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Short communication

Neonatal co-lesion by DSP-4 and 5,7-DHT produces adulthood behavioral sensitization to dopamine D_2 receptor agonists*

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Abstract:
To assess the possible modulatory effects of noradrenergic and serotoninergic neurons on dopaminergic neuronal activity, the noradrenergic and serotoninergic neurotoxins DSP-4 N-(2-chlorethyl)-N-ethyl-2-bromobenzylamine (50.0 mg/kg, *sc*) and 5,7-dihydroxytryptamine (5,7-DHT) (37.5 μg *icv*, half in each lateral ventricle), respectively, were administered to Wistar rats on the first and third days of postnatal ontogeny, and dopamine (DA) agonist-induced behaviors were assessed in adulthood. At eight weeks, using an HPLC/ED technique, DSP-4 treatment was associated with a reduction in NE content of the corpus striatum (> 60%), hippocampus (95%), and frontal cortex (> 85%), while 5,7-DHT was associated with an 80–90% serotonin reduction in the same brain regions. DA content was unaltered in the striatum and the cortex. In the group lesioned with both DSP-4 and 5,7-DHT, quinpirole-induced (DA D_2 agonist) yawning, 7-hydroxy-DPAT-induced (DA D_3 agonist) yawning, and apomorphine-induced (non-selective DA agonist) stereotypies were enhanced. However, SKF 38393-induced (DA D_1 agonist) oral activity was reduced in the DSP-4 + 5,7-DHT group. These findings demonstrate that DA D_2- and D_3-agonist-induced behaviors are enhanced while DA D_1-agonist-induced behaviors are suppressed in adult rats in which brain noradrenergic and serotoninergic innervation of the brain has largely been destroyed. This study indicates that noradrenergic and serotoninergic neurons have a great impact on the development of DA receptor reactivity (sensitivity).

Key words:
DSP-4, 5,7-DHT, biogenic amines, brain, dopaminergic, behavior, rats

Introduction

A host of neurotoxins are now available to aid studies on the function of central neurotransmitter systems. 6-Hydroxydopamine (6-OHDA), a norepinephrine (NE) isomer introduced in 1967, produces prominent and overt destruction of both dopamine (DA)-containing and NE-containing neurons [20, 23, 33]. In an

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analogous manner, hydroxyl-analogs of 5-hydroxytryptamine (5-HT), namely 5,6- and 5,7-dihydroxytryptamine (5,6-DHT; 5,7-DHT), are neurotoxic to 5-HT-containing neurons [4, 5]. A disadvantage of these neurotoxins is that they fail to cross the blood-brain barrier, thereby requiring direct injection into the brain (*icv*).

The neurotoxin N-(2-chlorethyl)-N-ethyl-2-bromobenzylamine (DSP-4) was subsequently found to cross the blood-brain barrier and produce long-lasting inactivation of NE neurons. DSP-4 thus can be injected peripherally (*sc*, *ip*). It produces a dramatic long-lasting reduction in NE levels in the brain and periphery of adult rats, although there is recovery over time in the periphery [32]. DSP-4, when injected into newborn rats, also produced a virtually permanent reduction of NE in the frontal cortex, spinal cord (and other brain regions), and increased the NE content of the cerebellum – the latter effect representing reactive proliferative sprouting of proximal axons of the dorsal bundle [6, 7].

In our recent studies, we have shown that a variety of behavioral functions are altered following DSP-4 treatment of neonatal rats [9, 29]. Seemingly, these findings are reflective of reduced sensitivity of the central dopaminergic system [9, 30] and increased sensitivity of the central serotoninergic system [16, 24].

The aim of the present study was to examine the behavioral reactivity of central dopaminergic neurons following simultaneous ontogenetic lesioning of central noradrenergic and serotoninergic neurons.

Materials and Methods

Animals

Newborn male Wistar rats were divided into four groups. The first group was injected with DSP-4 (Sigma Chem. Co., St. Louis, MO, USA) (50.0 mg/kg, *sc*) on the 1st and 3rd days after birth between 9.00–10.00 h, and on the 3rd day with saline *icv* (5 µl in each lateral ventricle) between 14.00–15.00 h.

The second group was injected with saline (1.0 ml/kg, *sc*) on the 1st and 3rd days of life, and with 5,7-DHT (150 g *icv*, base form, half in each lateral ventricle) on the 3rd day between 14.00–15.00 h.

The third group was injected with DSP-4 (50.0 mg/kg, *sc*) on the 1st and 3rd days, and with 5,7-DHT (*icv*) on the 3rd day as described above.

The fourth group (control) was injected with saline *sc* and *icv* only, as described above.

Litters remained with dams until the 21st day after birth and then were placed in individual cages according to sex. All rats were kept under a 12 h light : 12 h dark cycle in a well ventilated room at 22 ± 1°C. Rats had free access to food and tap water. This study was approved and controlled by the Local Bioethics Committee for Animals at the Medical University of Silesia (decision no. 11/04 issued on 17.03.2004) and performed in accordance with principles and guidelines described in the NIH booklet "Care and Use of Laboratory Animals".

Behavioral and biochemical studies were conducted when rats reached the age of 8 weeks.

Biochemical study

Biogenic amine assay

Rats were scarified by decapitation and the brains were immediately excised and placed on ice. The striatum, hippocampus, frontal cortex, and cerebellum were separated at 0°C, placed on dry ice, weighed, and stored at –70°C, until use. Dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), norepinephrine (NE), 3-methoxy-4-hydroxyphenylglycol (MOPEG), 5-hydroxytryptamine (5-HT), and 5-hydroxyindole-3-acetic acid (5-HIAA) were estimated by an HPLC/ED technique according to Magnusson et al. [27]. Results are expressed as ng/g of wet tissue. Each group consisted of 5–6 rats.

Behavioral study

Locomotor activity

Rats from each group were individually placed in transparent glass cages (48 × 26 × 36 cm), and were allowed to acclimate for 30 min. Then, saline was injected, and 10 min later locomotor activity (time spent walking, sniffing, grooming, and rearing) was recorded in seconds during a 10-min session. Immedi-

ately afterwards, 3.0 mg/kg, *ip* of quinpirole (dopamine D_2/D_3 receptor agonist) was injected, and observations were repeated at 30 and 60 min [8]. The experiment was performed by an experienced observer.

Exploratory activity

After the rats had acclimated to the laboratory environment for 30 min, rats from each group were injected *ip* with saline. At 10 min, each rat was placed in the center of a wooden platform, 100 cm square, surrounded by a 40-cm fence to prevent escape. The flat platform had 4 rows of 4 holes each, 7 cm in diameter and 20 cm apart. The number of times (during a 3-min period) that each rat stuck its head beneath the interaural line into any hole was recorded [15]. Then, quinpirole 3.0 mg/kg, *ip* or SKF 38393 1.0 mg/kg, *ip* was injected, and observations were repeated at 30 and 60 min.

Yawning activity

Yawning activity was evaluated by quinpirole and 7-OH-DPAT according to Kostrzewa and Brus [22]. After a 1 h adaptation period, each male rat was injected *ip* with saline, and the number of yawns was counted for 60 min. Then, each rat was injected *ip* with the lowest dose of quinpirole or 7-OH-DPAT [14, 21], and the number of yawns was counted for an additional 60 min. The same rats were challenged on subsequent days with escalating doses of both agonists, one dose per day, and were observed as above.

Oral movements

Oral movements (vacuous chewing movements) were evoked by SKF 38393, a selective DA D_1 agonist. After acclimating to the laboratory environment, rats were treated with SKF 38393 in escalating daily doses of 0, 0.1, 0.3, or 1.0 mg/kg, *ip.* Number of oral movements was counted for 1 min every 10 min during a 60 min observation period. Oral activity represents the number of oral movements occurring during the cumulative six 1-min sessions [8].

Stereotyped behavior

Rats were individually placed in transparent glass cages (48 × 26 × 36 cm) on fresh wood-chip bedding, and were allowed to acclimate for 30 min. Then, all rats were injected with apomorphine 1.0 mg/kg, *sc*, a non-selective DA receptor agonist. Every 15 min after the injection, and up to 90 min, stereotyped behavior of each rat was measured by the scoring method established by Creese and Iversen [12] on a scale of 0–6.

Statistical analyses

Each behavioral study group consisted of eight rats. Data from all biochemical or behavioral studies were analyzed by two-way ANOVA and the post-ANOVA test by Newman-Keuls. A p value of < 0.05 was considered significant.

Results and Discussion

DSP-4, alone or in combination with 5,7-DHT, reduced the adulthood level of NE by approximately 60% in striatum, 90% in frontal cortex, and 95% in hippocampus. 5,7-DHT, alone or in combination with DSP-4, reduced the adulthood level of 5-HT by 85–90% in striatum, 90% in frontal cortex, and 80–85% in hippocampus. Reductions in 5-HIAA were less severe than changes in endogenous 5-HT contents after 5,7-DHT treatment (Tab. 1). The endogenous level of DA in striatum and frontal cortex remained unaltered by DSP-4 and 5,7-DHT treatments.

Spontaneous locomotor activity (after saline injection) was lower in the group lesioned with 5,7-DHT – with or without DSP-4 co-treatment (Fig. 1). This is in line with Chia et al. [11], but others have presented opposite results [25]. At 1 h, quinpirole-induced locomotor activity was not different from the 5,7-DHT group (in comparison to saline treatment), while additional destruction of noradrenergic system (5,7-DHT + DSP-4 group) increased DA D_2 receptor-mediated (quinpirole-induced) locomotor activity ($p < 0.05$; *vs*. the 5,7-DHT alone group).

Exploratory behavior after saline injection was lowest in the 5,7-DHT-lesioned group. Acute quinpirole treatment reduced exploration in all tested groups, but the effect was most notable in the control group (Fig. 2). It is worth noting that others also showed that quinpirole, which selectively blocks the release of CNS DA, produced a dose-dependent and

Tab. 1. Endogenous levels of biogenic amines and metabolites in the brain of adult rats lesioned neonatally with DSP-4 and/or 5,7-DHT (x ± SEM; n = 6)

Brain region	Treatment	Endogenous level of biogenic amine or metabolite (ng/g, tissue wet wt.)					
		DA	DOPAC	HVA	5-HT	5-HIAA	NE
Striatum	Control	9072 ± 106	885 ± 51	807 ± 80	562 ± 42	307 ± 55	507 ± 43
	DSP-4	9905 ± 382	808 ± 66	855 ± 66	550 ± 55	332 ± 39	188* ± 25
	5,7-DHT	10005 ± 203	863 ± 73	980 ± 105	62* ± 21	96 ± 22	441 ± 59
	DSP-4 + 5,7-DHT	10025 ± 125	922 ± 69	859 ± 62	88* ± 32	102 ± 36	207* ± 26
Frontal cortex	Control	235 ± 43	61 ± 10	49 ± 7	244 ± 19	202 ± 19	345 ± 18
	DSP-4	223 ± 25	63 ± 12	41 ± 8	231 ± 15	192 ± 18	27* ± 7
	5,7-DHT	258 ± 36	58 ± 20	35 ± 7	22* ± 9	35* ± 13	333 ± 27
	DSP-4 + 5,7-DHT	238 ± 23	61 ± 7	39 ± 7	25* ± 8	35* ± 17	47* ± 13
Hippocampus	Control	–	–	–	255 ± 21	221 ± 16	323 ± 34
	DSP-4	–	–	–	263 ± 26	198 ± 22	15* ± 8
	5,7-DHT	–	–	–	43* ± 14	47* ± 13	355 ± 47
	DSP-4 + 5,7-DHT	–	–	–	49* ± 15	56* ± 16	19* ± 6

* $p < 0.05$ as compared to control

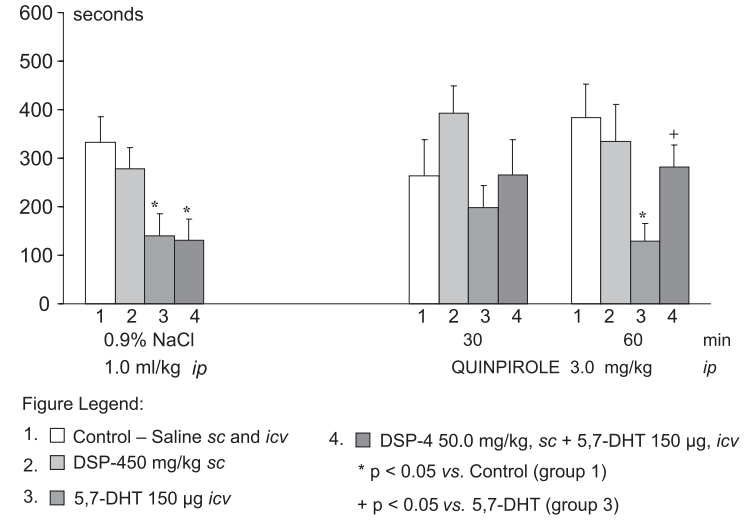

Fig. 1. Effect of quinpirole on locomotor activity in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (× ± SEM; n = 8)

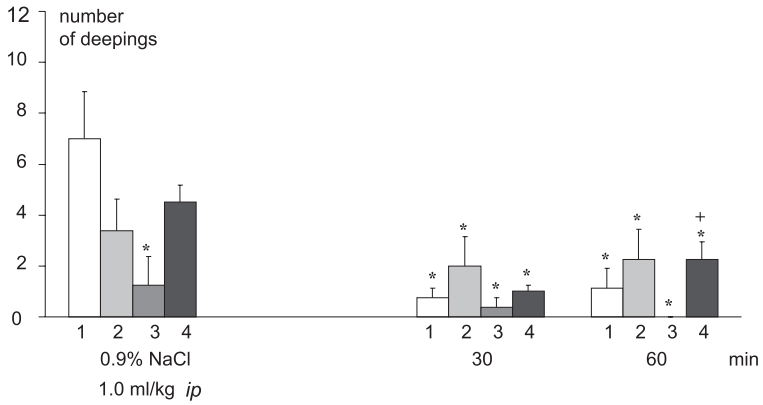

Fig. 2. Effect of quinpirole on exploratory activity in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (× ± SEM; n = 8). Figure legend is the same as in Figure 1

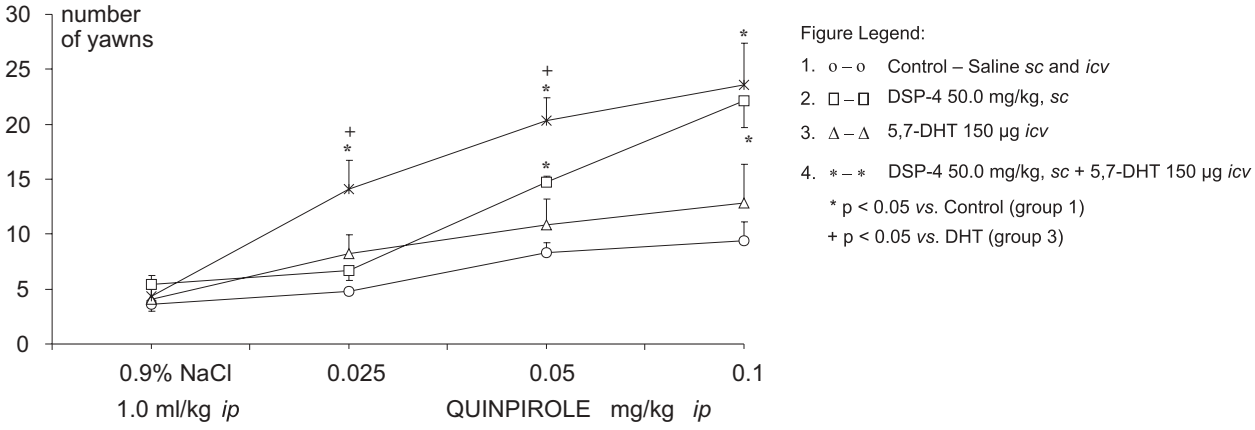

Fig. 3. Effect of quinpirole on yawning behavior in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (× ± SEM; n = 8)

virtually complete abolition of exploration and all movement in the novel cage test [26].

Quinpirole at 0.025 to 0.1 mg/kg, *ip* induced yawning in all groups, but the effect was more prominent in the group lesioned with DSP-4 alone; and the effect was greatest in the group that was co-lesioned with DSP-4 and 5,7-DHT (Fig. 3). 7-OH-DPAT induced yawning to a lesser extent compared to quinpirole, but the 7-OH-DPAT effect was greatest in the group co-lesioned with DSP-4 and 5,7-DHT (Fig. 4). This is in agreement with Okuyama et al. [31] who demonstrated that yawning elicited by apomorphine, but not by physostigmine, was enhanced either by p-chlorophenylalanine administration (5-HT synthesis inhibitor) or 5,7-DHT treatment. Also apomorphine-induced (1.0 mg/kg, *sc*) stereotyped activity was higher at 15, 30, and 45 min in the DSP-4 and 5,7-DHT co-lesioned group versus control. The stereotypy score in the former group was approximated at 6.0, while the score in the control group was approximated at 4.5 (Fig. 6). It is worth noting that noradrenergic as well as serotoninergic systems have a great impact on the density of DA receptors and consequently on the reactivity to agonists [1–3]. Harro et al. [19] demonstrated that DSP-4 treatment resulted in DA D_2 receptor upregulation in the striatum as evidenced by [^{3}H]-raclopride binding. D-Amphetamine (1.5 mg/kg) caused a similar increase in locomotor activity in control and DSP-4-pretreated animals not familiar with the apparatus. These data suggest that supersensitivity of DA D_2 receptors develops after locus coeruleus denervation, but that the enhanced efficacy of amphetamine in DSP-4-treated rats is masked by neophobia. Perhaps co-lesion of NA and 5-HT unmask supersensitivity of DA D_2 receptor as we showed in the present study.

The DA D_1 receptor agonist SKF 38393 induced a virtually identical maximum in the numbers of oral movements in all groups, except for the group co-lesioned with DSP-4 and 5,7-DHT. In the latter group, SKF 38393 had virtually no effect (Fig. 5). Makihara et al. [28] found that in the mouse, vertical jaw movements and tongue protrusions are regulated by oppositional D1-like : D2-like interactions. This may, at least in part, explain the findings of the current work where we showed overreactivity of DA D_2 receptor in 5,7-DHT plus DSP-4 co-lesioned group and diminished reactivity of DA D_1.

In our previous study we found that DSP-4, when administered to newborn rats on the 1st and 3rd days of postnatal life, altered adulthood behaviors induced by DA D_1-, D_2- and D_3-receptor agonists or antagonists [9]. DSP-4 also reduced the DA synthesis rate in striatum and decreased frontal cortical microdialysate levels of NA, DA, DOPAC, and HVA, following amphetamine challenge [9, 30]. It cannot be excluded that the latter effects occurred because of direct action of DSP-4 on the central dopaminergic system. DSP-4 also prevented ontogenetic quinpirole priming (sensitization) for quinpirole-induced yawning [30]. Neonatal DSP-4 lesioning is also associated with desensitization of the central serotonin 5-HT_{1A} receptor [13]. In those animals, susceptibility to seizures induced by $GABA_A$ antagonists and sleep induced by $GABA_A$ agonists occurred, showing that GABAergic neurotransmission in the prefrontal cortex of adult rats was vividly modified [6, 7]. There are also data showing

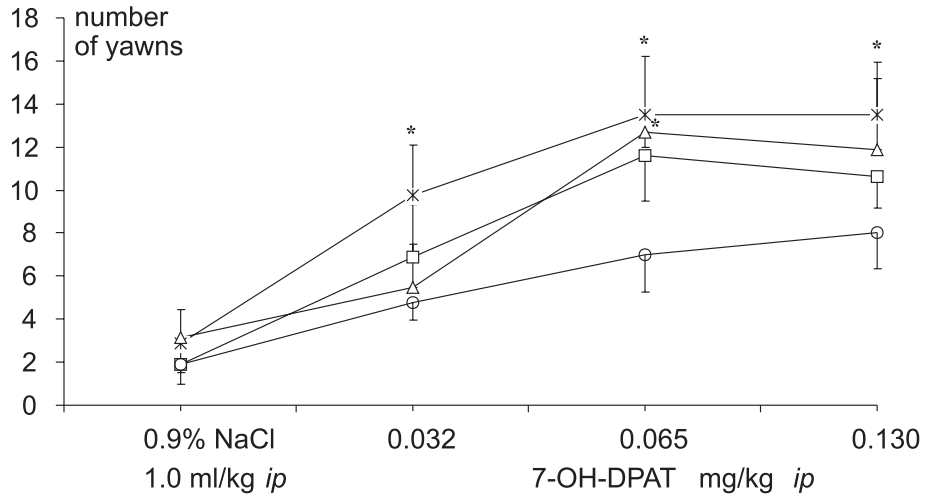

Fig. 4. Effect of 7-OH-DPAT on yawning behavior in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (x ± SEM; n = 8). Figure legend is the same as in Figure 3

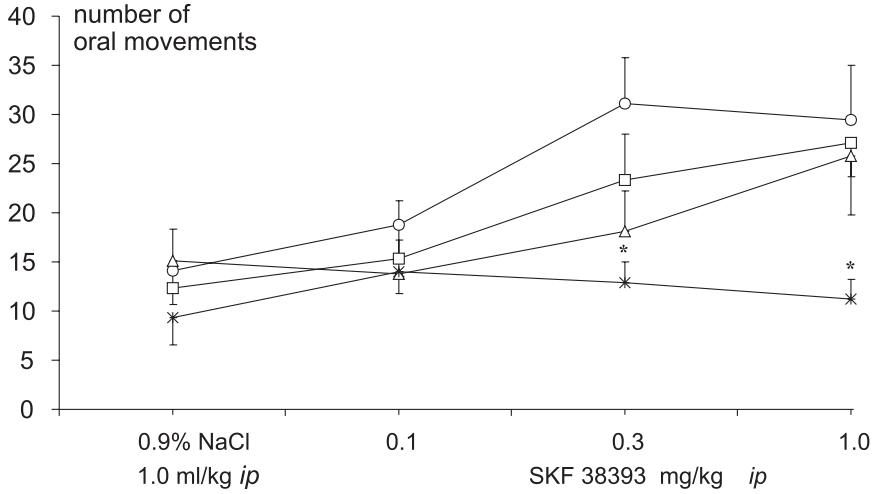

Fig. 5. Effect of SKF 38393 on oral activity in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (× ± SEM; n = 8). Figure legend is the same as in Figure 3

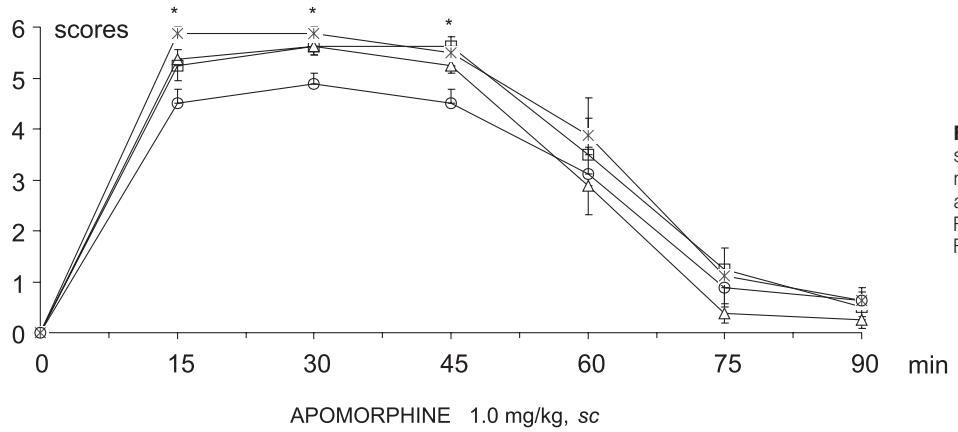

Fig. 6. Effect of apomorphine on stereotyped behavior in adult rats neonatally lesioned with DSP-4 and 5,7-DHT (× ± SEM; n = 8). Figure legend is the same as in Figure 3

that the neonatal lesion of central dopaminergic neurons by intracerebral (*icv*) injection of 6-OHDA intensified activity of the central serotoninergic system, as examined by biochemical, histochemical, and behavioral studies [8, 10, 16–18]. These findings demonstrate that neonatal 6-OHDA treatment produces ontogenic long-lived supersensitization of the central serotoninergic system in adult rats.

In conclusion, we demonstrated that DA D_2- and D_3-agonist-induced behaviors are enhanced while DA D_1-agonist-induced behaviors are suppressed in adult rats in which brain noradrenergic and serotoninergic innervation of brain was largely destroyed. This study indicates that noradrenergic and serotoninergic neurons have a great impact on the development of DA receptor reactivity (sensitivity).

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