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Autoregulation of dopamine synthesis in subregions of the rat nucleus accumbens

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Abstract

The discovery of a core–shell dichotomy within the nucleus accumbens has opened new lines of investigation into the neuronal basis of psychiatric disorders and drug dependence. In the present study, the autoregulation of dopamine synthesis in subdivisions of the rat nucleus accumbens was examined. We measured the accumulation of L-3,4-dihydroxyphenylalanine (DOPA) after the inhibition of aromatic L-amino acid decarboxylase with 3-hydroxylbenzylhydrazine (NSD-1015, 100 mg kg^{-1}) as an in vivo index of dopamine synthesis. The effect of the dopamine D_1/D_2 receptor agonist apomorphine (0, 20, 100, 500 μg kg^{-1}) and the dopamine D_2/D_3 receptor agonist quinpirole (0, 20, 100, 500 μg kg^{-1}) on dopamine synthesis was determined in the dorsolateral core, ventromedial shell, and rostral pole of the nucleus accumbens. DOPA accumulation was also measured in the frontal cortex, olfactory tubercle, and caudate nucleus of the same rats for comparative purposes. The results show that the three sectors of the nucleus accumbens had similar basal levels of DOPA. Both apomorphine and quinpirole produced a decrease in the dopamine synthesis rate in all brain regions examined. In general, the dopamine D_2/D_3 receptor agonist quinpirole produced a significantly greater decrease in DOPA accumulation than the dopamine D_1/D_2 receptor agonist apomorphine. Within the nucleus accumbens, we found no core–shell differences in the agonist-induced suppression of dopamine synthesis, but the rostral pole was less sensitive to the highest dose of both dopamine agonists. These results suggest that differences in dopamine function between the core and shell might not involve region-specific differences in the receptor-mediated autoregulation of dopamine neurotransmission. Moreover, the blunted effect of dopamine agonists in the rostral pole illustrates that this region of the accumbens is functionally distinct, possibly due to a lower dopamine receptor reserve when compared to the core and shell.

Keywords: Dopamine synthesis; L-DOPA (L-3,4-dihydroxyphenylalanine) accumulation; Nucleus accumbens; (Rat)

1. Introduction

Accumulating evidence indicates that the nucleus accumbens is a heterogenous structure that can be divided into at least three well-defined regions: (1) the dorsolateral core, which primarily connects to somatic motor output systems; (2) the ventromedial shell with its ventral caudomedial, dorsal caudomedial (septal pole or cone) and rostral parts, which is more intimately linked to viscero-endocrine effector systems; and (3) the rostral pole (Heimer et al., 1991, 1997; Voorn et al., 1989; Wright and Groenewegen, 1996; Zahm, 1999, 2000; Zahm and Brog, 1992). A further subdivision of the nucleus accumbens is based on the discovery of clusters of efferent neurons which receive rather specific sets of afferents that may be recruited differentially by goal-directed behaviors, stimulus–reward associations, and reinforcement induced by addictive drugs (Pennartz et al., 1994; Zahm, 2000). Finally, an additional level of the organization of the nucleus accumbens may be the existence of structural and functional gradients in its rostro-caudal axis (Caboche et al., 1993; Heidbreder and Feldon, 1998; Heidbreder et al., 1999; Mathieu et al., 1996; Ranaldi and Beninger, 1994; Rogard et al., 1993; Voorn and Docter, 1992).

Several morphometric (Tan et al., 1995), immunohistochemical (Zahm, 1992), in vivo electrochemical (David et

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al., 1998; Jones et al., 1996; Wieczorek and Kruk, 1995), and in vivo neurochemical (Hedou et al., 1999; Heidbreder and Feldon, 1998; Heidbreder et al., 1999; King et al., 1997; Pierce and Kalivas, 1995) studies of the dopamine systems in subterritories of the nucleus accumbens have demonstrated that higher concentrations of dopamine are observed in the core of the nucleus accumbens compared with its shell counterpart (but see Barrot et al., 1999, 2000). Furthermore, individual dopamine axons in the nucleus accumbens shell contain lower densities of both vesicular and plasmalemmal dopamine transporters compared with the nucleus accumbens core (Nirenberg et al., 1997).

An important aspect of dopamine neuronal function is the regulation of dopamine synthesis and release by dopamine D_2 autoreceptors (Wolf and Roth, 1990). Few studies have examined dopamine autoreceptor responsiveness in the nucleus accumbens core and shell. Deutch and Cameron (1992) compared the effects of various dopaminergic drugs in subregions of the nucleus accumbens. These investigators found that the dopamine D_2 receptor antagonist haloperidol stimulated dopamine utilization to a greater extent in the nucleus accumbens core when compared to the shell, but this effect was modest and only one dose of haloperidol was tested. Presumably the stimulatory effect of haloperidol on dopamine metabolism is due to blockade of dopamine autoreceptors in nerve terminals.

The purpose of the present study was to compare the dopamine receptor-mediated regulation of dopamine synthesis in subregions of the rat nucleus accumbens. We used the method of L-3,4-dihydroxyphenylalanine (DOPA) accumulation after decarboxylase inhibition as an in vivo index of tyrosine hydroxylase activity (Carlsson et al., 1972; Broadhurst and Briley, 1988). Specifically, the effect of the dopamine D_1/D_2 receptor agonist apomorphine and the dopamine D_2/D_3 receptor agonist quinpirole on dopamine synthesis was determined in the nucleus accumbens core and shell. The rostral pole of the nucleus accumbens was also examined because the core–shell dichotomy is reportedly less clear in this region (see Zahm and Brog, 1992). Finally, accumulation of DOPA was measured in the frontal cortex, olfactory tubercle, and caudate nucleus for comparative purposes.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, Wilmington, MA), weighing 250–300 g, were housed two per cage in standard vivarium conditions (lights on: 0700–1900 h) with free access to food and water. Animals were maintained in facilities fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and experiments were carried out in accordance with the Animal Care and Use Committee of the National Institute on Drug Abuse (NIDA), Intramural Research Program (IRP).

2.2. Drug treatments

Two separate groups of rats were used in these studies: one group ($N = 28$ rats) received the dopamine D_1/D_2 dopamine receptor agonist apomorphine whereas the other group ($N = 28$ rats) received the dopamine D_2/D3 dopamine receptor agonist quinpirole. Rats were brought into the testing room in their home cages. After a 2-h acclimation period, rats received single s.c. injections of either test drug (20, 100, and 500 $\mu g\ kg^{-1}$) or water vehicle. Fifteen minutes later, all rats received single i.p. injections of the decarboxylase inhibitor 3-hydroxylbenzylhydrazine (NSD-1015, 100 mg kg^{-1}). Thirty minutes after NSD-1015 (i.e., 45 min after test drug or vehicle), rats were sacrificed by decapitation. Brains were rapidly removed, immediately frozen on dry ice, and stored at -80°C. Experiments were conducted between 1100 and 1400 h.

2.3. Microdissection procedures

Frozen brains were mounted rostral side up onto microtome specimen holders and were placed into a cryostat chamber (Model 5030, Bright Instrument, Huntington, England) set at -8°C. Coronal sections (300 μm in thickness) were cut beginning at A3000 μm and ending at A1500 μm relative to bregma, as described by Palkovits and Brownstein (1988). Sections were mounted on glass slides, and discrete brain regions were microdissected using stainless steel needle tubing of 825 or 1625 μm inner diameter (i.d.) as summarized in Table 1. That portion of the nucleus accumbens anterior to the genu of the corpus callosum (i.e., anterior to A2400 μm relative to bregma) was designated as the rostral pole. The nucleus accumbens core and shell regions were dissected according to the method of Deutch and Cameron (1992). Briefly, the nucleus accumbens core was removed first using a dissecting needle of i.d. 825 μm; the anterior commissure served as the dorsolateral border for the core sample. The nucleus accumbens shell was subsequently removed by superimposing a dissecting needle of i.d. 1625 μm over the void left by the removal of the core sample. The frontal cortex, olfactory tubercle, and caudate nucleus were removed as previously described (Baumann et al., 1993).

2.4. High-pressure liquid chromatography (HPLC) assay procedures

Tissue punches from a given region were diluted in 100 μl of cold 0.1 N $HClO_4$ containing 100 μM Na_2EDTA and homogenized using a motor-driven pestle. Homogenates were centrifuged at 15,000 rpm for 15 min. The

Table 1
Microdissection of subregions of the nucleus accumbens and other forebrain regions

Brain region	Anterior coordinates (μM)[a]	Number of sections	Number of punches[b]	Punch diameter (μm)
Nucleus accumbens, rostral pole	A3000–2700	2	4	1625
Nucleus accumbens, core	A2400–1800	3	6	825
Nucleus accumbens, shell	A2400–1800	3	6	1625
Frontal cortex	A3000–2400	3	6	1625
Olfactory tubercle	A2400–2100	2	–	knife[c]
Caudate nucleus	A2400–2100	2	4	1625

[a]Coordinates refer to the rostral surface as per the maps of Palkovits and Brownstein (1998).
[b]All punches were removed bilaterally.
[c]Olfactory tubercle was removed using a microdissecting knife.

supernatants were assayed for the concentrations of DOPA, using HPLC separation followed by electrochemical detection (Baumann et al., 1993). Tissue pellets were resolubilized in 1.0 N NaOH and assayed for protein (Bradford, 1976). Aliquots (20 μl) of supernatant were injected onto a C-18 column that was coupled to an ESA Coulochem Model 5100A electrochemical detection system (Environmental Sciences Associates, Bedford, MA, USA). A recirculating mobile phase containing 50 mM sodium phosphate monobasic (final pH 2.75), 250 μM Na_2EDTA, 0.025% sodium octane sulfonic acid and 25% methanol was pumped at a flow rate of 0.7 ml min^{-1}. A WISP 710B automatic injector module (Waters Associates) was used to deliver all samples and standards onto the column. Chromatographic data were directly exported to a MAXIMA 820 software system (Waters Associates) for peak amplification, integration and analysis. Peak heights of unknowns were compared to the peak heights of DOPA. Complete

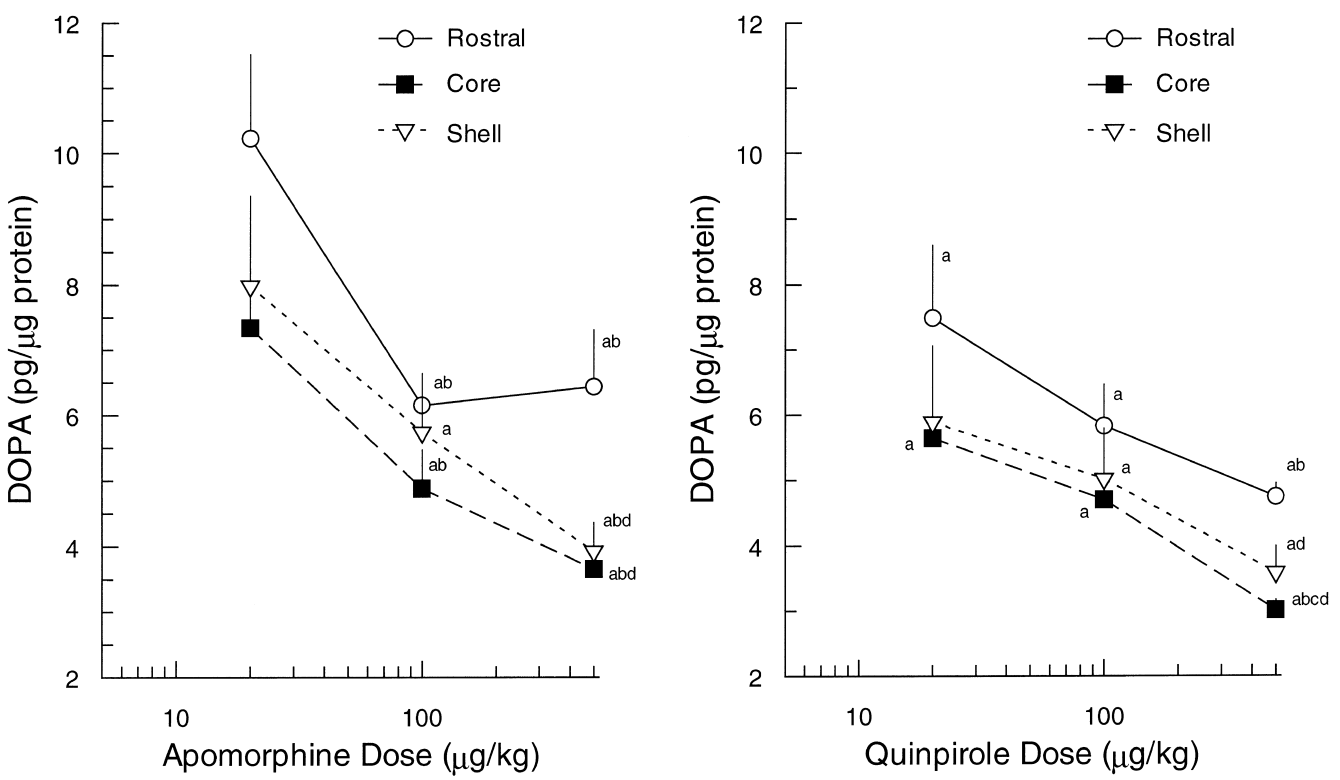

Fig. 1. Effects of apomorphine and quinpirole (20–500 μg kg^{-1}) on the hydroxylation rate of tyrosine as measured by the accumulation of L-3,4-dihydroxyphenylalanine (DOPA) in the dorsolateral core, ventromedial shell, and rostral pole of the nucleus accumbens. The concentrations of DOPA (pg μg^{-1} protein) following vehicle administration in the apomorphine group were as follows: nucleus accumbens rostral, 11.43 ± 0.95; nucleus accumbens core, 9.51 ± 1.4; nucleus accumbens shell, 10.01 ± 1.7. The concentrations of DOPA (pg μg^{-1} protein) following vehicle administration in the quinpirole group were as follows: nucleus accumbens rostral, 10.39 ± 0.58; nucleus accumbens core, 9.07 ± 1.4; nucleus accumbens shell, 9.37 ± 1.6. Data are represented as mean ± S.E.M. values for each dose of apomorphine or quinpirole. (a) vs. vehicle; (b) vs. 20 μg kg^{-1}; (c) vs. 100 μg kg^{-1}; (d) vs. nucleus accumbens rostral; significant at $P < 0.05$ according to unpaired and paired *t*-tests.

standard curves (10–500 pg) were run daily before each set of samples, and these standard curves were linear over a wide range of concentrations. The lower limit of detectability (3 × baseline noise level) was 2 pg DOPA. All data are expressed as pg of DOPA per μg of protein.

2.5. Data analysis

Basal levels of DOPA were analysed by using an analysis of variance (ANOVA) with a repeated measurements factors of brain region (nucleus accumbens rostral, nucleus accumbens core, nucleus accumbens shell, olfactory tubercle, caudate nucleus, and frontal cortex). The effects of apomorphine and quinpirole on DOPA accumulation were analysed by a $2 \times 4 \times 6$ ANOVA with main factors of dopamine agonist (apomorphine vs. quinpirole) and dose (0, 20, 100, and 500 μg kg^{-1}) and a repeated measurements factor of brain region (nucleus accumbens rostral, nucleus accumbens core, nucleus accumbens shell, olfactory tubercle, caudate nucleus, and frontal cortex). Separate $2 \times 4 \times 3$ ANOVAs with main factors of dopamine agonist (apomorphine vs. quinpirole) and dose (0, 20, 100, and 500 μg kg^{-1}) and a repeated measurements factor of either nucleus accumbens subregion (nucleus accumbens rostral, nucleus accumbens core, nucleus accumbens shell) or brain region (olfactory tubercle, caudate nucleus, and frontal cortex) were also applied to the data obtained from the three subterritories of the nucleus accumbens and three remaining brain regions examined in the present study. In the case of significant main effects, the differences between individual means were assessed with the post hoc Fisher's Protected test. Statistical significance was set at a probability level of 0.05 for all tests.

3. Results

3.1. Basal concentrations of DOPA

Basal concentrations of DOPA (pg μg^{-1} protein) were significantly different across brain regions. An overall ANOVA with a repeated measurements factors of brain region (nucleus accumbens rostral, nucleus accumbens core, nucleus accumbens shell, olfactory tubercle, caudate nucleus, and frontal cortex) yielded a significant effect of

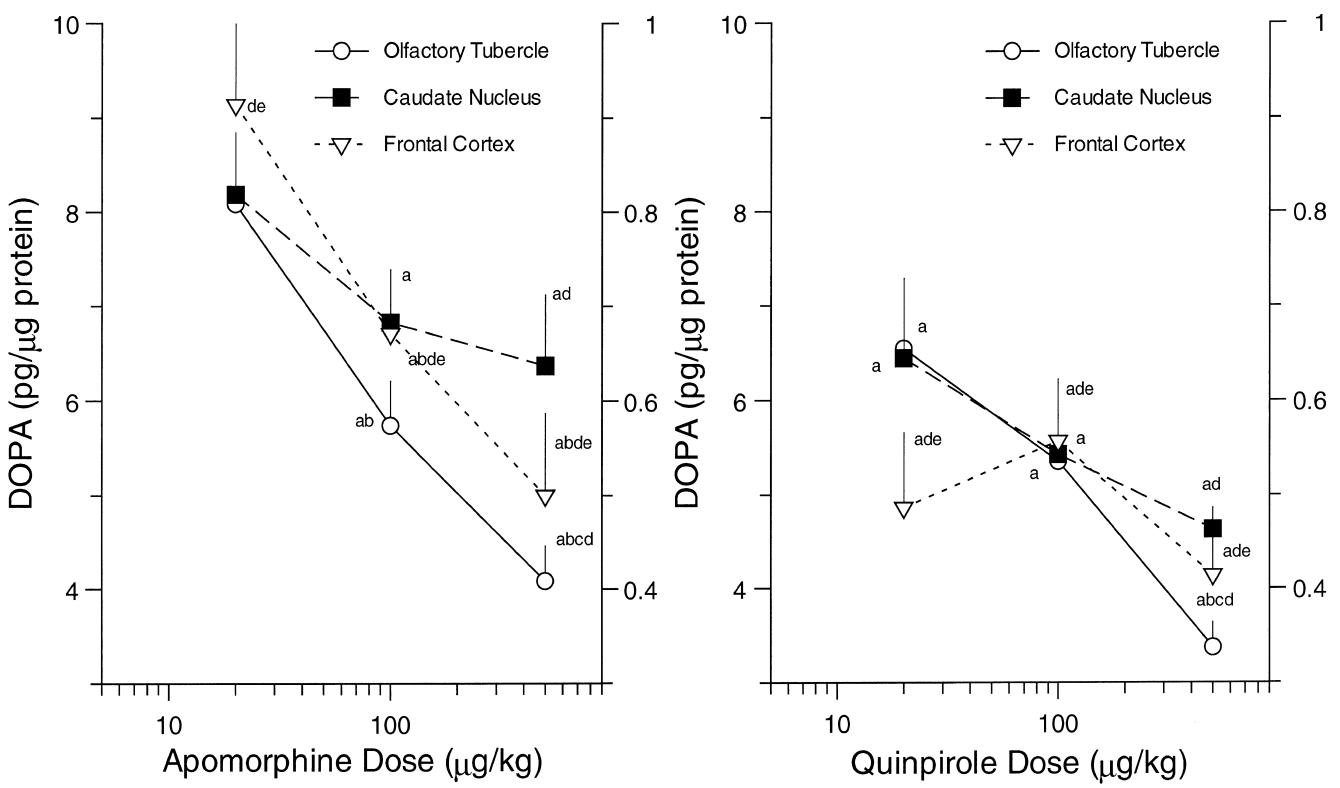

Fig. 2. Effects of apomorphine and quinpirole (20–500 μg kg^{-1}) on the hydroxylation rate of tyrosine as measured by the accumulation of L-3,4-dihydroxyphenylalanine (DOPA) in the olfactory tubercle and caudate nucleus (left ordinate) as well as frontal cortex (right ordinate). The concentrations of DOPA (pg μg^{-1} protein) following vehicle administration in the apomorphine group were as follows: olfactory tubercle, 10.33 ± 1.36; caudate nucleus, 10.24 ± 0.9; frontal cortex, 1.17 ± 0.12. The concentrations of DOPA (pg μg^{-1} protein) following vehicle administration in the quinpirole group were as follows: olfactory tubercle, 9.97 ± 1.15; caudate nucleus, 9.07 ± 0.69; frontal cortex, 0.94 ± 0.06. Data are represented as mean ± S.E.M. values for each dose of apomorphine or quinpirole. (a) vs. vehicle; (b) vs. 20 μg kg^{-1}; (c) vs. 100 μg kg^{-1}; (d) vs. olfactory tubercle; (e) vs. caudate nucleus; significant at $P < 0.05$ according to unpaired and paired *t*-tests.

brain region ($F(5,65) = 25.8$; $P < 0.0001$). Further analyses with the post hoc Fisher's Protected test confirmed that the three main compartments of the nucleus accumbens have similar basal levels of DOPA (nucleus accumbens rostral: 10.9 ± 0.56 pg μg^{-1}; nucleus accumbens core: 9.3 ± 0.95 pg μg^{-1}; nucleus accumbens shell: 9.7 ± 1.15 pg μg^{-1}). The frontal cortex had the lowest basal levels of DOPA (1.06 ± 0.07 pg μg^{-1}) when compared with the other brain regions, including the olfactory tubercle (10.16 ± 0.85 pg μg^{-1}), and caudate nucleus (9.67 ± 0.6 pg μg^{-1}).

3.2. DOPA accumulation in response to apomorphine and quinpirole

Both apomorphine and quinpirole produced a decrease in DOPA levels in all six brain regions dissected in the present study (Figs. 1 and 2). Quinpirole produced a significantly bigger decrease in DOPA accumulation compared with apomorphine. An overall ANOVA with main factors of dopamine agonist (apomorphine vs. quinpirole) and dose (0, 20, 100, and 500 $\mu g\ kg^{-1}$) and a repeated measurements factor of brain region (nucleus accumbens rostral, nucleus accumbens core, nucleus accumbens shell, olfactory tubercle, caudate nucleus, and frontal cortex) revealed significant effects of dopamine agonist ($F(1,48) = 7.9$; $P < 0.007$), dose ($F(3,48) = 38.3$; $P < 0.0001$) and brain region ($F(5,240) = 105.1$; $P < 0.0001$) as well as a significant brain region $\times$ dose interaction ($F(15,240) = 3.7$; $P < 0.0001$). A separate ANOVA applied to the data from subterritories of the nucleus accumbens yielded significant effects of dopamine agonist ($F(1,48) = 5.1$; $P < 0.05$), dose ($F(3,48) = 29.3$; $P < 0.0001$) and nucleus accumbens subregion ($F(2,96) = 10.05$; $P < 0.0001$). The post-hoc Fisher's Protected test confirmed that the rostral subregion of the nucleus accumbens was less sensitive to the effects of both dopamine agonists compared with the nucleus accumbens core ($P < 0.0001$) and shell ($P < 0.01$), which did not differ from each other ($P = 0.3$). A separate ANOVA applied to the data from the frontal cortex, olfactory tubercle, and caudate nucleus yielded significant effects of dopamine agonist ($F(1,48) = 6.6$; $P < 0.01$), dose ($F(3,48) = 24.8$; $P < 0.0001$) and brain region ($F(2,96) = 466.8$; $P < 0.0001$) as well as significant brain region $\times$ dopamine agonist and brain region $\times$ dose interactions ($F(2,96) = 3.8$; $P < 0.05$ and $F(6,96) = 14.5$; $P < 0.0001$). The post hoc Fisher's Protected test confirmed that the frontal cortex was significantly different from both the olfactory tubercle ($P < 0.0001$) and caudate nucleus ($P < 0.0001$) which did not differ from each other ($P = 0.05$).

4. Discussion

The main goal of the present study was to compare the autoregulation of dopamine synthesis in subdivisions of the rat nucleus accumbens. To achieve this aim, we used the method of DOPA accumulation after decarboxylase inhibition as an index of dopamine synthesis in microdissected brain regions. Both apomorphine and quinpirole produced a decrease in the accumulation of DOPA in all six brain regions examined.

In general, the dopamine D_2/D_3 receptor agonist quinpirole produced a significantly greater decrease in DOPA accumulation compared with the dopamine D_1/D_2 receptor agonist apomorphine. Within the nucleus accumbens, the three main compartments had similar basal levels of DOPA. There were no core–shell differences in the agonist-induced suppression of dopamine synthesis, but the rostral pole was significantly less sensitive to the highest dose of both dopamine agonists compared with the core and shell. Thus, our findings suggest the rostral pole of the nucleus accumbens is functionally distinct from the core and shell regions.

Recent studies have shown that electrically evoked dopamine overflow, as measured by fast cyclic voltammetry, is significantly lower in the rostral pole of the nucleus accumbens when compared with either the shell or core subregions (Wieczorek and Kruk, 1995). Additionally, the IC_{50} value for quinpirole-induced reduction of electrically evoked dopamine overflow is threefold higher in the rostral pole than in the shell and core (Wieczorek and Kruk, 1995). Finally, the extent of dopamine overflow produced by 1 μM cocaine in superfused brain slice preparations has been shown to be twofold greater than that seen with 1 μM (−)-sulpiride in the rostral pole of the nucleus accumbens, whereas both compounds are equipotent in the shell and core subregions (Wieczorek and Kruk, 1995). These findings suggest that D_2 autoreceptor mechanisms are less important in the rostral pole of the nucleus accumbens, where dopamine uptake is the dominant mechanism regulating extracellular concentrations of dopamine. In contrast, both D_2 autoreceptors and dopamine uptake sites seem to play an equivalent role in the core and shell subterritories. The dopamine synthesis data presented herein agree with the notion that dopamine D_2 autoreceptor sensitivity in the rostral pole of the nucleus accumbens is blunted with respect to the core and shell regions.

In the present study, basal levels (pg μg^{-1} protein) of 5-hydroxytryptophan (5-HTP) were significantly higher in the nucleus accumbens shell (1.63 ± 0.2 pg μg^{-1}) compared with both the nucleus accumbens core (1.18 ± 0.2 pg μg^{-1}; $P < 0.05$) and rostral pole (1.02 ± 0.1 pg μg^{-1}; $P < 0.01$), suggesting that the shell subregion of the nucleus accumbens has the highest, whereas the rostral pole has the lowest, in vivo rate of serotonin (5-hydroxytryptamine; 5-HT) synthesis. Interestingly, recent studies have shown that the shell of the nucleus accumbens contains a higher density of 5-HT axons compared with the core which, in turn, contains a higher density of axons that are positive for the 5-HT transporter (SERT) (Brown and Molliver, 2000). In addition, both methamphetamine and *p*-chloroamphetamine produce extensive degeneration of

axons that co-express 5-HT and SERT in the rostral pole of the nucleus accumbens (Brown and Molliver, 2000). Further studies are warranted to study the effect of dopaminergic drugs on 5-HT synthesis, release, and metabolism in these three main subterritories of the nucleus accumbens.

The results of the present study indicate that basal DOPA levels were significantly lower in the frontal cortex compared with the other five brain areas. Previous studies (Bannon and Roth, 1983) have demonstrated that the rat mesoprefrontal dopamine neurons are devoid of synthesis and impulse-modulating autoreceptors. On the other hand, prefrontal dopamine turnover, measured as the rate of dopamine disappearance after inhibition of tyrosine-3-monooxygenase by α-methyltyrosine, is suppressed by apomorphine (50 $\mu g\ kg^{-1}$), confirming that prefrontal dopamine release is sensitive to regulation by dopamine receptor agonists (Galloway et al., 1986). Accumulation of DOPA in the frontal cortex has also been shown to be diminished after administration of dopamine receptor agonists, such as apomorphine, BHT-920, 3-[4-(4-phenyl)-1,2,3,6-tetrahydropyridyl-1] butyl indole (EMD 23 448) and 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine[(+)-3-PPP]. The apomorphine-induced inhibition of prefrontal, but not striatal, DOPA synthesis is blocked by either cessation of impulse-dependent dopamine release (after γ-butyrolactone) or by depletion of intraneuronal dopamine (after reserpine), suggesting that dopamine receptor agonists affect prefrontal dopamine synthesis only in the presence of dopamine release (Galloway et al., 1986). Furthermore, inhibition of frontal cortex synthesis by dopamine receptor agonists is associated with an increase in intraneuronal dopamine relative to m-hydroxybenzylamine-treated controls (Galloway et al., 1986), suggesting that agonist-induced synthesis inhibition in the frontal cortex is a consequence of activation of release-modulating autoreceptors with a subsequent decrease in dopamine release and increase in end product inhibition of tyrosine hydroxylation.

Altogether, the results of the present study show that the rostral pole of the nucleus accumbens is functionally distinct in terms of the autoregulation of dopamine synthesis. Our data coupled with the reported blunted sensitivity to quinpirole in the rostral pole at two different stimulation parameters (Wieczorek and Kruk, 1995) could be indicative of a lower receptor reserve and/or fewer dopamine D_2 autoreceptors when compared with the core and shell of the nucleus accumbens. Further studies are needed to more directly test this hypothesis.

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