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Brain Research 1038 (2005) 163–170
BRAIN RESEARCH
www.elsevier.com/locate/brainres

Research report

Asymmetrical changes of dopamine receptors in the striatum after unilateral dopamine depletion

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Accepted 10 January 2005

Abstract

Dopamine plays an important role in modulating synaptic transmission in the striatum and has great influence on the function of the basal ganglia. Degeneration of dopamine neurons in the substantia nigra (SN) is the major cause of many neurological disorders, and the reduction of dopamine innervation results in alterations of dopamine receptors in the striatum. It has been shown that the nigrostriatal dopamine system has functional and neurochemical asymmetry. To investigate the lateralization of dopamine receptors in the striatum after dopamine denervation, the present study used quantitative autoradiography to compare the changes in dopamine receptor binding in the left and right striatum in rats after unilateral dopamine depletion. In comparison to control levels, dopamine D_1-like receptor binding, labeled with [^{3}H]-SCH23390, in the dorsal striatum was reduced 2 weeks after unilateral lesions of the SN with 6-hydroxydopamine. D_1-like receptor binding was decreased in the ipsilateral striatum following unilateral lesions of either the left or right SN. The left and right striatum responded similarly to unilateral SN lesions, as there were no significant differences in the percent decrease in D_1-like binding in the two striata. In contrast, D_2-like receptor binding, labeled with [^{3}H]-spiroperidol, was significantly increased in the dorsal striatum following an ipsilateral SN lesion. Furthermore, the up-regulation of D_2-like receptors in the right striatum was significantly greater than that in the left striatum after an ipsilateral lesion. The asymmetrical up-regulation of striatal D_2 receptors after extensive dopamine depletion might contribute to the lateralization of the nigrostriatal system observed in some pathological conditions.

Theme: Neurotransmitters, modulators, transporters and receptors
Topic: Catecholamine receptors

Keywords: Striatum; Dopamine receptor; 6-OHDA; Lateralization; Autoradiography; Asymmetry

1. Introduction

The striatum is a major structure of the basal ganglia that is involved in the mediation of motor behaviors. Neurons in the striatum receive heavy dopaminergic innervation from the substantia nigra (SN). Dopamine modulates the function of striatal neurons by activation of its receptors in a complex manner [34]. For example, activation of dopamine D_2 receptors reduces AMPA glutamate receptor-mediated EPSPs, whereas activation of dopamine D_1 receptors enhances both AMPA and NMDA glutamate receptor-mediated responses [9,24,29]. The loss of dopaminergic neurons in the SN is the major cause of Parkinson's disease [1]. To reveal the mechanisms underlying the pathogenesis of Parkinson's disease, the impact of removal of dopaminergic innervation in the striatum has been extensively investigated. It has been shown that the sensitivity and number of D_2-like dopamine receptors in the striatum increase after the loss of dopamine neurons in the SN [13,26,33]. However, the results regarding the changes in D_1-like receptors after dopamine denervation are less consistent, with some

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doi:10.1016/j.brainres.2005.01.033

studies showing up-regulation and others showing down-regulation [3,5,20,38]. Such differential changes in D_1 and D_2 receptors might contribute to the functional alterations of striatal neurons observed after dopamine denervation. It has been shown that corticostriatal long-term potentiation is blocked in striatal neurons after dopamine denervation [8]. On the other hand, sensitization of locomotor responses following the administration of D_1 or D_2 receptor agonists is observed in animals with significant dopamine depletion [25,27].

The nigrostriatal dopamine system is one of the brain regions that shows functional and neurochemical asymmetry. Dopamine content, metabolism, and receptor activity differ between the left and right nigrostriatal system [16,31,46]. Such lateralization of the nigrostriatal system might be involved in the asymmetry of post-ischemic neuronal damage after unilateral dopamine depletion. Neurons in the dorsal striatum die within 24 h after transient cerebral ischemia [39], and dopamine might have detrimental effects on striatal neurons post-ischemia [19]. It has been shown that depletion of dopamine neurons in the SN by the neurotoxin 6-hydroxydopamine (6-OHDA) significantly reduces the neuronal damage in the striatum after ischemia [11,18]. However, such protection occurs only in the right striatum after a lesion of the right SN; removal of dopamine neurons in the left SN offers no protection to the left striatum following ischemia [41]. A recent study has indicated that such asymmetrical protection is not due to the difference in residual dopamine between the left and right striatum after unilateral dopamine depletion [45]. Another possible mechanism underlying such asymmetrical protection might be that the dopamine receptor alterations after dopamine depletion differ between the left and right striatum. However, it is not clear how dopamine receptors are specifically altered in the left or right striatum after dopamine depletion, and whether such alterations, if any, might be associated with the asymmetrical protection after ischemia.

To begin to address the above questions, the present study used quantitative receptor autoradiography to compare the changes in dopamine receptors in the left or right striatum after unilateral dopamine depletion. Although changes in D_1 and D_2 receptors are described throughout, it should be noted that the radioligand used to label D_1 receptors, [^{3}H]-SCH23390, binds to the D_1-like family of receptors, but does not discriminate between the D_1 and D_5 receptor subtypes. Similarly, the radioligand used to label D_2 receptors, [^{3}H]-spiroperidol, does not discriminate between the D_2, D_3, and D_4 receptor subtypes, all members of the D_2-like receptor family. Thus, observed changes in D_1 receptor binding may reflect changes in both D_1 and D_5 receptors, whereas changes in D_2 receptor binding could include changes in D_3 and D_4 receptors, as well as D_2 receptors. However, D_1 and D_2 receptors are the predominant subtypes found in the striatum, the area examined in this study.

2. Methods

All procedures were carried out in accordance with the United States Public Health Services Guide for Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee at the Indiana University School of Medicine.

2.1. Dopamine depletion

Male, adult Wistar rats (200–350 g) were randomly selected for depletion of dopamine neurons in the left or right SN. The depletion of dopamine was performed by unilateral administration of 6-OHDA hydrobromide (Sigma) into the SN [41,44]. The animals were anesthetized with a mixture of 1–2% halothane, 33% O_2, and 66% N_2. Desipramine (25 mg/kg, ip) was injected 30 min before 6-OHDA infusion to protect the noradrenergic pathways. The 6-OHDA was delivered stereotaxically into the SN region with two injections. One injection site was aimed at the rostrolateral SN (AP: 4.2 mm, ML: 2.0 mm, and DV: 8.0 mm, interaural, [37]), and the other site was aimed at the caudomedial SN (AP: 3.2 mm, ML: 1.5 mm, and DV: 8.0 mm). The 6-OHDA solution was freshly prepared in sterile distilled water, containing 0.1% ascorbic acid and 0.9% NaCl, in a volume of 2 μg/μl (calculated as the free base). The solution was adjusted to pH 5.5 and kept in a refrigerator until used. The volume of each injection was 2 μl containing 4 μg of 6-OHDA base. The 6-OHDA solution was slowly infused for 3–4 min through a 10-μl Hamilton syringe. The needle of Hamilton syringe was left in place for an additional 10 min after injection. Control animals were treated in the same manner, but received equivalent volumes of vehicle in lieu of 6-OHDA into either the left or right SN.

Ten to fourteen days after SN lesions, the rats were injected with the mixed D_1/D_2 receptor agonist apomorphine (0.5 mg/kg, sc) and observed for rotational behavior. Only rats that exhibited consistent contralateral turning (≥10 turn/min) for at least 20 min, a behavior indicating depletion of more than 90% of dopamine in the striatum [23], were used in the experiment. Immunocytochemistry was performed on sections containing SN or striatum randomly selected from 6 animals (3 left lesion, 3 right lesion) to further verify the extent of the lesion using antibodies against tyrosine hydroxylase (TH). Coronal cryostat sections (20 μm) were mounted on slides (see below) and post-fixed in 4% paraformaldehyde overnight. Sections were first incubated with 10% normal horse serum (NHS) in 0.5% Triton X-100, 0.01 M potassium phosphate-buffered saline (KPBS) for 2 h at room temperature. Then the sections were incubated in mouse monoclonal antibodies against TH (Chemicon) at a concentration of 1:1500 in KPBS with 10% NHS and 0.5% Triton overnight at 8 °C. After rinsing in KPBS, the sections were put into KPBS containing 1:200 biotinylated horse anti-mouse secondary antibodies (Vector Lab) for 2 h. After detection of peroxidase activity with diaminobenzidine as