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Ipsapirone enhances the dopamine outflow via 5-HT_{1A} receptors in the rat prefrontal cortex

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Abstract

In the present study, we investigated both the effect of ipsapirone on the dopamine outflow and its selectivity towards 5-HT_{1A} receptors in the rat prefrontal cortex. Using a brain microdialysis method in freely moving animals, it was found that ipsapirone, 5 and 10 mg/kg dose-dependently enhanced the outflow of dopamine, while 2.5 mg/kg was ineffective. The above effects of ipsapirone were mimicked by buspirone (2.5 and 5 mg/kg), another 5-HT_{1A} receptor agonist, but not 1-PP (1-pyrimidinylpiperazine, 5 mg/kg) – a centrally active metabolite of ipsapirone. The effect of ipsapirone (10 mg/kg) on the dopamine outflow in the rat prefrontal cortex was antagonized by 1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine (NAN-190, 1 mg/kg) and (*N*-tert-butyl-3-(4-(2-methoxyphenylpiperazin-1-yl)-2-phenylpropionamide (WAY 100135, 10 mg/k.g.), i.e. substances with agonistic/antagonistic and antagonistic properties in relation to 5-HT_{1A} receptors, respectively. NAN-190 (1 mg/kg) enhanced the outflow of dopamine, while WAY 100135 (10 mg/kg) failed to alter it. It is concluded that 5-HT_{1A} receptor agonists may be involved in the regulation of dopaminergic neurotransmission in the rat prefrontal cortex and may have therapeutic potential in the treatment of disorders associated with dysfunction of the mesocortical dopaminergic system.

Keywords: Dopamine; Cortex, prefrontal; 5-HT_{1A} receptor; Ipsapirone; WAY 100135; NAN-190; Microdialysis

1. Introduction

It has been reported that drugs operating via 5-HT_{1A} receptors may be involved in the regulation of dopaminergic neurotransmission in the mesolimbic and mesocortical dopaminergic systems. Specifically, it was shown that 8-hydroxy-dipropylaminotetralin (8-OH-DPAT), an agonist of 5-HT receptors belonging to the class of 5-HT_{1A} receptors (Van Wijngaarden et al., 1990) enhanced the outflow of dopamine as measured by brain micorodialysis in the rat prefrontal cortex (Rasmusson et al., 1994; Tanda et al., 1994). Moreover, it was found that 8-OH-DPAT enhanced the burst activity of dopaminergic neurons, especially those localized in the rat ventral tegmental area (Arborelius et al., 1993), i.e. the type of neuronal activity of dopaminergic neurons that was predominantly linked to the release of dopamine from its terminals (Gonon and Buda, 1985).

The above data seem to indicate that drugs operating via 5-HT_{1A} may be involved in the regulation of dopaminergic neurotransmission and, consequently, may have a clinical potential in the treatment of disorders associated with such dysfunctions of the dopaminergic neurotransmission as depression (Wędzony and Gołembiowska, 1993; Tanda et al., 1994), withdrawal syndrome (Gonon and Buda, 1985; Goldstein and Deutch, 1992; Deutch, 1993) fear (Rasmusson et al., 1994) and, possibly, responsiveness of animals to stress (Deutch et al., 1985, 1987, 1990). In the context of the above data and their possible clinical consequences, we thought that it might be of interest to extend the number of 5-HT_{1A} receptor agonists and to find out whether they were capable of altering dopaminergic neurotransmission as was already found for 8-OH-DPAT and buspirone (Rasmusson et al., 1994; Tanda et al., 1994). We chose the prefrontal cortex for the present study, since the electrophysiological and microdialysis studies mentioned above showed that dopaminergic neurons and terminals within the mesocortical dopaminergic system are more sensitive to the effects of 5-HT_{1A} receptor agonists than are other dopaminergic neurons (Arborelius

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et al., 1993; Tanda et al., 1994). A set of experiments was aimed at determining whether the observed effects of ipsapirone on dopaminergic neurotransmission in the rat prefrontal cortex were selective in their activation of 5-HT_{1A} receptors. For the above reasons, we investigated the effect of ipsapirone on dopaminergic neurotransmission in rats pretreated with WAY 100135, a novel and highly selective 5-HT_{1A} receptor antagonist (Fletcher et al., 1993; Lanfumey et al., 1993; Rhodes et al., 1993) and NAN-190 which – despite its agonistic-antagonistic properties in relation to 5-HT_{1A} receptors – is capable of differentiating between various 5-HT receptors (Deans et al., 1989; Chojnacka-Wójcik and Przegaliński, 1991; Rydelek Fitzgerald et al., 1990). All the experiments were performed on freely moving rats and a brain microdialysis method was used. Doses of ipsapirone and buspirone were chosen from experiments which had shown their anxiolytic and antidepressant properties, respectively (Przewłocka et al., 1990; Söderpalm and Engel, 1990; Chojnacka-Wójcik and Przegaliński, 1991; Sommermeyer et al., 1993).

2. Materials and methods

2.1. Animals

All the experiments were carried out on Wistar male rats weighing 200–250 g at the time of surgery. After delivery, the rats were allowed to become accustomed to the experimental room for at least 10 days and were kept in groups of 5/cage in the room at constant temperature with an artificial 12–12-h light–dark cycle (light on from 07:00 h until 19:00 h). All the experiments were performed between 09:00 h and 17:00 h. The rats had free access to standard laboratory food (LSM, Bacutil) and tap water.

2.2. Brain microdialysis

In in vivo microdialysis studies (for details, see Wędzony et al., 1994), the rats were anaesthetized with chloral hydrate (400 mg/kg i.p.) and fixed in a stereotaxic apparatus (David Kopf). Transcortical dialysis probes, prepared according to Imperato and Di Chiara (1985) (o.d. 0.2 mm, length 6 mm, molecular cutoff weight – 50 000), were implanted under stereotaxic control into the rat prefrontal cortex (prefrontal cortex and parts of frontal and sensorimotor cortices, cingulate cortex). The following coordinates, selected according to the Paxinos and Watson (Paxinos and Watson, 1986) stereotaxic atlas and to pilot studies, were used A: 3.2 mm; H: 2.8 mm from the surface of the skull. After implantation, the dialysis probes were attached to the skull with dental acrylic cement and the rats were left to recover. At 24 h after surgery, the rats were placed in plastic circular jars (35 cm in diameter) and the dialysis probes were attached to the Hamilton syringe held by a superfusion pump (Carnegie) with polyethylene tubing and a liquid swivel (Carnegie). The Ringer solution (NaCl 146.2 mM, KCl 4 mM, $CaCl_2 \times 2H_2O$ 2.4 mM; pH 7.2) was pumped at a constant rate of 2 μl/min. After approximately 2 h, when dopamine release had become stable (at least 3 consecutive samples differing by less than 10%) perfusates were collected every 25 min from microvials suspended on the inflow tubing and were immediately injected on the HPLC (high-performance liquid chromatography) column.

For measurement of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) a standard HPLC technique with electrochemical detection was used (BAS 400; detector BAS-LC-4B). The compounds were separated on a small bore column (ODS, Phase II, particle size 3 μm, 3.2/100 mm; BAS) and a mobile phase, consisting of 0.06 M citrate-phosphate buffer, pH 3.5, 0.27 mM EDTA, 0.32 mM sodium octyl sulphonate and 2.4% methanol, was used. The flow rate was set at 0.8 ml/min. The oxidation potential, measured vs. the reference Ag/AgCl electrode, was set at 0.65 V. In order to enhance the sensitivity of the detection system, the temperature of the detection cell was kept at 38°C and a dual glossy carbon electrode operating in the parallel mode was used in order to double the surface electrode. In order to reduce noise, a Shimadzu LC 10AD double-piston HPLC pump was applied. At the end of the experiment, the localization of each dialysis probe was identified histologically (Fig. 1). The mean dopamine concentration (pg/20 μl) in 3 consecutive fractions, preceding any pharmacological manipulation, was accepted as basal release. All the results are expressed as percentages of the basal release ± S.E.M.

2.3. Drugs and statistics

Buspirone (HCl) and NAN-190 (1-(2-methoxyphenyl)-4-[4-(2-phthalimido)butyl]piperazine, HBr) were purchased

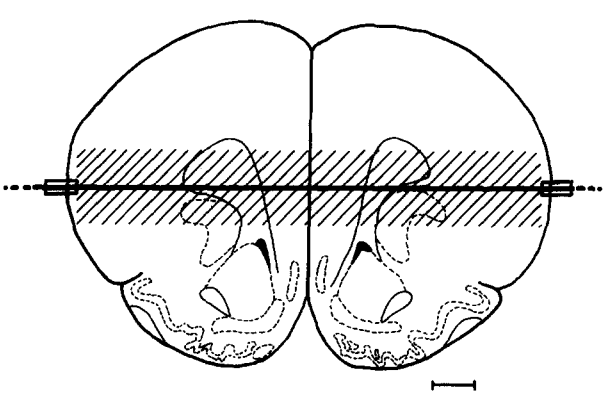

Fig. 1. Schematic representation of the placement of the transversal dialysis probe. The dashed area indicates the brain regions in which the majority of probes were found. When probes were outside the above regions, the data were not included. Planes according to the Paxinos and Watson stereotaxic atlas (Paxinos and Watson, 1986): interaural 11.7 mm, bregma 2.7 mm, scale bar 1 mm.

from RBI (USA); ipsapirone (HCl, was a gift of Troponwerke (Germany); WAY 100135 ((*N*-tert-butyl-3-(4-(2-methoxyphenylpiperazin-1-yl)-2-phenylpropionamide, HCl) and 1-PP (1-pyrimidinylpiperazine) were synthesized in Department of Chemistry of the Institute of Pharmacology, Polish Academy of Sciences. The drugs were given to rats in a vol. of 2 ml/kg body weight. All the other reagents were of HPLC grade and were purchased from Merck (Darmstad) or Sigma (Louisville).

In the brain microdialysis experiment, the data were expressed as percentages of the basal release found in three consecutive fractions before drug administration. The data were evaluated statistically by two-way analysis of variance (time vs. treatment), followed by the Dunnett test.

3. Results

3.1. Effects of ipsapirone and buspirone on the dopamine outflow

It was found that ipsapirone given in doses of 5 and 10 mg/kg enhanced the dopamine outflow in prefrontal cortex, whereas its 2.5 mg/kg dose was ineffective (Fig. 2). Similar effects were observed after administration of another agonist of 5-HT_{1A} receptors, buspirone (2.5 and 5 mg/kg) (Fig. 3). The effects of ipsapirone and buspirone on the dopamine outflow were followed by an increase of DOPAC and HVA concentrations, measured in superfusates (data not shown). The effects of ipsapirone (10, 5 mg/kg) and buspirone (2.5 and 5 mg/kg) on concentrations of DOPAC and HVA were well-correlated with changes in the dopamine outflow after the drugs tested (correlation coefficients were, respectively, 0.95, 0.98 and 0.98 for ipsapirone (5 and 10 mg/kg) and buspirone (5 mg/kg, data not shown). 1-PP (5 mg/kg) was without any effect on the dopamine outflow (Fig. 4).

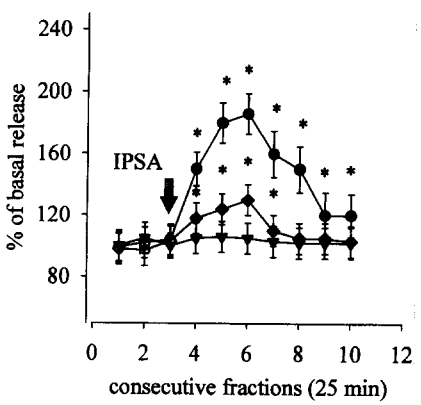

Fig. 2. The effects of the 5-HT_{1A} receptor agonist, ipsapirone (IPSA, 2.5, 5 and 10 mg/kg), on the outflow of dopamine in the rat prefrontal cortex. The data are shown as percentages of the basal release (mean ± S.E.M.); $n = 5–9$ animals in each group. Circles, IPSA 10 mg/kg; diamonds, IPSA 5 mg/kg; triangles, IPSA 2.5 mg/kg; open symbols, basal outflow. Arrow indicates time of drug administration. Asterisks indicate statistically significant differences between the effects observed after administration of ipsapirone and the basal outflow (open symbols). $P < 0.05$, Dunnett's test as a posthoc test after a two-way ANOVA (time vs. treatment).

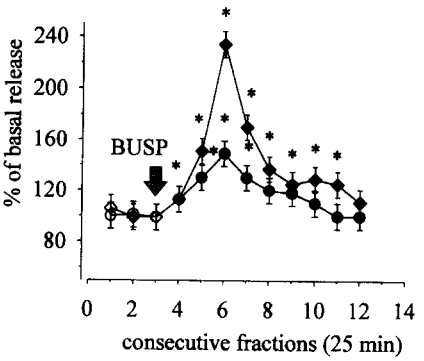

Fig. 3. The effects of the 5-HT_{1A} receptor agonist, buspirone (BUSP, 2.5 and 5 mg/kg), on the outflow of dopamine in rat prefrontal cortex. The data are shown as percentages of the basal release (mean ± S.E.M.); $n = 4–7$ animals for each group. Diamonds, buspirone 5 mg/kg; circles, 2.5 mg/kg. Open symbols, basal outflow. The time of drug administration is indicated by an arrow. Asterisks indicate statistically significant differences between the effects observed after administration of buspirone and the basal outflow (open symbols). $P < 0.05$, Dunnett's test, as a posthoc test after a two-way ANOVA (time vs. treatment).

3.2. Effects of NAN-190 and WAY 100135 on the ipsapirone-evoked alterations in dopamine outflow

NAN-190 in a dose of 1 mg/kg enhanced the dopamine outflow; that effect was followed by an increase in the DOPAC and HVA concentrations in superfusates (Fig. 5, left panel). In contrast to NAN 190, WAY 100135 (10 mg/kg) failed to alter the dopamine outflow (Fig. 5, right panel). WAY 100135 (10 mg/kg) and NAN-190 (1 mg/kg) antagonized the outflow of dopamine evoked by ipsapirone (10 mg/kg) (Fig. 5, left and right panel, respectively). The latter antagonistic effects were seen on both

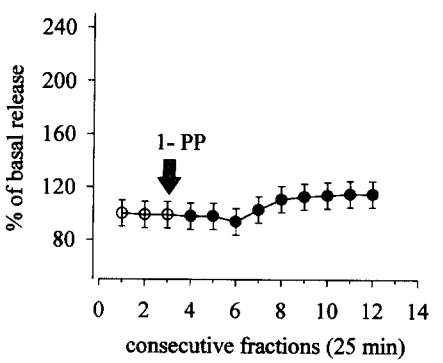

Fig. 4. The effects of 1-PP, an active metabolite of ipsapirone (5 mg/kg) on the outflow of dopamine in the rat prefrontal cortex. For further details, see Fig. 1 or Fig. 2.

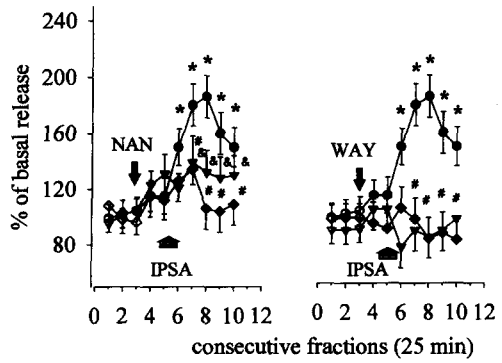

Fig. 5. The influence of NAN-190 and WAY 100135 on the alterations in the dopamine outflow evoked by ipsapirone. Left panel: NAN-190 (NAN; 1 mg/kg) was given 50 min (two fractions) before ipsapirone (IPSA; 10 mg/kg). Right panel: WAY 100135 (WAY; 10 mg/kg) was given 50 min (two fractions) before ipsapirone (IPSA; 10 mg/kg). Circles, vehicle and IPSA; diamonds, effects of IPSA on NAN- or WAY-pretreated animals (left and right panels, respectively); triangles, effects of NAN or WAY on vehicle-pretreated animals (left and right panels, respectively); The data are shown as percentages of the basal release (mean ± S.E.M.); $n = 8$ animals for each group. The time of drug administration is indicated with arrows. Asterisks indicate statistically significant differences between the effects observed after administration of ipsapirone in comparison to the basal outflow (open and filled circles); # differences between effects observed in vehicle + IPSA- and NAN + IPSA/WAY + IPSA-treated rats (left and right panels, respectively); and α differences between the effects observed after administration of NAN and the basal outflow; $P <$ at least 0.05; Dunnett's test as a posthoc test, after a two-way ANOVA (time vs. drug effect).

dopamine outflow and changes in the DOPAC and HVA concentrations (data not shown).

4. Discussion

Our present results indicated that 5-HT_{1A} receptor agonists, such as ipsapirone and buspirone, are capable of enhancing the outflow of dopamine in the rat prefrontal cortex, which suggests that the above drugs may enhance dopaminergic neurotransmission in the rat prefrontal cortex. The doses of ipsapirone and buspirone that effectively enhance dopaminergic neurotransmission have been found to be effective in experiments showing their antidepressant and anxiolytic properties (Przewłocka et al., 1990; Söderpalm and Engel, 1990; Chojnacka-Wójcik and Przegaliński, 1991; Wetzler et al., 1991; Sommermeyer et al., 1993), thus, it is conceivable that the enhanced dopaminergic tone in the rat prefrontal cortex might be linked with these drugs' therapeutic potential observed in experimental animals.

In the case of ipsapirone, we found that its effect was specific for activation of 5-HT_{1A} receptors, since the effects of ipsapirone were antagonized by NAN-190 and WAY 100135. The ability of WAY 100135 to antagonize the effect of ipsapirone seems to be of special importance, since it has been found that this drug is pure and highly selective 5-HT_{1A} receptor antagonist (Fletcher et al., 1993; Lanfumey et al., 1993; Rhodes et al., 1993). Although our experiments with 5-HT_{1A} receptor antagonists indicated that the observed effects were selective for 5-HT_{1A} receptors it was noteworthy that almost all 5-HT_{1A} receptor agonists, including 8-OH-DPAT, gepirone, buspirone and ipsapirone, displayed a nanomolar affinity for dopamine D_2 receptors expressed in Chinese hamster ovary-K1 cells, labelled with the dopamine D_2 receptor agonist, U-86172 (Piercey et al., 1994). In spite of the fact that such a high affinity of the above agonists has not been reported from dopamine receptor antagonist binding studies on membranes of the rat brain (Van Wijngaarden et al., 1990), the potent antagonistic properties of the above mentioned 5-HT_{1A} receptor agonists can also be seen in a functional test as their ability to antagonize the amphetamine-induced suppression of the firing rate of dopaminergic neurons in the pars compacta of the substantia nigra (Piercey et al., 1994). Thus, it has to be kept in mind that, in addition to blockade of the 5-HT_{1A} receptors, that of dopamine D_2 receptors has to be considered as a mechanism of the ipsapirone- and buspirone-induced enhancement of dopamine release. It seems of importance to determine whether 5-HT_{1A} antagonists, such as WAY 100135, are capable of altering the dopamine outflow enhanced by typical and atypical neuroleptics.

Since ipsapirone is metabolized to 1-PP, an active metabolite which is centrally effective, by activation of α_2-adrenoceptors (Nocoń et al., 1990), we also investigated whether it was capable of altering the dopamine outflow. However, when 1-PP was administered to rats in doses which lead to central concentrations similar to those seen after metabolism of ipsapirone 10 mg/kg (Nocoń et al., 1990) it fails to alter the outflow of dopamine, proving that the effect of ipsapirone does not result from the appearance of its centrally active metabolite.

We also have observed that NAN-190 and WAY 100135 given alone influence differentially dopaminergic neurotransmission in the prefrontal cortex. NAN-190 enhances dopamine outflow, while WAY 100135 is ineffective. Two previous findings may account for the above differences. First, NAN-190 has agonistic/antagonistic properties (Deans et al., 1989; Rydelek Fitzgerald et al., 1990; Boddeke et al., 1992), hence it is conceivable that it may display some effects typical of those of agonists, such as ipsapirone or buspirone, as regards dopamine outflow. Such agonistic properties of NAN-190 have also been observed in behavioral studies (Rydelek Fitzgerald et al., 1990). Second, in spite of its ability to differentiate between 5-HT receptors NAN-190 has α_1-adrenolytic activity (Van Wijngaarden et al., 1990). However, this latter mechanism cannot account for the dopamine releasing properties, since the enhancement of mesocortical dopaminergic neurotransmission evoked by stimulation of the locus coeruleus is antagonized by prazosin (Grenhoff et al., 1993).

In general, our present data extend some earlier reports which indicate that drugs operating via 5-HT_{1A} receptors might enhance dopaminergic neurotransmission in the rat prefrontal cortex. Functional meaning of the above phenomenon is not clear as yet. It is also not clear whether functional consequences might be linked with the observations that prefrontal cortex is involved in the pathogenesis of schizophrenia and depression (Goldstein and Deutch, 1992; Deutch, 1993; Tanda et al., 1994; Wędzony and Gołembiowska, 1993). Interestingly, it has been found that antidepressant drugs, such as desipramine and fluoxetine, enhance the outflow of dopamine in prefrontal cortex (Carboni et al., 1990; Tanda et al., 1994; Wędzony and Gołembiowska, 1993) and, thus, exert effects similar to those of ipsapirone, which has also been shown to possess not only anxiolytic but also antidepressant properties (Wetzler et al., 1991). It is also important to note that negative symptoms of schizophrenia are linked with hypofunction of the mesocortical dopaminergic system; hence drugs operating via 5-HT_{1A} receptors may also have some positive effects. Nonetheless, the above hypothesis should be put forward carefully, since 5-HT_{1A} receptor agonists, including 8-OH-DPAT, gepirone and ipsapirone, influence sensorimotoric gating in rats (Rigdon and Weatherspoon, 1992). However, in spite of this limitation, 5-HT_{1A} receptor agonists seem to display an interesting mode of action on dopaminergic neurotransmission, since 5-HT receptors of the 5-HT_{1A} subtype are not present in the striatum and nucleus accumbens but are present in prefrontal cortex in relatively high concentrations as was shown by autoradiographic and in situ hybridization studies (Miquel et al., 1992; Chalmers and Watson, 1991). Thus, 5-HT_{1A} receptor agonists are capable of modifying dopaminergic neurotransmission in the cortex but do not exert direct effects in the nucleus accumbens or striatum where their effects – if present – should only be a consequence of activation of cortical/hippocampal 5-HT_{1A} receptors.

The mesolimbic and mesocortical dopaminergic systems comprise major components of the neuronal circuit of incentive motivation which seems to be impaired in the state of depression (Carboni et al., 1990; Tanda et al., 1994; Wędzony and Gołembiowska, 1993), in schizophrenia (Goldstein and Deutch, 1992; Deutch, 1993) or withdrawal of addictive substances (Koob and Bloom, 1988; Nestler, 1992). On the basis of the finding that ipsapirone and buspirone enhance dopaminergic neurotransmission in the rat prefrontal cortex, which seems to be diminished in the process of schizophrenia and to be responsible for its negative symptoms (Deutch, 1993), it might be speculated that ipsapirone and other 5-HT_{1A} receptor agonists may, at least theoretically, possess some antipsychotic properties. Speculation about possible clinical effects of ipsapirone in the rat prefrontal cortex gains support from data which show that ipsapirone is capable of altering alcohol intake (Svensson et al., 1993, Wilde and Vogel, 1994) and neurotoxic effects of cocaine (Akbari et al., 1994), i.e. effects that may be directly associated with alterations in dopaminergic neurotransmission. Since dopaminergic neurotransmission in the subcortical dopaminergic structure is attenuated by enhancement of dopamine release in the prefrontal cortex it may be also assumed that our data offer an alternative mechanism which accounts for the antiaddictive effects of ipsapirone (Grace, 1993; Mitchell and Gratton, 1992; Olds, 1990).

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