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ACCUMBAL CORE: ESSENTIAL LINK IN FEED-FORWARD SPIRALING STRIATO-NIGRO-STRIATAL *IN SERIES* CONNECTED LOOP

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Abstract—The goal of the present study was to establish the behavioral role of the nucleus accumbens (Nacc) core in the feed-forward spiraling striato-nigro-striatal circuitry that transmits information from the Nacc shell toward the dorsal subregion of the neostriatum (DS) in freely moving rats. Unilateral injection of μ-opioid receptor agonist [D-Ala^2, *N*-Me-Phe^4,Gly^5-ol]-enkephalin (DAMGO; 1 and 2 μg), but not the δ_1-opioid receptor agonist [D-Pen^{2,5}]-enkephalin (4 μg) or the δ_2-opioid receptor agonist [D-Ala^2,Glu^4]-deltorphin (2 μg), into the ventral tegmental area (VTA) produced contraversive circling in a dose-dependent manner. The effect of DAMGO was μ-opioid receptor-specific, because the μ-opioid receptor antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH_2 (0.1 and 1 μg), which alone did not elicit any turning behavior, dose-dependently inhibited the effect of DAMGO. Injection of the dopamine D_1/D_2 receptor antagonist cis-(Z)-flupentixol (1 and 10 μg) into the Nacc shell ipsilaterally to the VTA significantly inhibited DAMGO (2 μg)-induced circling. Similar injections of cis-(Z)-flupentixol into the Nacc core inhibited DAMGO-induced circling, but, in addition, replaced circling by pivoting, namely turning behavior during which the rat rotates around its disfunctioning hindlimb. The present findings show that unilateral stimulation of μ-, but not δ-, opioid receptors in the VTA elicits contraversive circling that requires a relatively hyperdopaminergic activity in both the shell and the core of the Nacc at the opioid-stimulated side of the brain. The Nacc core plays an essential role in the transmission of information directing the display of pivoting that is elicited by an increased dopaminergic activity in the Nacc shell. It is concluded that the Nacc core is an essential link in the feed-forward spiraling striato-nigro-striatal circuitry that transmits information from the Nacc shell toward the DS in freely moving rats.

Key words: μ-opioid receptors, ventral tegmental area, turning pattern, dopamine D_1/D_2 receptors, nucleus accumbens.

INTRODUCTION

The nucleus accumbens (Nacc) is a crucial brain structure that connects the limbic brain with the motor brain: it transforms emotion into motion (Mogenson et al., 1980; Cools, 1988). It plays a key role in a variety of brain diseases varying from schizophrenia, attention deficit hyperactivity disorder to addiction. Today, these diseases can be treated only symptomatically, but not cured. The role of the Nacc in the pathophysiology and pharmacotherapy of the above-mentioned diseases is unknown. Extension of our present-day knowledge is required.

The Nacc is divided into at least two subregions, i.e. the Nacc shell and the Nacc core (Voorn et al., 1986; Heimer et al., 1991; Zahm and Brog, 1992; Brog et al., 1993; Meredith et al., 1993; Jongen-Rêlo et al., 1994). Both afferent and efferent projections (Voorn et al., 1986; Zahm and Heimer, 1990, 1993; Heimer et al., 1991; Deutch and Cameron, 1992; Zahm, 1992) and the dopaminergic neurotransmission inside the Nacc (Voorn et al., 1986; Bardo and Hammer, 1991; Zahm, 1991, 1992; Deutch and Cameron, 1992) differ between the Nacc shell and the Nacc core. To understand the pathophysiology of the above-mentioned diseases and to develop pharmacotherapies of these diseases, it is necessary to know the details of the circuitry to which the different parts of the Nacc belong.

Recently, we have shown in rats that the Nacc shell is directly or indirectly connected *in series* with the dorsal subregion of the neostriatum (DS; Ikeda et al., 2013), providing thereby evidence in favor of the so-called spiraling striato-nigro-striatal loop (Haber et al., 2000; Haber and Knutson, 2010). In fact, we have shown that stimulation of dopamine D_1 and D_2 receptors in the Nacc shell decreases dopamine release in the Nacc

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Abbreviations: ANOVA, analysis of variance; CTOP, D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH_2; DAMGO, [D-Ala^2,*N*-Me-Phe^4, Gly^5-ol]-enkephalin; deltorphin II, [D-Ala^2,Glu^4]-deltorphin; DPDPE, [D-Pen^{2,5}]-enkephalin; DS, dorsal subregion of the neostriatum; Nacc, nucleus accumbens; VLS, ventrolateral subregion of the neostriatum; VTA, ventral tegmental area.

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core, that in turn increases dopamine release in the ventrolateral subregion of the neostriatum (VLS), followed by a decrease of dopamine release in the DS (Kitamura et al., 1999; Ikeda et al., 2013).

During the past years it has become evident that the behaviors ''pivoting'' and ''circling'' are useful tools for tracing how information from the Nacc shell is transmitted toward other brain areas (Kitamura et al., 2001; Ikeda et al., 2004, 2009, 2012). Pivoting is marked by abnormal hindlimb backward stepping, tight head-to-tail turns of small diameter (< 20 cm) and spinning around one hindlimb, whereas circling is marked by normal hindlimb stepping, normal forelimb stepping and turns with large diameter (> 30 cm). Contraversive pivoting is specific for unilateral, simultaneous stimulation of the dopamine D_1 and D_2 receptors in the Nacc shell (Koshikawa et al., 1996; Kitamura et al., 1999; Ikeda et al., 2004, 2009, 2012; Moribe et al., 2005), whereas contraversive circling is specific for unilateral stimulation of cholinergic receptors in the Nacc shell (Koshikawa, 1994; Koshikawa et al., 1996; Ikeda et al., 2012): the turning is contraversive, when directed away from the side of stimulation (Koshikawa, 1994; Koshikawa et al., 1996; Kitamura et al., 1999; Ikeda et al., 2012).

Because stimulation of dopamine D_1 and D_2 receptors in the Nacc shell that elicits contraversive pivoting is found to activate the spiraling striato-nigro-striatal, feed-forward loop (see above), one might expect that the inhibition of the dopaminergic activity in the Nacc core also results in contraversive pivoting. However, detailed knowledge about the behavioral role of the Nacc core in this feed-forward loop is not yet available. Still, it is known that dexamphetamine that increases dopamine release in both the Nacc shell and, to a lesser degree, the Nacc core (Pontieri et al., 1995) elicits contraversive circling, but not contraversive pivoting (Pycock, 1980). These findings become understandable if one realizes that the dexamphetamine-induced increase of dopamine efflux in the Nacc core can counteract the decrease of dopamine efflux in this part of the brain as a consequence of the dexamphetamine-induced increase of dopamine efflux in the Nacc shell. According to this view, inhibition of the dopaminergic activity in the core results in pivoting, whereas activation of this dopaminergic activity suppresses pivoting and results in circling because the feed-forward striato-nigro-striatal loop ultimately enhances the dopaminergic activity in the DS and, consequently, does not result in a disfunctioning hindlimb (see Ikeda et al., 2013).

Three types of experiments were performed. First, the behavioral effects of drugs that selectively interact with either the μ-opioid receptors [agonist DAMGO ([D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]-enkephalin); antagonist CTOP (D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Phe-Thr-NH_2)] or the δ-opioid receptors [δ_1-opioid receptor agonist DPDPE ([D-Pen^{2,5}]-enkephalin); δ_2-opioid receptor agonist deltorphin II ([D-Ala^2,Glu^4]-deltorphin)] were studied after their administration into the ventral tegmental area (VTA). There are two reasons to expect that especially stimulation of the μ-opioid receptors elicits behavior inherent to activation of the dopaminergic neurons that arise in the VTA (see also: Broekkamp et al., 1979; Latimer et al., 1987; Spanagel et al., 1992): (a) stimulation of μ-opioid receptors in the VTA is known to result in an increase of dopamine release in the Nacc (Leone et al., 1991; Devine et al., 1993), and (b) μ-opioid receptor stimulation in the VTA increases locomotor activity (Joyce and Iversen, 1979; Möhler et al., 1979; Stinus et al., 1980; Kalivas et al., 1983), namely a behavior that requires an increased dopaminergic activity in the Nacc (Pijnenburg and van Rossum, 1973). Because the VTA is known to contain both μ-opioid receptors, and, to a significantly lesser degree, δ-opioid receptors (Mansour et al., 1987), the effects of stimulation of μ-opioid receptors were compared with those of δ-opioid receptors, although no behavioral effects were expected in view of the fact that δ-opioid receptor stimulation in the VTA results only in a marginal release of dopamine in the Nacc (Longoni et al., 1991; Pentney and Gratton, 1991; Devine et al., 1993). Second, the effect of an inhibition of both the dopamine D_1 and the D_2 receptors in the Nacc shell on the effects of intra-VTA injected DAMGO was analyzed to establish the involvement of dopaminergic receptors in the Nacc shell. Finally, the effect of an inhibition of both the dopamine D_1 and the D_2 receptors in the Nacc shell on the effects of intra-VTA injected DAMGO was analyzed to establish the involvement of dopaminergic receptors in the Nacc core. The present study shows that the Nacc core is an essential link in the chain of events triggered by dopaminergic activation of the Nacc shell.

EXPERIMENTAL PROCEDURES

Animals and surgery

Male Wistar rats (Saitama Experimental Animals Supply Co. Ltd., Saitama, Japan) weighing 190–210 g at the time of the operation were housed in cages (27 × 45 × 20 cm) that were kept at constant room temperature (23 ± 2 °C) and relative humidity (55 ± 5%) under a 12-h light–dark cycle (lights on at 0700 h), with free access to food and water.

For stereotactic implantation of cannulae, the rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotactic apparatus (Narishige, Tokyo, Japan). A guide cannula (0.5 mm o.d., 0.3 mm i.d., 6 mm length) was placed into the VTA (A 3.7 mm, V 1.8 mm, L 0.6 mm from the interaural line), the Nacc shell (A 10.6 mm, V 2.5 mm, L 0.8 mm from the interaural line) or the Nacc core (A 10.6 mm, V 3.0 mm, L 1.5 mm from the interaural line), according to the atlas of Paxinos and Watson (1998). The cannulae were secured to the skull with stainless screws and dental acrylic cement. The cannulae were angled 20° (the VTA) and 21° (the Nacc shell and the Nacc core) from the midsagittal plane to avoid the ventricular system. Damage to the target site was minimized by implanting the tips of the guide cannulae 2.5 mm (the VTA), 1.9 mm (the Nacc shell) or 1.2 mm (the Nacc core) above the desired injection site. A wire stylet was placed in the guide cannula to prevent occlusion. The