ELSEVIER

European Journal of Pharmacology 361 (1998) 27–33

ejp

Antipsychotic drugs induce similar effects on the release of dopamine and noradrenaline in the medial prefrontal cortex of the rat brain

Ben H.C. Westerink [a,*], Peter de Boer [a], Jan B. de Vries [a], Chris G. Kruse [b], Steve K. Long [b]

[a] *University Center for Pharmacy, Department of Medicinal Chemistry, Deusinglaan 1, 9713AV Groningen, Netherlands*
[b] *Solvay Pharmaceuticals, Department of CNS Pharmacology, P.O. Box 900, 1380 DA Weesp, Netherlands*

Received 18 June 1998; revised 21 September 1998; accepted 29 September 1998

Abstract

In the present study we have compared the effects of the classical antipsychotic drug haloperidol and four different atypical antipsychotics (clozapine, risperidone, olanzapine, ziprasidone) on extracellular levels of dopamine and noradrenaline in the medial prefrontal cortex (MPFC) of conscious rats. Haloperidol (10, 100 and 800 nmol/kg), clozapine (0.3, 1, 10 and 30 μmol/kg), risperidone (100 500 and 5000 nmol/kg), olanzapine (10, 100 and 500 nmol/kg) and ziprasidone (10, 100 and 1000 nmol/kg) were administered subcutaneously to rats. All compounds induced increases in dialysate levels of dopamine and noradrenaline in the medial prefrontal cortex. The increases induced by the four antipsychotic agents in extracellular levels of dopamine and noradrenaline displayed a striking co-variation both in dose and time. A similar co-variation was seen in the decrease of dopamine and noradrenaline, after administration of a low dose (30 nmol/kg, s.c.) of the dopamine $D_{2/3}$ receptor agonist (+)-7-hydroxy-2-(*N*,*N*-di-*n*-propylamino) tetralin ((+)-7-OH-DPAT). It is concluded that there is a close coupling between the release of dopamine and noradrenaline in the medial prefrontal cortex. The mechanism of action of this interaction, that might be of importance for a better understanding of the mechanism of action of antipsychotic drugs, is discussed.

Keywords: Antipsychotic; Frontal cortex; Microdialysis; Noradrenaline; Dopamine

1. Introduction

A common property of most if not all antipsychotic drugs is the capacity to increase the release of dopamine in various forebrain regions (Carlsson and Lindqvist, 1963; Imperato and Di Chiara, 1984; Volonté et al., 1997). This effect is traditionally explained by a negative feedback receptor response that is triggered by blockade of presynaptic D_2 dopamine receptors. There is evidence that this mechanism acts at the level of the dopaminergic nerve terminals (Di Chiara et al., 1977; Westerink and DeVries, 1989), although somatodendritic autoreceptors may also play a certain role (Westerink et al., 1996).

Antipsychotic drugs are clinically divided in two groups: the typical neuroleptics that induce extrapyramidal effects and the atypical neuroleptics that cause relatively few of these side-effects. For more than two decades clozapine has been the classical example of an atypical antipsychotic drug. Recently several atypical antipsychotics been developed and drugs such as risperidone, olanzapine, seroquel, sertindone, amperozide en ziprasidone are now available as possible alternatives for the traditional neuroleptic treatment of psychosis.

The two groups of antipsychotic agents can also be divided pharmacologically. There is increasing evidence that the antipsychotic activity of these agents is correlated with stimulation of the release of dopamine from mesolimbic-mesocortical dopamine neurons localized in the nucleus accumbens shell and medial prefrontal cortex, whereas the extrapyramidal side effect correlate with activation of nigrostriatal dopamine neurons (Moghaddam and Bunney, 1990; Nomikos et al., 1994; Hertel et al., 1996; Marcus et al., 1996; Stockton and Rasmussen, 1996; Volonté et al., 1997).

* Corresponding author. Tel.: +31-50-3633307; Fax: +31-50-3636908; E-mail: westerink@farm.rug.nl

0014-2999/98/$ - see front matter
PII: S0014-2999(98)00711-0

The dopamine neurons that project to the medial prefrontal cortex receive increasing attention, as the medial prefrontal cortex is a prominent structure in humans and probably an important target area for the antipsychotic drugs that are used to treat schizophrenia. Noradrenergic and dopaminergic projections converge in the medial prefrontal cortex and there is growing evidence of an interaction between dopaminergic and noradrenergic terminals in this region (Carboni et al., 1990; Tassin et al., 1992; Tanda et al., 1994; Gresch et al., 1995). However, the mechanism and regional specificity of the dopamine–noradrenaline interaction in the medial prefrontal cortex is at present far from clear.

To investigate further the relation between extracellular noradrenaline and dopamine in the medial prefrontal cortex, the effects of five different antipsychotics were studied. We have compared the effect of the classical antipsychotic drug haloperidol and four atypical antipsychotics (clozapine, risperidone, olanzapine, ziprasidone) on extracellular levels of both dopamine and noradrenaline in the medial prefrontal cortex of conscious animals.

After administration of five structurally different antipsychotic compounds it became evident that extracellular dopamine and noradrenaline in the PFC displayed a striking co-variation. A similar co-variation was seen in the decrease of dopamine and noradrenaline, after administration of a low dose of the dopamine $D_{2/3}$ receptor agonist (+)-7-hydroxy-2-(*N*,*N*-di-*n*-propylamino)tetralin ((+)-7-OH-DPAT). The mechanism of action of this interaction, that might be of importance for our understanding of the mechanism of action of antipsychotic pharmacotherapy, is discussed.

2. Materials and methods

2.1. Animals, drug treatment, and doses

Male albino rats of a Wistar-derived strain (275–320 g; Harlan, Zeist, The Netherlands) were used for the experiments. The rats were housed in plastic cages ($35 \times 35 \times 40$ cm^3) with light from 0700 h till 1900 h and had free access to food and water. After probe implantation and during the experiments the rats were individually housed in a plastic cage ($30 \times 30 \times 30$ cm^3). Experiments were carried out in the light cycle.

The following drugs were used: haloperidol and clozapine (Research Biochemicals International, Natick, MA, USA), olanzapine (kindly donated by Eli Lilly, Indianapolis, USA), risperidone (kindly donated by Janssen Pharmaceuticals, Beerse, Belgium) and ziprasidone (kindly donated by Pfizer, Groton, CT, USA). *R*-(+)-7-OH-DPAT was synthesized by Dr. D. Dijkstra in our Institute by known methods.

The experiments were approved by the Animal Care Committee of the Faculty of Mathematics and Natural Science of the University of Groningen.

2.2. Surgery and brain dialysis

Microdialysis was performed with home-made I-shaped cannulas. The dialysis tube was prepared from polyacrylonitrile/sodium methalyl sulfonate copolymer (ID: 0.22 mm; OD: 0.31 mm; AN 69, Hospal, Bologna, Italy). Coordinates of the probe-implantation were: A/P 3.0, L/M 1.2, and V/D −5.0; from bregma point and dura, respectively. The probes were implanted during general chloralhydrate anaesthesia (400 mg/kg, i.p.) and local application of lidocaine (10%).

Microdialysis experiments were carried out 24 h after implantation of the probes. An on-line microdialysis approach was used in which the probes were perfused with a Ringer solution at a flow rate of 2.0 μl/min (CMA100 Infusion Pump, Carnegie, Stockholm, Sweden). Fifteen minutes fractions were collected. The composition of the

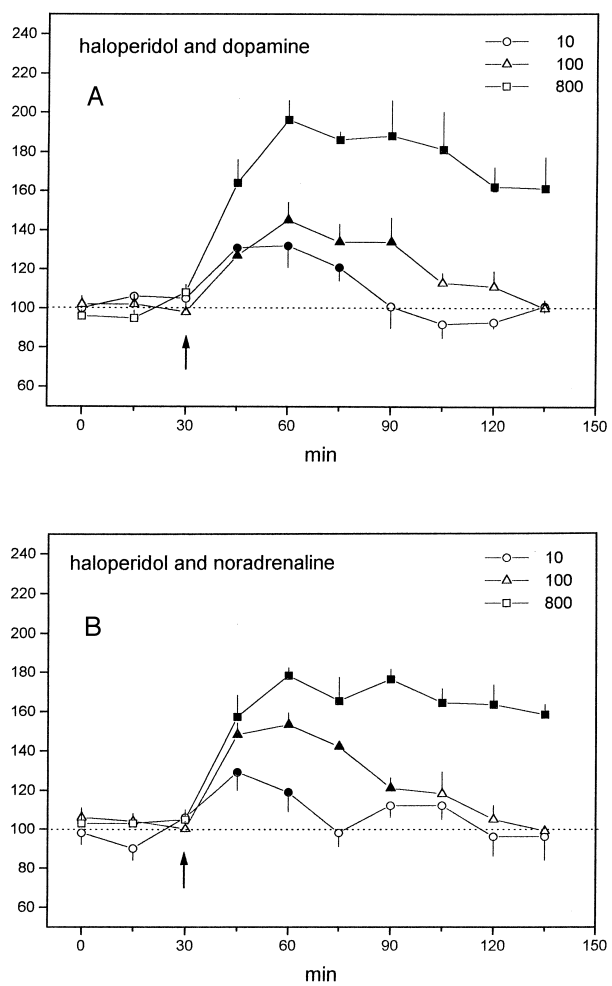

Fig. 1. Effect of haloperidol (10, 100 and 800 nmol/kg, s.c.) on the extracellular content of dopamine (A) and noradrenaline (B) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

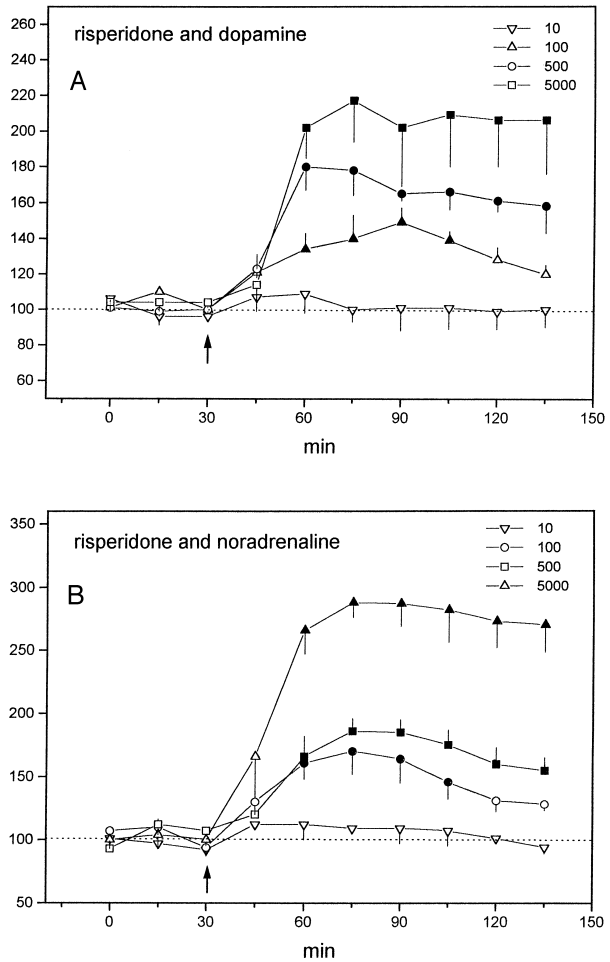

Fig. 2. Effect of risperidone (10, 100, 500 and 5000 nmol/kg, s.c.) on the extracellular content of dopamine (A) and noradrenaline (B) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

Ringer solution was (in mM): NaCl, 140.0; KCl, 4.0; $CaCl_2$, 2.4; and $MgCl_2$, 1.0.

When the experiment was terminated, the rat was given an overdose of chloral hydrate and the brain was fixed with 4% paraformaldehyde via intracardiac perfusion. Coronal sections (40 μm thick) were made, and dialysis probe placement was verified according to the atlas of Paxinos and Watson (1982).

2.3. Chemical assays

Noradrenaline and dopamine were simultaneously quantified by high performance liquid chromatography with electrochemical detection. A Shimazu pump (LC-10AD) was used in conjunction with an electrochemical detector (ESA). The potential of the first cell was set as +175 mV; the second cell as −250 mV. A reverse-phase column (150 × 4.7 mm^2, Supelco LC18; Belonte, PA) was used. The mobile phase consisted of a mixture of 0.1 M of sodium acetate adjusted to pH 4.1 with acetic acid, 1.8 mM octanesulfonic acid, 0.3 mM Na_2EDTA, and 120 ml/l methanol. The flow rate was 1.0 ml/min. The detection limit of the assay was about 2 fmol per sample (on-column).

2.4. Expression of results and statistics

All values given are expressed as percentages of controls ± S.E.M. The average concentration of three stable samples (less than 10% variation) before handling was considered as the control and was defined as 100%. Data were analyzed by a non-parametric repeated measurement One-way analysis of variance on ranks (Friedman's test), followed by the Dunnett's multiple comparisons test when appropriate. Individual time points of two time–effect

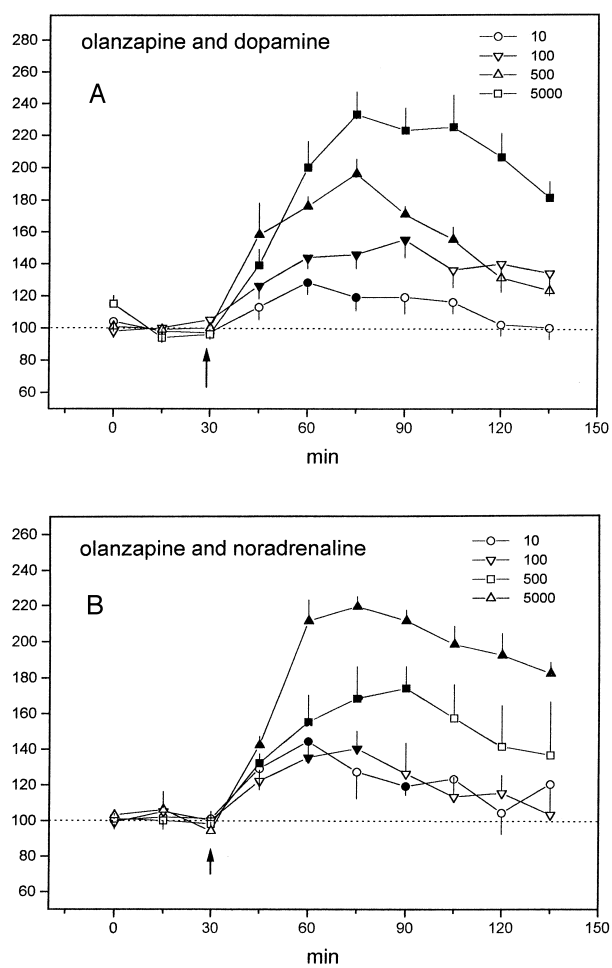

Fig. 3. Effect of olanzapine (10, 100, 500 and 5000 nmol/kg, s.c.) on the extracellular content of dopamine (A) and noradrenaline (B) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

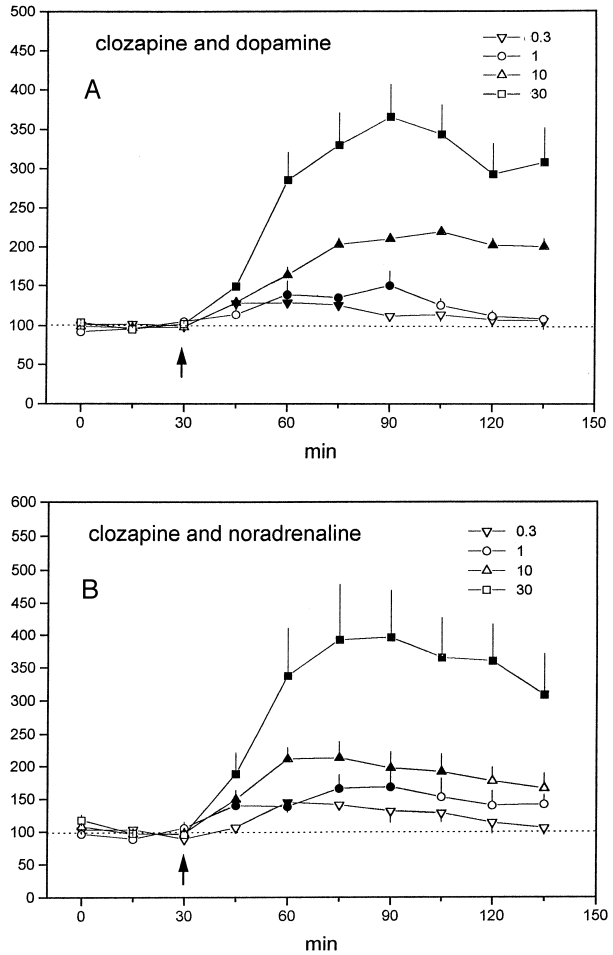

Fig. 4. Effect of clozapine (0.3, 1, 10 and 30 μmol/kg, s.c.) on the extracellular content of dopamine (A) and noradrenaline (B) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

curves were compared with the Mann–Whitney rank sum test. The level of significance was set at $p < 0.05$.

3. Results

3.1. Basal values

The basal values of noradrenaline and dopamine in dialysates of the medial prefrontal cortex from the different experiments did not differ. Therefore they are grouped here together. The mean basal value (± S.E.M.) was, for noradrenaline: 1.36 ± 0.04 fmol/min ($n = 75$) and for dopamine: 0.65 ± 0.05 fmol/min ($n = 78$).

3.2. Effects of haloperidol, clozapine, olanzapine, risperidone and ziprasidone on extracellular levels of dopamine and noradrenaline in the prefrontal cortex

Haloperidol was administered s.c. in three different doses (10, 100 and 800 nmol/kg) to rats. Fig. 1 shows that haloperidol increased the extracellular levels of both dopamine as well as noradrenaline. A dose of 800 nmol/kg induced an increase in both the dopamine as well as noradrenaline levels to about 180% of control values. Two hours after administration of the highest dose of haloperidol the extracellular levels of the two catecholamines were still significantly increased.

Risperidone was administered s.c. in four different doses (10, 100, 500 and 5000 nmol/kg) to rats. Fig. 2 shows that risperidone increased the extracellular levels of both dopamine as well as noradrenaline. The effect on noradrenaline was somewhat more pronounced (maximal effects about 280% of controls) than the effects on dopamine (maximal effects about 220% of controls); the time effect curve for dopamine and noradrenaline were very similar. Two hours after administration of the two highest doses of risperidone, the extracellular levels of the two catecholamines were still significantly increased.

Olanzapine was administered s.c. in four different doses (10, 100 and 500 and 5000 nmol/kg) to rats. Fig. 3 shows

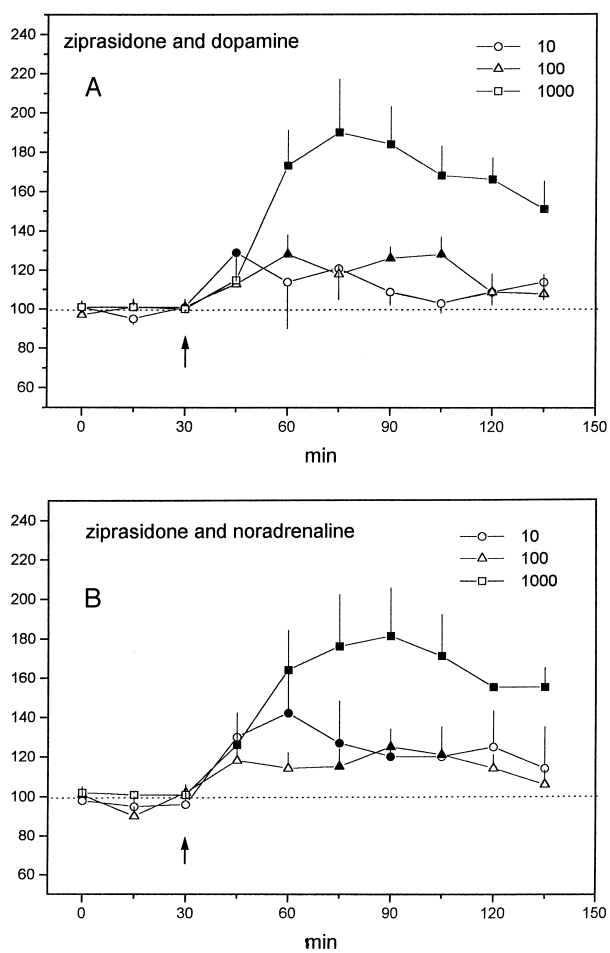

Fig. 5. Effect of ziprasidone (10, 100 and 1000 nmol/kg, s.c.) on the extracellular content of dopamine (A) and noradrenaline (B) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

that olanzapine increased the extracellular levels of both dopamine as well as noradrenaline. Both the dose–effect curve and the time effect curve for dopamine and noradrenaline were very similar. The highest dose increased the levels of the two catecholamines to about 220–230% of control values. Two hours after administration of the highest dose of olanzapine the extracellular levels of the two catecholamines were still increased.

Clozapine was administered s.c. in four different doses (0.3, 1, 10 and 30 μmol/kg) to rats. Fig. 4 shows that clozapine increased the extracellular levels of both dopamine as well as noradrenaline. Both the dose–effect curve and the time effect curve for dopamine and noradrenaline were very similar. The highest dose of clozapine (30 μmol/kg) induced increase in both the dopamine as well as noradrenaline levels up to 400% of controls; these increases were much larger than seen after the highest dose of haloperidol, risperidone and olanzapine.

Ziprasidone was administered s.c. in three different doses (10, 100 and 1000 nmol/kg) to rats. Fig. 5 shows that ziprasidone increased the extracellular levels of both dopamine as well as noradrenaline. Both the dose–effect curve and the time effect curve for dopamine and noradrenaline were very similar. The highest dose increased the levels of the two catecholamines to 180–190% of control values. Two hours after administration of the highest dose of ziprasidone the extracellular levels of the two catecholamines were still increased.

3.3. Effect of (+)-7-OH-DPAT on extracellular levels of noradrenaline and dopamine in the medial prefrontal cortex

To further investigate the involvement of $D_{2/3}$ dopamine receptors in the coupling between dopamine and noradrenaline release, the potent $D_{2/3}$ dopamine receptor agonist (+)-7-OH-DPAT was administered s.c. in a relatively low dose of 30 nmol/kg (Damsma et al., 1993). This dose of (+)-7-OH-DPAT reduced both extracellular levels of dopamine and noradrenaline in the medial prefrontal cortex to about 60–70% of controls (Fig. 6). Time curves of the effects were very similar. There was no clear effect on the behaviour of the animal; the rats remained their resting position after administration of the drug.

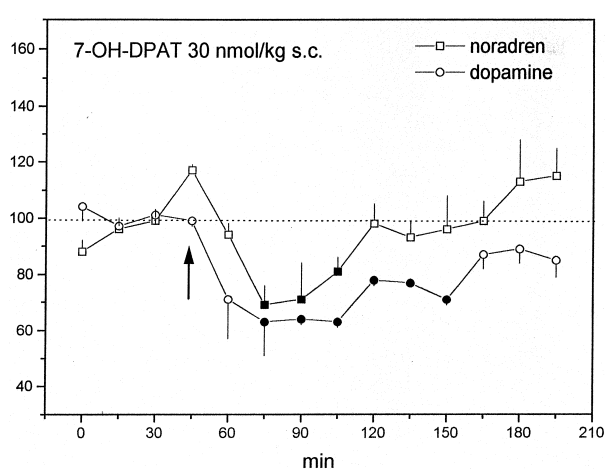

Fig. 6. Effect of 7-OH-DPAT (30 nmol/kg, s.c.) on the extracellular content of dopamine (circles) and noradrenaline (squares) in the medial prefrontal cortex. Values are expressed as percent of controls ± S.E.M. ($n = 4$–6). Closed circles are statistically significantly different from control values ($p < 0.05$).

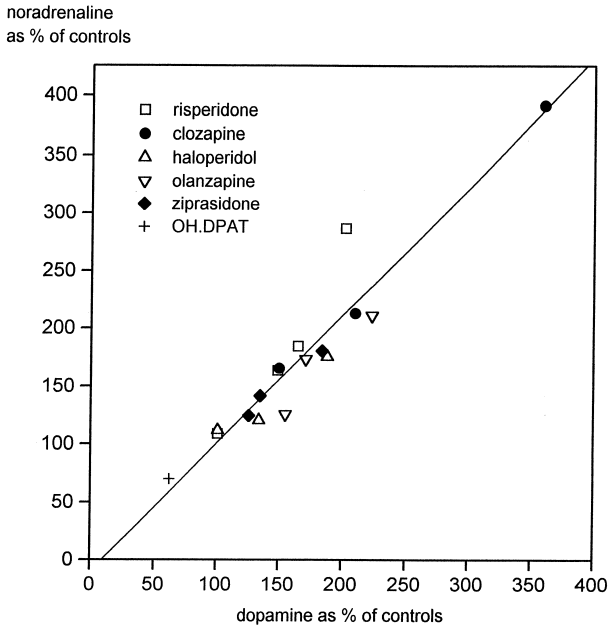

Fig. 7. Comparison of the maximal changes of extracellular dopamine and noradrenaline in the medial prefrontal cortex, induced by five antipsychotics and 7-OH-DPAT. Data are taken from Fig. 1Fig. 2Fig. 3Fig. 4Fig. 5Fig. 6.

3.4. Comparison of drug induced changes in extracellular noradrenaline and dopamine in the medial prefrontal cortex

In Fig. 7 the effects of (+)-7-OH-DPAT and the various doses of antipsychotics on extracellular dopamine and noradrenaline the medial prefrontal cortex are compared. Of each antipsychotic the three highest doses were included. Depicted are the maximal effects expressed as percent of controls as shown in Figs. 1–6. Linear regression analysis revealed a clear linear correlation: $r = 0.95$; $p = 6.3 \times 10^{-7}$; $y = 10.1 + 0.83x$ indicating that the release of noradrenaline and dopamine is closely correlated under these pharmacological conditions.

4. Discussion

It is evident from the present results, as summarized in Fig. 7, that the five studied antipsychotic drugs (haloperi-

dol, olanzapine, clozapine, risperidone and ziprasidone) as well as the dopamine receptor agonist (+)-7-OH-DPAT induced parallel changes in the extracellular levels of dopamine as well as noradrenaline in the medial prefrontal cortex. In addition the time curves for the various drug effects were remarkably similar. Apparently the release of dopamine and noradrenaline is closely coupled in the medial prefrontal cortex under these pharmacological conditions.

The present result with (+)-7-OH-PAT is in agreement with an observation made by Rosetti et al. (1989) who reported that the selective D_2 dopamine receptor agonist LY 171555 decreased both extracellular dopamine and noradrenaline in the medial prefrontal cortex.

The question of course arises on the mechanism of action that is responsible for the unexpected co-variation in dopamine and noradrenaline. There is growing evidence in the literature for an interaction between dopaminergic and noradrenergic terminals that is specific for the medial prefrontal cortex. Cortical cells are differentially regulated by dopamine and noradrenaline when compared with neurones in non-cortical brain areas and, in addition, the two transmitters influence the sensitivity of each others receptors (Tassin et al., 1992). It has also been suggested that noradrenergic terminals contribute to the removal of dopamine from the extracellular fluid, as the noradrenaline transporter has a similar affinity for noradrenaline and dopamine (Carboni et al., 1990; Tanda et al., 1994; Gresch et al., 1995). A recent study in our laboratory showed that specific chemical stimulation of the locus coeruleus induced similar effects in the release of dopamine and noradrenaline in the PFC (Kawahara et al., submitted), indicating that the activity of the locus coeruleus neurons may influence the release of dopamine in the medial prefrontal cortex.

A first explanation of the noradrenaline–dopamine relation might be found in an equal co-localization of presynaptic receptors on both types of neurons. The receptor that is often implicated in the stimulation of the release of dopamine, is the D_2 dopamine receptor. Although the presence of D_2 dopamine autoreceptors in the medial prefrontal cortex was questioned in earlier literature (Bannon et al., 1982), the present results with (+)-7-OH-DPAT and the reported literature data on dopamine receptor agonists (Ozaki et al., 1989; Gobert et al., 1996) clearly indicate the functional presence of $D_{2/3}$ dopamine autoreceptors in this brain region. However clozapine, the compound that induced the most pronounced increase in the extracellular catecholamines (Fig. 4), is only a weak D_2 receptors antagonist. It is emphasized that pure D_2 dopamine receptor antagonists, based on the benzamide structure such as sulpiride and raclopride have few and only transient effects on the release of dopamine in the medial prefrontal cortex (Moghaddam and Bunney, 1990; Andersson et al., 1995), in contrast to the striatum (Westerink and DeVries, 1989; See et al., 1991).

Receptors other than $D_{2/3}$ dopamine receptors are probably implicated in the antipsychotic induced stimulation of the release of dopamine and noradrenaline in the medial prefrontal cortex. Several heteroreceptors have been identified that might contribute to the increase in of dopamine release in the medial prefrontal cortex. Andersson et al. (1995) provided evidence that blockade of 5-HT_2 serotonin receptors is responsible for the expression of D_2 dopamine receptor antagonistic effects in the medial prefrontal cortex. In a recent study, Rollema et al. (1997) showed that the large increase in dopamine release (between 200–400% of controls) that is seen with the high doses of clozapine is related to the 5-HT_{1A} serotonin receptor agonistic properties of clozapine. Interestingly the large increase in the release of dopamine after the highest dose of clozapine, was also present in the noradrenaline levels (Fig. 4B). α_2-Adrenoceptors might also play a role in the dopamine–noradrenaline interaction, as systemic administration of the α_2-adrenoceptor agonist clonidine decreased both noradrenaline as well as dopamine release in the PFC (Gresch et al., 1995). In this respect it is also of interest that combined blockade of α_2 and 5-HT_2 serotonin receptors produces large increases of extracellular dopamine in the medial prefrontal cortex (Tanda et al., 1996).

It is concluded that 5-HT_{1A}, 5-HT_2, D_2 as well as α_2-adrenoceptors might contribute to the close correlation between the release of noradrenaline and dopamine in the medial prefrontal cortex. If the concerted action of these receptors is responsible for the observed co-variation, it implicates that both types of neurons possess a similar population of heteroreceptors. In this explanations the two neurotransmitter systems are correlated but not coupled.

A second explanation might be found in anatomical connections between dopamine and noradrenaline neurons (Tassin et al., 1992; Grenhoff et al., 1993). However, the evidence for such functional anatomical connection is not convincing at the present time. A third explanation for the dopamine–noradrenaline interaction might be related to the observation that noradrenergic terminals contribute to the removal of dopamine from the extracellular fluid, as the noradrenaline transporter has a similar affinity for dopamine and noradrenaline (Carboni et al., 1990; Tanda et al., 1994).

It is evident that additional experiments are indicated to elucidate the mechanism of action of the parallel increase in extracellular dopamine and noradrenaline in the medial prefrontal cortex, that was seen after administration of the five antipsychotics. It remains first to be established whether the two neurotransmitter systems are coupled or correlated. Experiments using local infusions or selective lesions of the locus coeruleus or ventral tegmental area are in progress in our laboratory to further elucidate the mechanism of this interaction.

As the effects of antipsychotic drugs on the release of dopamine in the medial prefrontal cortex are often related to the clinical effects that these drugs induce in psychotic

patients, the question arises on the role of noradrenaline in this respect. A possible implication of the present findings is that stimulation of the release of noradrenaline in the medial prefrontal cortex is crucial for antipsychotic effects of these drugs. If so the dopamine–noradrenaline interaction in the medial prefrontal cortex is likely to play a central role in the mechanism of action of antipsychotics.

References

Andersson, J.L., Nomikos, G.G., Marcus, M., Hertel, P., Mathé, J.M., Svensson, T.H., 1995. Ritanserin potentiates the stimulatory effects of raclopride on neuronal activity and dopamine release selectively in the mesolimbic dopaminergic system. Naunyn-Schmiedeberg's Arch. Pharmacol. 352, 374–385.

Bannon, M.J., Reinhard, J.F., Bunney, E.B., Roth, R.H., 1982. Unique response to antipsychotic drugs is due to absence of terminal autoreceptors in mesocortical dopamine neurons. Nature 296, 444–446.

Carboni, E., Tanda, G.L., Frau, R., Di Chiara, G., 1990. Blockade of the noradrenaline carrier release increases extracellular dopamine concentration in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. J. Neurochem. 55, 1067–1070.

Carlsson, A., Lindqvist, M., 1963. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. 20, 140–144.

Damsma, G., Bottema, T., Westerink, B.H.C., Tepper, P.G., Dijkstra, D., Pugsley, T.A., MacKenzie, R.G., Heffner, T.G., Wikström, H., 1993. Pharmacological aspects of *R*-(+)-7-OH-DPAT, a putative dopamine D_3 ligand. Eur. J. Pharmacol. 249, R9–R10.

Di Chiara, G., Porceddu, M.L., Spano, P.F., Gessa, G.L., 1977. Haloperidol increases and apomorphine decreases striatal dopamine metabolism after destruction of striatal dopamine-sensitive adenylate-cyclase by kainic acid. Brain Res. 130, 374–382.

Gobert, A., Lejeune, F., Rivet, J.-M., Cistarelli, L., Millan, M.J., 1996. Dopamine D_3 (auto)receptors inhibit dopamine release in the frontal cortex of freely moving rats in vivo. J. Neurochem. 66, 2209–2212.

Grenhoff, J., Nisell, M., Ferre, S., Aston-Jones, G., Svensson, T.H., 1993. Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus of the rat. J. Neural Transm. 93, 11–25.

Gresch, P., Sved, A.F., Zigmond, M.J., Finlay, J., 1995. Local influence of endogenous norepinephrine on extracellular dopamine in the rat medial prefrontal cortex. J. Neurochem. 65, 111–116.

Hertel, P., Nomikos, G., Iurlo, M., Svensson, T.H., 1996. Risperidone: regional effects in vivo on release and metabolism of dopamine and serotonin in the rat brain. Psychopharmacology 124, 74–86.

Imperato, A., Di Chiara, G., 1984. Trans-striatal dialysis coupled to reverse phase high performance liquid chromatography with electrochemical detection: a new method for the study of the in vivo release of endogenous dopamine and metabolites. J. Neurosci. 4, 966–977.

Marcus, M.M., Nomikos, G.G., Svensson, T.H., 1996. Differential action of typical and atypical antipsychotic drugs o dopamine release in the core and the shell of the nucleus accumbens. Eur. Neuropsychopharmacol. 6, 29–38.

Moghaddam, B., Bunney, B.S., 1990. Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J. Neurochem. 54, 1755–1760.

Nomikos, G.G., Iurlo, M., Andersson, J.L., Kimura, K., Svensson, T.H., 1994. Systemic administration of amperozide, a new atypical antipsychotic drug, preferentially increases dopamine release in the rat medial prefrontal cortex. Psychopharmacology 115, 147–156.

Ozaki, N., Nakahara, D., Miura, H., Kasahara, Y., Nagatsu, T., 1989. Effect of apomorphine on in vivo release of dopamine and its metabolites in the prefrontal cortex and the striatum, studied by a microdialysis method. J. Neurochem. 53, 1861–1864.

Paxinos, G., Watson, C., 1982. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.

Rollema, H., Lu, Y., Schmidt, A.W., Zorn, S.H., 1997. Clozapine increases dopamine release in prefrontal cortex by 5-HT_{1A} receptor activation. Eur. J. Pharmacol. 338, R3–R5.

Rosetti, Z.L., Pani, L., Portas, C., Gessa, G., 1989. Brain dialysis provides evidence for D_2-dopamine receptors modulating noradrenaline release in the rat frontal cortex. Eur. J. Pharmacol. 163, 393–395.

See, E., Sorg, B.A., Chapman, M.A., Kalivas, P.W., 1991. In vivo assessment of release and metabolism of dopamine in the ventrolateral striatum of awake rats following administration of dopamine D_1 and D_2 receptor agonists and antagonists. Neuropharmacology 30, 1269–1274.

Stockton, M.E., Rasmussen, K., 1996. Electrophysiological effects of olanzapine, a novel antipsychotic, on A9 and A10 dopamine neurons. Neuropsychopharmacology 14, 97–105.

Tanda, G., Carboni, E., Frau, R., Di Chiara, G., 1994. Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential?. Psychopharmacology 115, 285–288.

Tanda, G., Bassareo, V., Di Chiara, G., 1996. Mianserin markedly and selectively increases extracellular dopamine in the prefrontal cortex as compared to the nucleus accumbens of the rat. Psychopharmacology 123, 127–130.

Tassin, J.P., Trovero, F., Herve, D., Blanc, G., Glowinski, J., 1992. Biochemical and behavioural consequences of interactions between dopaminergic and noradrenergic systems in rat prefrontal cortex. Neurochem. Int. 20, 225S–230S.

Volonté, M., Monferini, E., Cerutti, M., Fodritto, F., Borsini, F., 1997. BMG80, a novel potential antipsychotic drug: evidence for multireceptor actions and preferential release of dopamine in prefrontal cortex. J. Neurochem. 69, 182–190.

Westerink, B.H.C., DeVries, J.B., 1989. On the mechanism of neuroleptic induced increase in striatal dopamine release: brain dialysis provides direct evidence for mediation by autoreceptors localized on nerve terminals. Neurosci. Lett. 99, 197–202.

Westerink, B.H.C., Kwint, H.F., deVries, J.B., 1996. The pharmacology of mesolimbic dopamine neurons: a dual-probe microdialysis study in the ventral tegmental area and nucleus accumbens of the rat brain. J. Neurosci. 16, 2605–2611.