivity in the striatum (94). Moreover, dopamine D1- and D2-receptor agonists potentiate the effects of somatostatin on somatostatin-receptor binding, inhibition of adenyl cyclase activity, and accumulation of inositol 1,4,5-trisphosphate (95). In behavioral studies, somatostatin in the striatum has also been found to play a regulatory role in dopamine-dependent behavior. Intra-striatal injection of cysteamine, which selectively reduces somatostatin levels, blocks apomorphine-induced stereotypy (96). These neurochemical and behavioral findings show that somatostatin in the striatum plays an important role in dopaminergic functions.

In contrast to the striatum, the role of somatostatin in the Nacc has received less attention. Neurochemical studies have indicated that the perfusion of somatostatin into the Nacc increases dopamine release in the same area (97). To determine the function of accumbal somatostatin on dopamine-dependent behavior, we examined the role of somatostatin on dopamine-dependent behavior. Somatostatin significantly potentiated the contraversive pivoting induced by the mixture of SKF 38393 and quinpirole unilaterally injected into the Nacc shell (Fig. 2E) (98). This potentiating effect of somatostatin was significantly antagonized by the somatostatin-receptor antagonist cyclosomatostatin, which alone did not significantly modify the contraversive pivoting induced by the mixture of SKF 38393 and quinpirole injected unilaterally into the Nacc shell (99). Somatostatin has been reported to increase dopamine release in the Nacc (97). Moreover, in the striatum, somatostatin increases dopamine release via the glutamatergic system, especially via AMPA and NMDA receptors (93). We have shown that the shell-specific, dopaminergic pivoting is mediated by both AMPA and NMDA receptors in the same area (see above and ref. 35). Therefore, one can speculate that somatostatin increases dopamine release via the glutamatergic system, including AMPA and NMDA receptors,
in the Nacc shell. Another possibility is that somatostatin increases dopamine release caused by inhibiting GABA release, since somatostatin has been found to regulate GABA release presynaptically in the striatum (99). Thus, the potentiating effect of somatostatin on the contraversive pivoting induced by dopamine D_{1}/D_{2}-receptor stimulation in the Nacc shell may be due to additional stimulation of dopamine D_{1} and D_{2} receptors caused by increased dopamine. It is also possible that somatostatin regulates dopamine-receptor functions postsynaptically in the potentiating effect of somatostatin because dopamine and somatostatin-receptor activation may work in a co-operative manner on postsynaptic sites, possibly via second messenger pathways or common targets (100).

3. Conclusion

The present study focused on the modulation of the shell-specific, dopaminergic pivoting by glutamate, GABA, noradrenaline, acetylcholine, opioid, orexin, and somatostatin in the Nacc shell: these modulations vary across the different neurotransmitters, neuropeptides, and their corresponding receptors (Table 1). It has been shown that the dopaminergic pivoting is funneled from the Nacc shell via the SNc, the ventrolateral striatum, and the substantia nigra pars reticulata towards the pedunculopontine tegmental nucleus (15, 18, 21). Thus, this pathway is likely to be controlled by these neurotransmitters in the Nacc shell, implying that all functions mediated via this pathway are sensitive to modulation by compounds that selectively interact with one or more of these neuroactive compounds. As mentioned above, the shell-specific, dopaminergic pivoting is just used as a tool to trace the nature of the interactions of dopamine with other neuroactive compounds and vice versa as well as a tool to trace the pathways involved in the transmission of accumbal dopamine-dependent information across the brain: it has no face validity with any of the known functions of accumbal dopamine. Given the well-known therapeutic effects of drugs that enhance accumbal dopamine, in patients suffering from depression, ADHD or Parkinson’s disease, agents that directly or indirectly stimulate the activity at the level of the receptors shown in Table 1, are predicted to have a therapeutic efficacy as well. On the other hand, it is predicted that agents that directly or indirectly inhibit the activity at the level of the receptors shown in Table 1, are therapeutically effective in patients suffering from schizophrenia, because drugs that reduce the accumbal dopaminergic activity in such patients are therapeutically effective. The putative advantage of using drugs that indirectly alter the activity at the level of the accumbal dopamine receptors is that

<table>
<thead>
<tr>
<th>Table 1. Summary of the role of each neuroactive compound on accumbens-specific behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Glutamate receptors</td>
</tr>
<tr>
<td>NMDA*</td>
</tr>
<tr>
<td>AMPA*</td>
</tr>
<tr>
<td>GABA receptors</td>
</tr>
<tr>
<td>GABAB</td>
</tr>
<tr>
<td>Acetylcholine receptors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adrenaline receptors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serotonin receptors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Opioid receptors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Orexin receptors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Somatostatin receptors</td>
</tr>
</tbody>
</table>

*Stimulation indirectly affects accumbal dopamine-dependent pivoting. Up arrow: increases behavior, down arrow: decreases behavior.
such drugs do not alter the sensitivity of the involved dopamine receptors and, therefore, result in less unwanted side-effects than drugs that directly affect the dopamine receptors.

In conclusion, since both accumbal dopamine, as well as the above-mentioned pathway, play a crucial role in a great variety of neurological and psychiatric diseases such as depression, drug addiction, ADHD, schizophrenia, and Parkinson’s disease, it is suggested that drugs that selectively interfere with one or more of these non-dopaminergic compounds, are promising candidates for treating these diseases.

Acknowledgments

This study was partly supported by a grant for promotion of multidisciplinary research projects from the Ministry of Education, Culture, Sports, Science, and Technology (N.K., A.R.C.); the Promotion and Mutual Aid Corporation for Private Schools in Japan (H.I., N.K.); and Grant-in-Aid for Scientific Research (23792133 to H.I.) from Japan Society for Promotion of Science.

References

16 Koshikawa N, Kitamura M, Kobayashi M, Cools AR. Contralateral turning elicited by unilateral stimulation of dopamine D2 and D3 receptors in the nucleus accumbens of rats is due to stimulation of these receptors in the shell, but not the core, of this nucleus. Psychopharmacology. 1996;126:185–190.
28 Sesack SR, Pickel VM. In the rat medial nucleus accumbens,
hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. Brain Res. 1990; 527:266–279.

29 Sessack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol. 1992;320:145–160.

30 Young AB, Fagg GE. Excitatory amino acid receptors in the brain: membrane binding and receptor autoradiographic approaches. 1990;11:126–133.

31 Imperato A, Honoré T, Jensen LH. Dopamine release in the nucleus caudatus and in the nucleus accumbens is under glutamatergic control through non-NMDA receptors: a study in free-moving rats. Brain Res. 1990;530:223–228.


38 Pulvirenti L, Swerdlow NR, Koob GF. Nucleus accumbens NMDA antagonist decreases locomotor activity induced by cocaine, heroin or accumbens dopamine, but not caffeine. Pharmacol Biochem Behav. 1991;40:841–845.


75 Kalivas PW, Widerlöv E, Stanley D, Breese G, Prange AJ Jr. Enkephalin action on the mesolimbic system: a dopamine-depen-


