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Short communication

Effects of prazosin on the dopaminergic neurotransmission in rat brain

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Abstract

Effects of systemic and local administration of prazosin, an α_1-adrenoceptor antagonist, on dopaminergic neurotransmission in the caudate putamen and nucleus accumbens were characterized in microdialysis experiments. Prazosin (10 mg/kg s.c.) resulted in blood pressure reduction, however, did not alter dopamine release in the two examined brain areas. In contrast, local administration of prazosin (10 μM) via the microdialysis probe resulted in a clear attenuation of dopamine output, indicating that tonically activated α_1-adrenoceptors stimulate dopamine release in the caudate putamen as well as in the nucleus accumbens. The relevance of this finding for antipsychotics exhibiting antagonism at α_1-adrenoceptors is discussed.

Keywords: α_1-Adrenoceptor; Blood pressure; Dopaminergic neurotransmission; Microdialysis; Prazosin

1. Introduction

Prazosin (Minipress) is a specific competitive α_1-adrenoceptor antagonist. Due to its peripheral α_1-adrenoceptor blocking action, the compound is used clinically in the treatment of hypertension (for a review see Reid and Vincent, 1986). In recently published congress abstracts the group of Maher (Yu et al., 1992; Acworth et al., 1993) claimed that hypotension affects central monoamine release in the striatum. The authors found that hypotension induced by either hydralazine or nitroprusside promoted striatal dopamine release (Yu et al., 1992; Acworth et al., 1993). To characterize the general sensitivity of dopamine measurements using microdialysis for blood pressure changes, the effects of prazosin were investigated in the caudate putamen and the nucleus accumbens. Animals were treated subcutaneously with 10 mg/kg prazosin, a dose leading to a decrease of blood pressure. For characterization of the local effects of prazosin in both brain areas, the drug was administered directly into the brain via the microdialysis probe. The concentration of prazosin in the perfusion medium was 10 μM. Using the latter experimental design only nerve cells in the vicinity of the implanted microdialysis probe were affected by the drug.

2. Material and methods

2.1. Test substances and solutions

Prazosin (obtained from Biotrend, Cologne, Germany) solutions were freshly prepared on every experimental day. For subcutaneous administration prazosin was solubilized in 50% (v/v) dimethyl sulfoxide (DMSO) solution, when administered locally prazosin was solubilized in DMSO and diluted with Krebs-Ringer solution resulting in a final concentration of 0.1% (v/v) DMSO.

2.2. Blood pressure measurements

Systolic blood pressure was measured in trained conscious rats by a noninvasive tail microphone technique. Each individual value represents the mean of triplicate measurements. For each treatment group 6–12 animals were used.

2.3. Microdialysis

Microdialysis and subsequent chemical analysis by high pressure liquid chromatography (HPLC) were

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performed essentially as described by Imperato and Di Chiara (1984) and Westerink et al. (1987) using a fully automated on-line sample injection system. For implantation of microdialysis probes (Carnegie Medicin/Axel Semrau, Sprockhövel, Germany) male Wistar rats (Winkelmann, Borchen, Germany) weighing 200–250 g were anesthetized with chloralhydrate (400 mg/kg i.p.). Probes with a 3 mm loop were used for the caudate putamen, while those implanted in the nucleus accumbens had 2 mm loops. Interaural line coordinates for the caudate putamen were frontal 9.2 mm, lateral 2.8 mm, and horizontal 6.0 mm, those for the nucleus accumbens were frontal 10.6 mm, lateral 1.4 mm, and horizontal 3.6 mm (Paxinos and Watson, 1982). All microdialysis perfusion experiments commenced 24 h after surgery with freely moving rats. The steel cannulae were connected by means of polyethylene tubing to a perfusion pump (Carnegie Medicin, Stockholm, Sweden) and to a sample loop (100 μl) of the electrically actuated injector (Latek, Eppelheim, Germany). The injector was set to remain in the load position for 18 min, and subsequently moved to the injection position for 2 min, after which the cycle was repeated. Microdialysis probes were perfused with Krebs-Ringer solution (128 mM NaCl, 5 mM KCl, 2.7 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 10 mM glucose, 20 mM Hepes, pH 7.4) at 3 μl/min. Dopamine was analyzed by HPLC in conjunction with electrochemical detection. Separation was achieved by using a mobile phase (75 mM Na-acetate, 0.5 mM *n*-octyl sulfate (Na^+ salt), 0.1 mM EDTA, 0.01% (v/v) dibutylamine, 10% (v/v) MeOH, pH 4.0) delivered by a pump (Waters, Eschborn, Germany) at 1.0 ml/min, and a C18 reversed phase stationary phase (250 × 4.6 mm, Nucleosil C18, 5 μm, M & W Chromatographie Technik, Berlin, Germany). Detection was accomplished by setting the glassy carbon working electrode at 700 mV against the Ag/AgCl reference electrode of the electrochemical detector (LC4B, BAS/Axel Semrau, Sprockhövel, Germany). The chromatograms were registered and processed by using a Turbochrom III chromatography software (Perkin Elmer/Axel Semrau, Sprockhövel, Germany). After receiving five similar values for the amount of dopamine in the dialysates, vehicle or prazosin was subcutaneously or locally administered. Results were expressed as percent of the mean of the respectively five pre-application (−80 to 0 min) values. Animal groups consisted of five or six animals.

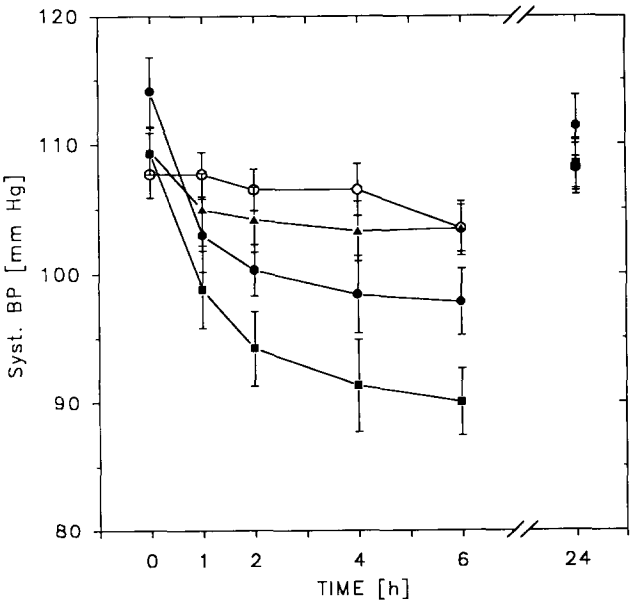

Fig. 1. Influence of subcutaneous administration of prazosin on systolic blood pressure. Measurements were performed in trained conscious rats by a noninvasive tail microphone technique. Each value represents the mean of triplicate measurements. Treatment groups consisted of 6 or 12 animals. Symboles are open circles for vehicle ($n = 6$), filled triangles for 3.15 mg/kg ($n = 6$), filled circles for 10 mg/kg ($n = 12$), and filled squares for 31.5 mg/kg prazosin ($n = 6$).

3. Results

3.1. Effects of subcutaneously administered prazosin on blood pressure and dopaminergic neurotransmission

Effects of prazosine on systolic blood pressure are shown in Fig. 1. Administration of vehicle solution did not affect blood pressure. In contrast, 4 h after drug administration, prazosin dose-dependently decreased blood pressure. Prazosin in doses of 3.15, 10, and 31.5 mg/kg s.c., resulted in blood pressure reductions of 6, 16, and 18 mm Hg, respectively. Maximal effect of blood pressure reduction was observed after 6 h; however, even 1 h after administration a reduction of blood pressure was observable.

For measuring dopamine release in the caudate putamen or the nucleus accumbens, microdialysis probes were implanted into both brain areas. After monitoring the extracellular levels of dopamine for 100 min, vehicle or prazosin was administered subcutaneously in a volume of 2 ml/kg. Vehicle administration did not result in a profound change in the content of dopamine in the caudate putamen, while a slight decrease was provoked in the nucleus accumbens (minimum 85% of pre-administration value). Very similar observations were made after administration of 10 mg/kg prazosin (Fig. 2).

3.2. Effects of locally administered prazosin on dopaminergic neurotransmission

For technical reasons blood pressure measurements were not performed in rats locally treated with pra-

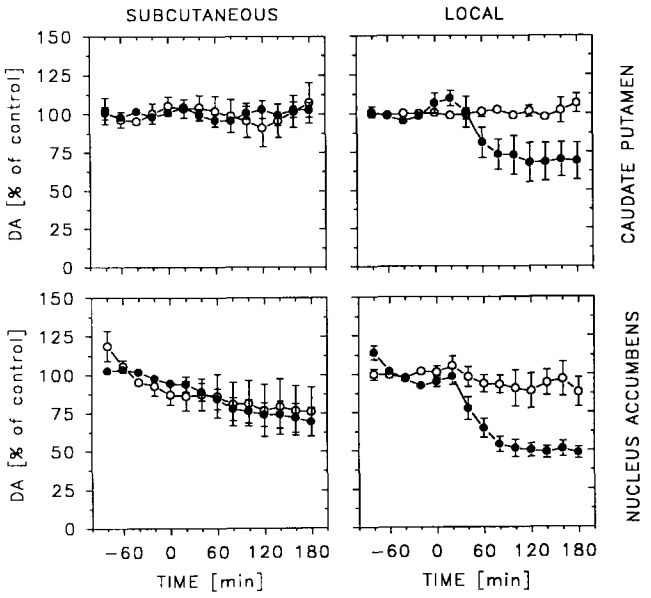

Fig. 2. Effects of subcutaneous (10 mg/kg) or local (10 μM) administration of prazosin (filled circles) or vehicle solution (open circles) on extracellular levels of dopamine in caudate putamen and nucleus accumbens of conscious freely moving rat. Each point represents the mean ± S.E.M. of 5 or 6 independent experiments.

zosin. However, from a general observation of the animals, no hint for a profound decrease of blood pressure was observed in this treatment group. Local administration of prazosin (10 μM) via the microdialysis probe into the caudate putamen or the nucleus accumbens resulted in a decrease of dopamine release. In the caudate putamen dopamine levels were reduced to about 70% of those before drug administration. The effect was maximal after about 2 h. In the nucleus accumbens the dopamine release attenuation was even more pronounced. Dopamine release was attenuated to about 50% of the level before drug administration. Again, the maximal effect was observed after about 2 h.

4. Discussion

4.1. Systemic administration of prazosin

Recent reports (Yu et al., 1992; Acworth et al., 1993) stated that dopamine release in the striatum is elevated after reduction of blood pressure by hydralazine or nitroprusside. To investigate whether blood pressure reduction is generally associated with increased dopaminergic neurotransmission, the effects of the hypotension-inducing drug prazosin were characterized in microdialysis experiments measuring the dopamine release in two rat brain areas. The results obtained in the first part of the present study (systemic administration of prazosin) indicate that reduction of blood pressure is not necessarily associated with an increase of striatal dopamine release in the caudate putamen (or the nucleus accumbens). Therefore, the increase of dopamine release by blood pressure reduction observed by the group of Maher (Yu et al., 1992; Acworth et al., 1993) might only be relevant for their special treatment regimen and the hypotension-inducing drugs used by them.

4.2. Local administration of prazosin

Local administration of prazosin via the microdialysis probe clearly decreased dopamine release. Besides achievement of higher brain levels of prazosin this administration route circumvents the possibility of an exclusion of the drug from the brain by the blood-brain barrier. The prazosin-induced dopamine release attenuation supports the hypothesis of the existence of a facilitative noradrenergic input to mesolimbic and nigrostriatal dopaminergic pathways. This hypothesis is based on the observation that noradrenergic mechanisms significantly modify locomotor activity and stereotypy, behaviors which are mediated by dopaminergic neurotransmissions in the nucleus accumbens and the caudate nucleus (Jackson et al., 1975; Kelly et al., 1975, Pijnenburg et al., 1976; Staton and Salomon, 1984). Noradrenaline containing neurons originating in the locus coeruleus give rise to a divergent and widespread innervation of the rat central nervous system, including dopamine-rich regions (Jones and Moore, 1979; Simon et al., 1979). More direct evidence for the facilitatory influence of locus coeruleus noradrenergic neurons on dopamine release has been obtained in microdialysis studies showing that lesions of the locus coeruleus with either 6-hydroxydopamine or the noradrenergic neurotoxin DSP-4 resulted in reduced dopamine levels in the caudate nucleus and in the nucleus accumbens (Lategan et al., 1990, 1992). The results obtained in the present study support these findings and indicate that the stimulatory effects of noradrenaline on dopaminergic neurotransmission might be (at least partially) mediated via α_1-adrenoceptor.

The results obtained after local administration of prazosin are especially interesting from a psychopharmacological point of view, since psychoactive compounds having α_1-adrenoceptor antagonistic properties might influence dopaminergic neurotransmission by this property. Antagonism at the α_1-adrenoceptor is not uncommon for psychoactive compounds. Most of the currently used antipsychotics exhibit, besides antidopaminergic properties, also α_1-adrenoceptor antagonistic effects. This is especially the case for the atypical neuroleptic clozapine where this property might contribute to the unique pharmacological profile of this compound (Breier et al., 1993). Although α_1-adreno-

ceptor antagonism is generally associated with peripheral side effects, the present study reveals that α_1-adrenoceptors in the brain might be very interesting targets for pharmacological approaches to treat central nervous system (CNS) disorders. This might be at least true for those CNS disorders for which alterations of the dopaminergic neurotransmission are discussed. Further studies will be necessary to characterize the localization of the α_1-adrenoceptors, as well as to determine which α_1-adrenoceptor subtype(s) is (are) involved in the modulation of dopamine release.

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