

DSP-4 prevents dopamine receptor priming by quinpirole

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Abstract

Repeated treatments of rats with the dopamine (DA) D₂ receptor agonist quinpirole, consistently produce long-lived DA D₂ receptor supersensitization, by the process that has been termed *priming*. Rats so-primed in ontogeny behaviorally demonstrate adulthood enhancement of low-dose quinpirole-induced yawning. Because 1) dopaminergic neurons originate in midbrain nuclei (substantia nigra and ventral tegmental area), and 2) noradrenergic neurons originate in pontine (locus coeruleus) and medullary areas, it might be presumed that these two monoaminergic systems are independent, not interdependent. However, in the present study we demonstrate that there was an attenuation of quinpirole-enhanced yawning at 8 weeks in rats that were 1) primed by repeated neonatal quinpirole HCl treatments (50 µg/kg per day SC) during the first ten days of postnatal ontogeny, and 2) lesioned at 3 days after birth with DSP-4 (*N*-2-chloroethyl-*N*-ethyl-2-bromobenzylamine hydrochloride, 50 mg/kg SC). Dose–effect curves indicated a 23–45% reduction in yawning by DSP-4 treatment of quinpirole-primed rats, acutely treated as adults with quinpirole (25, 50, or 100 µg/kg). Effectiveness of DSP-4 is reflected by the 95% and 99% reductions in norepinephrine contents of frontal cortex and hippocampus, respectively (HPLC/ED method). The findings are supportive of a modulatory role of noradrenergic fibers on dopamine receptor priming (supersensitization) in rat brain.

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1. Introduction

Low-dose dopamine (DA) receptor agonists are known to induce yawning in rats (Gower et al., 1984; Longoni et al., 1987; Serra et al., 1987; Stoessl et al., 1987; Yamada et al., 1990) — possibly by actions at D₂ and/or D₃ receptors (Kostrzewa and Brus, 1991a,b; Damsma et al., 1993). Through a series of studies started around 1990, we found that yawning responses to the dopamine D₂ agonist, quinpirole, could be enhanced if rats were repeatedly treated neonatally with a daily dose of quinpirole, as low as 50 µg/kg per day; and for as little as 11 days (Kostrzewa et al., 1993b). This process is known as receptor *priming* (i.e., receptor supersensitization) (Kostrzewa, 1995), and it persists life-long even after a priming period as short as 11 days (Oświećimska et al., 2000). Rats primed in adulthood with high doses of quinpirole, display locomotor sensitization to acute

quinpirole treatments (Szechtman et al., 1998; Szumlinski et al., 2000). Moreover, repeated quinpirole injections have been used to model obsessive-compulsive disorder (Szechtman et al., 1998, 2001).

In another series of studies we found that serotonin (5-HT) systems in brain had a dramatic modulatory influence on DA systems, particularly in reference to DA D₁ and D₂ receptor sensitization. In rats that were lesioned as neonates with 6-hydroxydopamine (6-OHDA) to largely destroy dopaminergic innervation and induce DA receptor supersensitization in striatum (Kostrzewa and Gong, 1991; Gong et al., 1993a), it was shown that 5-HT receptor supersensitization also developed (Gong and Kostrzewa, 1992). In addition, denervation with 5,7-dihydroxytryptamine (5,7-DHT) (Brus et al., 1994) or with 5-HT₂ receptor antagonist treatments (Gong et al., 1992) were found to largely attenuate DA receptor behavioral sensitization (Gong et al., 1992, 1993b, 1994; Kostrzewa et al., 1992, 1993a, 1998; Plech et al., 1995). Further evidence of a 5-HT modulatory effect on DA receptor sensitization, relates to the fact that an enhanced quinpirole response was observed in rats lesioned with

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5,7-DHT (Brus et al., 1995). An association between DA D₁ receptors and yawning behavior has been reported (Diaz-Romero et al., 2005).

The impetus for study of an interaction of 5-HT and DA systems relates to their coordinate innervation of much of the brain, particularly the striatum. Also, noradrenergic neuronal influence on dopaminergic activity was first noted thirty years ago (Antelman and Caggiula, 1977; Kostowski et al., 1974; Ungerstedt, 1974), and recently, the selective NE reuptake inhibitor atomoxetine was shown to coordinately increase both NE and DA levels in prefrontal cortex (Bymaster et al., 2002). Atomoxetine (Strattera, Eli Lilly, Co.) was introduced as therapy of human hyperactivity — a largely childhood disorder that had been treated primarily by dopaminomimetics, namely amphetamine and methylphenidate. This series of developments serves as a rationale for the present investigation.

To approach the relatively selective destruction of noradrenergic innervation of brain, the neurotoxin DSP-4 [*N*-(2-chloroethyl)-*N*-ethyl-2-bromo-benzylamine] was selected. Ross et al. (1973), Ross (1976), and Ross and Renyi (1976) had shown that DSP-4 crosses the blood–brain barrier to alkylate the norepinephrine (NE) transporter and ultimately destroy noradrenergic neurons. Accordingly, DSP-4 was administered to rats shortly after birth to destroy noradrenergic nerves, while rats were tested in adulthood for responses to the DA agonist quinpirole. In essence, the study was performed in a manner analogous to others performed by us, in which an association was found between 5-HT systems and their role in modulating DA receptor sensitization status.

2. Materials and methods

2.1. Animals and treatment

Wistar albino pregnant rats were bred in a home colony and housed at 22 ± 1 °C and 12 h L:12 h D cycle (lights on at 0700 h) and allowed free access to food and water. The study was approved and controlled by the local Bioethical Committee for Animals of the Medical University of Silesia (permission no 23/02 issued on 17.10.2002). All procedures were in conformity to the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Newborn rats were treated with quinpirole HCl (SIGMA, St. Louis, MO, USA) (50 µg/kg SC), daily from the 1st to 11th days of postnatal life. Control neonates were injected in the same way with saline (2.0 ml/kg SC) (Kostrzewa et al., 1993b). Half the rats from the above two groups were injected additionally with either saline vehicle or DSP-4 (50 mg/kg SC) on the 1st and 3rd days of postnatal life.

2.2. Assessment of brain biogenic amine and metabolite content

At 8 weeks after birth groups of control and DSP-4-treated rats (5 or 6 rats per group) were decapitated, and brains were immediately excised and placed on ice. Because priming in earlier studies did not alter tissue levels of NE and DA in intact and 6-OHDA-lesioned rats, primed groups were not included for brain tissue analysis. Frontal cortex, hippocampus and striatum were separated, placed on dry ice, weighed and stored at –70 °C, pending assay. Norepinephrine (NE), 3-methoxy-4-hydroxyphenylglycol (MOPEG), dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were assayed by an HPLC/ED technique (Magnusson et al., 1980).

2.3. Behavioral assessment in rats

Rats from the above four groups were observed for yawning behavior in the following way (Kostrzewa and Brus, 1991b). Each rat was placed in a single clear plastic cage in a quiet, well-ventilated and well-lighted room, and allowed at least 30 min for acclimation. Rats were observed simultaneously in groups of 4 (one per cage, each rat from a different group). After the acclimation period, each rat from the four groups was injected IP with saline vehicle (1.0 ml/kg IP) and observed for 60 min for yawning behavior (i.e., numbers of yawns), beginning immediately after injection. At the end of this session, each rat was injected IP with a challenge dose of quinpirole HCl (25 µg/kg IP) and observed for another 60 min. Rats were then returned to their respective home cage. On the next day the same rats were re-acclimated in individual cages, then injected with quinpirole HCl (50 µg/kg IP) and observed in the same manner for numbers

Table 1
Effect of DSP-4 (50 mg/kg SC), administered on the 1st and 3rd days of postnatal life, on biogenic amine levels in frontal cortex, hippocampus and striatum of adult rats ($\bar{x} \pm \text{SEM}$; $n=6-7$)

Biogenic amines, ng/g of wet tissue		NE	MOPEG	DA	DOPAC	HVA	5-HT	5-HIAA
Frontal cortex	Control	482.60 ± 29.20	207.77 ± 12.83	263.90 ± 28.77	53.60 ± 3.99	60.97 ± 5.14	281.33 ± 20.87	118.57 ± 9.95
	DSP-4	23.54* ± 3.33	162.84 ± 10.98	270.78 ± 42.32	60.79 ± 7.72	78.40 ± 5.63	216.02 ± 31.67	115.26 ± 17.34
Hippocampus	Control	392.05 ± 13.48	139.58 ± 6.02	8.05 ± 0.80	=	=	274.58 ± 8.93	145.67 ± 6.24
	DSP-4	5.57* ± 0.78	117.28 ± 7.08	2.25 ± 0.43	=	=	207.55 ± 15.40	149.86 ± 6.71
Striatum	Control	156.81 ± 7.31	=	9900.60 ± 543.22	886.52 ± 53.510	919.63 ± 28.67	446.99 ± 23.28	408.07 ± 20.40
	DSP-4	155.43 ± 9.57	=	9043.26 ± 561.79	810.27 ± 56.07	1114.01 ± 78.41	445.36 ± 27.85	632.75 ± 68.47

Explanation:

* $P < 0.01$ as compared to the control.

= not detectable.

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