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Short communication

The atypical antipsychotic sertindole enhances efflux of dopamine and its metabolites in the rat cortex and striatum

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Abstract

Previous studies have shown that sertindole (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2 imidazolidinone), an atypical antipsychotic drug that is a potent 5-HT_{2A} and dopamine D_2 receptor antagonist, preferentially affects mesocorticolimbic rather than mesostriatal dopamine neurons. Using in vivo microdialysis in conscious rats, we investigated the effects of sertindole on dopamine release and metabolism in the striatum and the medial prefrontal cortex. Systemic administration of sertindole dose dependently enhanced dopamine release in the medial prefrontal cortex and the striatum to the same extent.

Keywords: Sertindole; Antipsychotic, atypical; Dopamine; Microdialysis

1. Introduction

The atypical antipsychotic sertindole (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2 imidazolidinone) has been found to alleviate both positive and negative symptoms of schizophrenia without producing extrapyramidal side effects (Zimbroff et al., 1997). Behavioral and electrophysiological animal studies have shown that sertindole shares the limbic selectivity of clozapine, preferentially affecting mesolimbico-cortical, as opposed to nigrostriatal dopaminergic neurons (Sanchéz et al., 1991; Skarsfeldt, 1992; Domeney et al., 1994). Atypical antipsychotics such as sertindole and clozapine induce stronger Fos protein immunoreactivity in the medial prefrontal cortex than in the dorsolateral striatum (Fink-Jensen and Kristensen, 1994). In vitro, sertindole has very high affinity for 5-HT_{2A}, dopamine D_2, and α_1-adrenoceptors (Sanchéz et al., 1991). An ex vivo homogenate binding study indicated that sertindole has the most pronounced effect on 5-HT_{2A} receptors (Hyttel et al., 1992), and Meltzer and colleagues have suggested that the atypical profile of antipsychotic drugs such as clozapine is due to their preference for 5-HT_{2A} over D_2 receptors (Meltzer and Nash, 1991).

A number of studies have indicated that the negative symptomatology in schizophrenia is often associated with functional impairment of frontal cortex and mesocortical dopaminergic transmission (Weinberger, 1987). Recent microdialysis studies in rats have indicated that acute administration of atypical antipsychotics such as clozapine, amperozide, MDL 100,907 {*R*-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidine-methanol} and BIMG 80 {5-methoxy-3-[*N*-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,5,6-tetrahydropyridin-3-ylmethyl]-1*H*-indole} preferentially enhances mesocortical dopaminergic activity, as opposed to the activity of the nigrostriatal system (Moghaddam and Bunney, 1990; Pehek et al., 1993; Nomikos et al., 1994; Pehek and Yamamoto, 1994; Schmidt and Fadayel, 1995; Hertel et al., 1996; Volonté et al., 1997). Recently, Fink-Jensen et al. (1996) reported the effect of sertindole on interstitial levels of 3,4-dihydroxyphenylacetic acid (DOPAC) in microdialysis experiments, but they did not examine dopamine levels. Thus, it was of interest to determine more precisely the effects of sertindole administration on dopamine release and metabolism in the prefrontal cortex and the striatum. In addition, the influence of sertindole on extracellular concentrations of 5-hydroxytryptamine in the frontal cortex was also as-

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sessed, because previous microdialysis studies indicated that atypical antipsychotics such as risperidone and amperozide augmented cortical 5-HT release (Hertel et al., 1996; Ichikawa et al., 1998).

2. Materials and methods

2.1. Surgery and microdialysis

The procedures used in this study were approved by the Animal Investigation Committee of our Institute.

In vivo microdialysis experiments were performed as previously described (Watanabe et al., 1998). Male Wistar rats (300–350 g) were stereotaxically implanted, under anesthesia (sodium pentobarbital 50 mg/kg, i.p.), with microdialysis probes 24 h before the experiment in either the medial prefrontal cortex (anterior, +4.2 mm; lateral, +0.5 mm; ventral, −5.0 mm relative to the bregma and the dura surface) or the striatum (anterior, +2.4 mm; lateral, +2.5 mm; ventral −6.5 mm), according to the atlas of Pellegrino and Cushman (1967).

The perfusion experiments were performed on unrestrained animals. Ringer's solution (147 mM Na^+, 4 mM K^+, 1.26 mM Ca^{2+}, 1 mM Mg^{2+} and 152.5 mM Cl^-, pH 6.5) was perfused at a constant flow rate of 2 μl/min. Perfusates for the measurement of dopamine, DOPAC, and homovanillic acid (HVA) were collected every 20 min, and dialysate samples (20 μl) were injected with an autoinjector into a high-performance liquid chromatograph (HPLC) (EICOM EP-300, EICOM, Japan). Dopamine, DOPAC, and HVA in the dialysate from the striatum, and DOPAC and HVA in the dialysate from the medial prefrontal cortex were separated with a reverse-phase ODS column (Eicompak MA-5ODS, Japan). The mobile phase consisted of 0.1 M citrate–acetate buffer (pH 3.9) containing EDTA (5 mg/l), sodium octanesulfonate (190 mg/l), and 16% methanol. Dopamine in the dialysate collected from the medial prefrontal cortex was separated with a reverse-phase ODS column (Eicompak CA-5ODS, Japan). The mobile phase consisted of 0.1 M phosphate buffer (pH 6.0) containing EDTA (50 mg/l), sodium octanesulfonate (500 mg/l), and 20% methanol.

To measure 5-HT in the medial prefrontal cortex, 40 μl of perfusate collected from the medial prefrontal cortex was directly injected into the HPLC system every 20 min by autoinjector. 5-HT in the dialysate was separated with a reverse-phase ODS column (Eicompak CA-5ODS, Japan). The mobile phase consisted of 0.1 M phosphate buffer (pH 6.0) containing EDTA (50 mg/l), sodium octanesulfonate (250 mg/l), and 23% methanol.

2.2. Drugs

Sertindole (free base) was obtained from H. Lundbeck (Copenhagen, Denmark). The drug was dissolved in 0.05 N HCl and injected intraperitoneally at doses of 1 and 10 mg/kg. These doses are comparable to those used by previous investigators to examine the effects of sertindole on Fos protein expression and DOPAC release (Fink-Jensen and Kristensen, 1994; Fink-Jensen et al., 1996).

2.3. Data analysis

All data were calculated as percent changes from dialysate basal concentrations, with 100% defined as the average of the final three preinjection values. We used the method of summary measures according to the technique described by Matthews et al. (1990) to extract the overall effects of the drugs from the serial dialysis data. In the first stage, the area under the curve (AUC) was calculated as a summary of the response by adding the areas under the graph of the concentration of dialysate dopamine, DOPAC, or HVA from 0 to 300 min post-treatment, and 5-HT from 0 to 180 min post-treatment. Thereafter, statistical comparisons were performed between the groups on the AUC data by using the Mann–Whitney *U*-test or Kruskal–Wallis test followed by the multiple comparison test.

3. Results

3.1. Effects of systemic sertindole on dialysate concentrations of dopamine, DOPAC, and HVA in the medial prefrontal cortex and the striatum

The overall mean basal values (mean ± S.E.M., fM/20 min) of dopamine, DOPAC, and HVA were 8.8 ± 0.4, 2045 ± 220, 2054 ± 128 in the medial prefrontal cortex ($n = 45$), and 176 ± 8, 42398 ± 1324, 22252 ± 669 in the striatum ($n = 36$).

The effects of systemic sertindole treatment on dialysate concentrations of dopamine and its metabolites (DOPAC and HVA) in the medial prefrontal cortex and the striatum are shown in Figs. 1 and 2. Systemic administration of sertindole dose dependently induced statistically significant increases in the content of dopamine in the dialysates from both the medial prefrontal cortex and the striatum. Sertindole at 1 mg/kg increased dopamine concentrations in the dialysates from the medial prefrontal cortex and the striatum to 124% and 148% of the baseline values, respectively. At 10 mg/kg, sertindole increased dopamine efflux from the medial prefrontal cortex and the striatum to 188% and 160% of the baseline values, respectively. The effects of sertindole on dopamine release at both the high and the low dose were statistically comparable in the medial prefrontal cortex and in the striatum.

Systemic administration of the low and high doses of sertindole dose dependently increased the extracellular concentrations of DOPAC and HVA in both the medial prefrontal cortex and the striatum. The effects of the low dose of sertindole (1 mg/kg) on DOPAC and HVA con-

centrations were comparable in the striatum and in the prefrontal cortex. At 1 mg/kg, sertindole increased the concentrations of DOPAC and HVA in the dialysates from the prefrontal cortex to approximately 140% and 150%, respectively. At this dose, sertindole increased the dialysate concentrations of both DOPAC and HVA from the striatum to approximately 130%. At 10 mg/kg, however, sertindole increased cortical concentrations of DOPAC and HVA to 280% and 290%, respectively, in comparison with the baseline samples. The high dose of sertindole (10 mg/kg) raised dialysate DOPAC and HVA concentrations in the striatum to 200% and 250%, respectively. Thus, the high dose of sertindole (10 mg/kg) induced a statistically significant increase in the AUC of DOPAC in the medial prefrontal cortex as compared with the striatum, i.e., 1940 ± 297 vs. 1145 ± 114 ($P < 0.05$). The effects of sertindole (10 mg/kg) on HVA release, however, were not significantly different in the medial prefrontal cortex and the striatum.

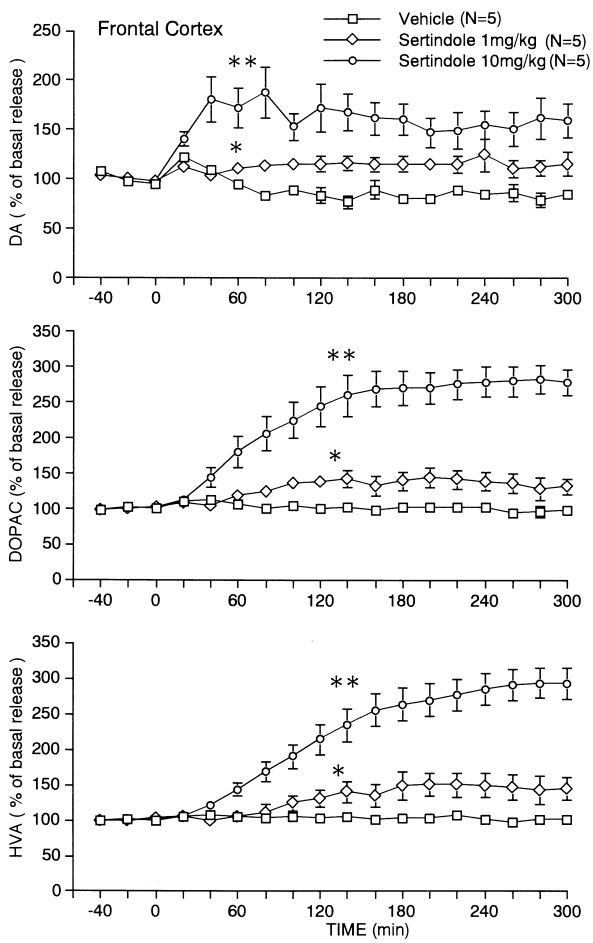

Fig. 1. Effects of systemic administration of sertindole on extracellular release of dopamine (DA), DOPAC, and HVA in the cortical region. Data are means ± S.E.M. (bars) values, and are expressed as percentages of the basal levels. The AUC was calculated by adding the areas under the graphs of the concentration of dialysate dopamine, DOPAC, or HVA from 0 to 300 min postinjection. Statistical comparisons of the AUC data were performed among the groups as described in Section 2: $* P < 0.05$, $** P < 0.01$ as compared with vehicle-treated controls. N = number of experimental animals.

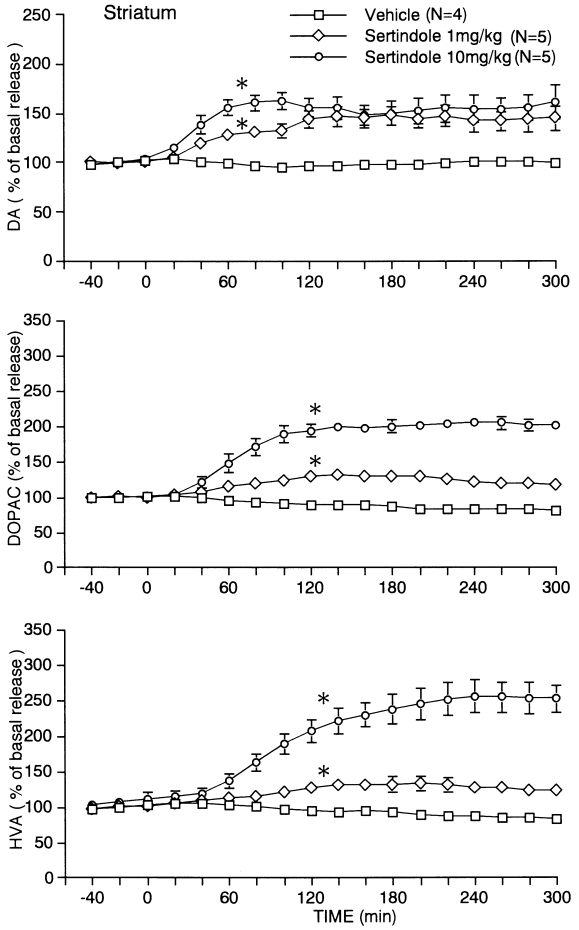

Fig. 2. Effects of systemic administration of sertindole on extracellular release of dopamine (DA), DOPAC, and HVA in the striatal region. Data are means ± S.E.M. (bars) values, and are expressed as percentages of the basal levels. The AUC was calculated by adding the areas under the graphs of the concentration of dialysate dopamine, DOPAC, or HVA from 0 to 300 min postinjection. Statistical comparisons of the AUC data were performed among the groups as described in Section 2: $* P < 0.05$ as compared with vehicle-treated controls. N = number of experimental animals.

3.2. Effects of sertindole on dialysate concentrations of 5-HT from the medial prefrontal cortex

The overall mean basal value of 5-HT in the prefrontal cortex was 7.1 ± 0.5 fM/20 min ($n = 30$). Sertindole showed no significant effects on the extracellular concentration of 5-HT as compared with vehicle only controls in the prefrontal cortex throughout the 3-h sample collection (data not shown).

4. Discussion

Fink-Jensen et al. (1996) reported the effect of sertindole on DOPAC release alone, and this is the first study to

investigate more precisely the effects of the novel antipsychotic sertindole on dopamine release and metabolism by in vivo microdialysis in conscious rats.

The present results demonstrated that sertindole enhanced the efflux of dopamine and its metabolites (DOPAC and HVA) in both the medial prefrontal cortex and in the striatum. At the high-dose, sertindole increased DOPAC release to a greater extent in the prefrontal cortex than in the striatum. Our results confirmed the previous observation of a preferential increase in DOPAC release after sertindole treatment in the prefrontal cortex relative to the dorsolateral striatum (Fink-Jensen et al., 1996). Previous studies suggested that DOPAC is produced by the presynaptic intraneuronal metabolism of dopamine (Watanabe et al., 1998). Thus, sertindole may preferentially augment dopamine metabolism in the medial prefrontal cortex compared with the striatum. These results are in line with previous behavioral, biochemical, and electrophysiological findings suggesting a selective action of sertindole on corticolimbic structures (Sanchéz et al., 1991; Skarsfeldt, 1992; Domeney et al., 1994; Fink-Jensen and Kristensen, 1994). However, we cannot explain why sertindole did not exert a preferential effect on dopamine release in the medial prefrontal cortex with respect to the striatum.

Since sertindole possesses high affinity for dopamine D_2 receptors in vitro and ex vivo (Sanchéz et al., 1991; Hyttel et al., 1992), the D_2 receptor-blocking ability of sertindole may have mediated its effects on the release of dopamine and its metabolites from the striatum in the present study. This is in line with previous reports indicating that all D_2 receptor antagonists consistently increase dopamine release and metabolism in the striatum (Westerink and de Vries, 1989; Moghaddam and Bunney, 1990; See et al., 1991). Atypical antipsychotics, such as risperidone and olanzapine, also increase dopamine release to a similar extent in the prefrontal cortex and the striatum (Hertel et al., 1996; Volonté et al., 1997). This lack of regional selectivity of risperidone, olanzapine, and sertindole is in contrast with the notion that one facet of antipsychotic 'atypicality' may be preferential increases in cortical dopamine release (Pehek et al., 1993). Thus, taken together with previous reports (Hertel et al., 1996; Volonté et al., 1997), the present results suggest that as long as atypical antipsychotics show high affinity for dopamine D_2 receptors (such as sertindole, risperidone, and olanzapine), they can stimulate dopamine release from the striatum via blockade of presynaptic D_2 receptors (Westerink and de Vries, 1989).

Previous investigations showed that the atypical antipsychotic clozapine and the selective 5-HT_{2A} receptor antagonist ritanserin increased cortical dopamine levels when infused locally, indicating that atypical antipsychotic drugs may increase mesocortical dopamine release by antagonizing 5-HT_{2A} receptors located in the prefrontal cortex (Pehek and Yamamoto, 1994; Pehek, 1996). Ex vivo binding experiments and behavioral experiments have shown that sertindole has the most pronounced effect on 5-HT_{2A} receptors of any receptor studied (Sanchéz et al., 1991; Hyttel et al., 1992). Thus, it is conceivable that inhibition of 5-HT_{2A} receptors by sertindole may contribute to the stimulatory action of this drug on dopamine release within the terminal areas of the mesocortical projection. Zimbroff et al. (1997) reported that sertindole was significantly more effective than placebo for the treatment of negative symptoms. The therapeutic efficacy of sertindole on negative symptoms may be attributable to its ability to facilitate prefrontal cortical dopaminergic activity through blockade of 5-HT_{2A} receptors.

In the present study, sertindole did not affect 5-HT release in the prefrontal cortex. These results are at variance with previous reports showing an enhancement of 5-HT release in the prefrontal cortex after treatment with atypical antipsychotic drugs such as risperidone and amperozide (Hertel et al., 1996; Ichikawa et al., 1998). However, the results for the effects of atypical antipsychotics on 5-HT release are equivocal, and Ichikawa et al. (1998) reported that olanzapine and MDL100,907 had no effect on extracellular 5-HT levels. Thus, at present, we can draw no conclusions concerning the effects of atypical antipsychotics on 5-HT release.

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