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DSP-4 prevents dopamine receptor priming by quinpirole

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Abstract

Repeated treatments of rats with the dopamine (DA) D_2 receptor agonist quinpirole, consistently produce long-lived DA D_2 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.

Keywords: DSP-4; Quinpirole; Dopamine; Dopamine receptor; Receptor priming; Receptor supersensitivity; Yawning; Rats

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 D_2 and/or D_3 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 D_2 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 (Oświęcimska 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 D_1 and D_2 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-HT_2 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 D_1 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 (x±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.

of yawns. On the third day yawning behavior was again observed in the same manner after the highest dose of quinpirole HCl (100 μg/kg IP). Each group for yawning behavior consisted of 8 rats.

3. Data analysis

Biochemical and behavioral data from treated and control groups of rats were compared by analysis of variance (ANOVA), followed by post-ANOVA test of Newman–Keuls.

4. Results

4.1. Effects of DSP-4 treatment on biogenic amine and metabolite levels in frontal cortex, hippocampus and striatum of rats (Table 1)

In rats treated on the first and third days of postnatal life with DSP-4 (50 μg/kg SC), and terminated at 8 weeks, the endogenous NE content of frontal cortex and hippocampus was reduced by 95.1% and 98.6%, respectively ($P<.01$). There was no change in striatal NE content. Also, in frontal cortex, hippocampus and striatum there was no consistent change in the NE metabolite MOPEG, nor in DA and its metabolites DOPAC and HVA, nor in 5-HT and its metabolite 5-HIAA (Table 1).

4.2. Effect of DSP-4 treatment on quinpirole-induced yawning behavior in primed and non-primed adult rats (Fig. 1)

In adult male rats treated daily with quinpirole (50 μg/kg per day) from the 1st to 11th days of postnatal life and tested at 8 weeks, there was a significant increase in quinpirole-induced (25–100 μg/g) yawning ($P<.01$) (Fig. 1).

In the group lesioned neonatally with DSP-4 and not quinpirole-primed, quinpirole-induced yawning number was no different from that observed in the saline control group. More significantly, at the 25, 50 and 100 μg/kg doses of quinpirole, the enhanced quinpirole effect in quinpirole-primed rats was absent in the group that was primed and also lesioned neonatally with DSP-4 (Fig. 1).

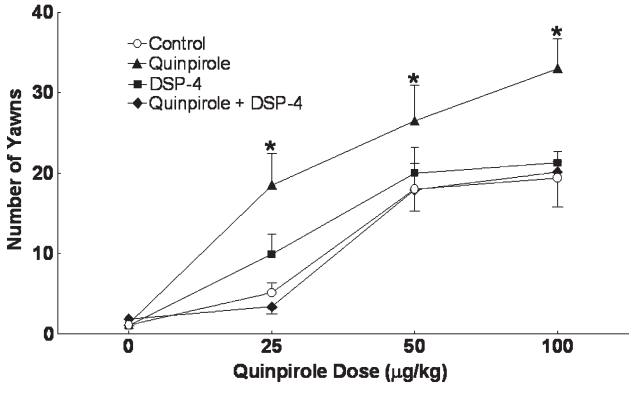

Fig. 1. Quinpirole-induced yawing in adult male rats treated SC daily for the first 11 days of postnatal life with saline or quinpirole HCl (50 μg/kg); plus vehicle or DSP-4 (50 mg/kg SC) on the 1st and 3rd days of postnatal life. Each group consisted of 8 rats. Values indicate mean and S.E.M. Circles: vehicle/vehicle; triangles: quinpirole/vehicle; squares: vehicle/DSP-4; x: quinpirole/DSP-4. *, $P<.05$, quinpirole/saline group vs. saline control group; $^{+}P<.05$, quinpirole/saline vs. quinpirole/DSP-4 group.

5. Discussion

The present findings confirm our earlier studies showing that the complex of DA D_2/D_3 receptors can be sensitized during postnatal ontogeny by repeated daily treatments with low dose quinpirole (Kostrzewa and Brus, 1991b, 1993b). The quinpirole dose used in this study, 60-times lower than that used in our first study (Kostrzewa and Brus, 1991b), is consistent with other studies in which this low dose was used to prime D_2 receptors (Oświęcimska et al., 2000; Kostrzewa et al., 2004; Nowak et al., 2004). This also is in accord with the suggestion that the yawning response may be a partially dopamine D_3 receptor-mediated event (Kostrzewa and Brus, 1991a) because quinpirole has an affinity 113-times higher for the D_3 vs. D_2 receptor (Sokoloff et al., 1990). Not all DA-induced behaviors are enhanced by quinpirole priming (Kostrzewa et al., 1990; Brus et al., 2003).

DSP-4 is a relatively selective neurotoxin for both central and peripheral noradrenergic neurons (Jaim-Ethceverry and Zieher, 1980; Jaim-Etcheverry, 1998; Brus et al., 2004). The mechanism through which DSP-4 produces the above effect is not well understood. However, it is recognized that DSP-4 has selective affinity for the NE transporter to which it is bound, and then spontaneously cyclizes to an aziridinium derivative which alkylates the transporter (Ross et al., 1973). Because swollen noradrenergic fibers (i.e., tyrosine hydroxylase immunofluorescent axons) were seen in the hippocampus in the absence of electron microscopic changes and in the absence of silver degeneration staining of DSP-4-treated rats, it has been proposed that DSP-4 may produce a dysfunctional but not destructive effect on noradrenergic neurons (Booze et al., 1988). However, swollen axonal preterminals enriched in tyrosine hydroxylase or norepinephrine are a hallmark of nerve terminal degeneration (Jacobowitz and Kostrzewa, 1971), and there is newer evidence indicating that DSP-4 is neuronally destructive (Zhang et al., 1995). It appears that there are two phases in the response of noradrenergic axons to DSP-4 administration: an acute phase characterized by the precipitous loss of transmitter, and a neurodegenerative phase in which dopamine-β-hydroxylase is lost with accompanying structural damage (Fritschy et al., 1990). It must be added that DSP-4 in the central noradrenergic system induces permanent neurodestructive loss of NE-containing neurons (Jaim-Etcheverry, 1998; Brus et al., 2004).

DSP-4 injected in newborn rodents produces long term biochemical and morphological changes in the central noradrenergic system (Jaim-Etcheverry, 1998). In our laboratory we confirmed the above results on noradrenergic neurons following DSP-4 treatment (50 μg/kg SC per day) on the 1st and 3rd days of postnatal life (Brus et al., 2004). As shown in the present study, DSP-4 alters noradrenergic input to hippocampus and frontal cortex, without impairing dopaminergic and serotoninergic inputs into these regions or in the striatum.

Despite evidence of relatively selective effects of DSP-4 on the noradrenergic system in brain, the present findings indicate

that an enhanced quinpirole behavioral response to quinpirole in primed rats was attenuated by ontogenetic DSP-4 treatment — as our preliminary findings had indicated (Brus et al., 2004; Labus et al., 2004; Nowak et al., 2004). In summary, because intact central noradrenergic innervation is important for expression of a priming response, it appears that noradrenergic systems are important regulators of dopaminergic systems in brain. The effectiveness of atomoxetine, a selective norepinephrine reuptake-inhibitor for treatment of hyperactivity, may be dependent, at least in part, on such a noradrenergic–dopaminergic modulatory interaction.

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