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Differential effects of repeated administration of novel antipsychotic drugs on the activity of midbrain dopamine neurons in the rat

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Abstract

Five potential antipsychotics (i.e. risperidone, olanzapine, seroquel, ziprasidone and amperozide) were given daily for 21 days to rats and the effect on the number of spontaneously active dopamine neurons in ventral tegmental area and substantia nigra pars compacta was determined. Standard electrophysiological measurements (i.e. single unit recording technique) were used. Risperidone, olanzapine and amperozide showed some selectivity (at one particular dose) for decreasing the number of active dopamine neurons in the ventral tegmental area. However, risperidone induced a U-shaped dose-response curve. The highest dose of amperozide inhibited the activity in substantia nigra pars compacta, showing a liability to induce extrapyramidal side-effects. Seroquel and ziprasidone inhibited the activity in both areas indicating a classical antipsychotic profile (i.e. high liability to cause extrapyramidal side-effects).

Keywords: Risperidone; Olanzapine; Seroquel; Ziprasidone; Amperozide; Schizophrenia; Ventral tegmental area; Substantia nigra pars compacta; (Rat)

1. Introduction

Antipsychotic agents have proven to be efficacious in the treatment of psychotic disorders. However, most of the compounds currently available are highly liable to cause neurological side-effects (extrapyramidal side-effects, i.e. dystonia, parkinsonian-like symptoms and akathesia). Several decades of research have focused on attempts to develop new antipsychotics without the ability to produce extrapyramidal side-effects, but so far only clozapine is regarded as an antipsychotic agent without extrapyramidal side-effects (Bruhwyler et al., 1990).

The discovery of clozapine as an antipsychotic without extrapyramidal side-effects has triggered research into the mechanism of action of clozapine that is responsible for its unique clinical profile.

Based on the favorable clinical profile of clozapine, new approaches have been tried and several potential neuroleptics with mixed receptor profiles are currently at various stages either in clinical development (e.g. sertindole (Sánchez et al., 1991), olanzapine (Moore et al., 1993), seroquel (Saller and Salama, 1993), ziprasidone (Seeger et al., 1993) and amperozide (Christensson and Gustafsson, 1985)) or just been marketed (risperidone) (Chouinard et al., 1993).

Several reports have shown that repeated treatment with neuroleptics causes a decrease in the number of spontaneously active dopamine cells in the mesolimbic system and suggest that this effect could contribute to the antipsychotic efficacy of a compound. In addition, a decrease in the number of active dopamine neurons in the nigrostriatal system should account for the development of extrapyramidal side-effects (Bunney and Grace, 1978; White and Wang, 1983; Chiodo and Bunney, 1985). Indeed, questions have been raised as haloperidol failed to induce depolarization inactivation of dopamine neurons in unanesthetized rats (Mereu et al., 1994).

In order to evaluate new potential neuroleptic compounds, subchronic experiments (at least 3 weeks' treatment) using electrophysiological techniques can be used to demonstrate limbic selectivity by measuring the preferential decrease in the number of spontaneously active dopamine neurons in the ventral tegmental area compared with the substantia nigra pars compacta in rats.

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The aim of the present study was to show whether repeated daily treatment with some of the new potential antipsychotics is able to reduce the number of active midbrain dopamine neurons in young rats.

2. Materials and methods

2.1. Animals and surgery

The methods have been described previously (Skarsfeldt, 1992,1993). Briefly, young (3-month-old) male Wistar rats weighing 225–230 g at the beginning of the experiments were used. The animals were anaesthetized with chloral hydrate (2.4 mmol/kg i.p. = 400 mg/kg). A catheter was placed in the femoral vein for maintenance of chloral hydrate anaesthesia (480 μmol/kg i.v. = 80 mg/kg). The rat was mounted in a stereotaxic instrument and a hole was drilled (3 × 3 mm) in the left side of the skull overlying the ventral tegmental area and substantia nigra pars compacta. Body temperature was kept at 37 ± 1°C by means of a heating pad.

Recording of spontaneously active dopamine neurons was performed with single-barrel glass electrodes filled with either 2% pontamine sky blue dissolved in 5 M sodium acetate or 2 M sodium acetate. The tip diameter was approximately 5 μm and electrode resistance varied between 2 and 5 MΩ. Eight electrode penetrations per area were made in the dorsal-ventral direction from 6.0 to 8.5 mm below the dura through substantia nigra pars compacta and ventral tegmental area.

The initial track in each rat was located 3.0 mm anterior to lambda and 0.7 mm (ventral tegmental area) or 2.2 mm (substantia nigra pars compacta) lateral to the midline; the final track was located 3.3 mm anterior to lambda and 0.9 mm lateral (ventral tegmental area) or 2.4 mm (substantia nigra pars compacta) to the midline. The distance between the posterior-anterior steps was 0.1 mm while the distance between lateral steps was 0.2 mm.

2.2. Identification of dopamine neurons

The dopamine neurons were identified as previously described by Bunney et al. (1973). In short, the dopamine neurons were characterized by: (1) slow irregular firing pattern (0.5–10 Hz), (2) triphasic action potentials with a predominant positive component, a negative component and a minor positive component with an overall duration of more than 2.5 ms. The position of the electrode tip was marked at the end of most experiments by passing a negative current (10 μA) through the electrode barrel for 2 min, resulting in the deposition of a blue spot of pontamine sky blue. Occasionally, serial frozen sections of the rat brain were cut at 46-μm intervals to locate the position of the blue spot.

2.3. Drugs

The following compounds were used: risperidone (Janssen, Belgium) (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one) (molecular weight: 411) and olanzapine (Ly 170063) (2-methyl-10-(4-methyl-1-piperazinyl)-4*H*-thieno[2,3-*b*][1,5]-benzodiazepine) (molecular weight: 313) were dissolved in 0.1 M acetic acid and diluted in saline. Seroquel (ICI 204636) (11-(4-[2-2-hydroxyethoxy)ethyl)-1-piperazinyl)dibenzo[*b*, *f*][1,4]thiazepine, fumarate (molecular weight: 500) and amperozide (Kabi Pharmacia, Sweden) (*N*-ethyl-4-[4,4-bis(*p*-fluorophenyl)butyl]-1-piperazine-carboxamide) (molecular weight: 438) were dissolved in saline and ziprasidone (CP-88,059) (5-[2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl]-6-chloro-1,3-hydro-2*H*-indol-2-on) (molecular weight: 413) was dissolved in 0.1 M sulfonic acid and diluted in distilled water. Olanzapine, seroquel and ziprasidone were synthesized by the Medicinal Chemistry Department, H. Lundbeck. The pH of drug solutions varied between 4 and 5. The compounds were administered via intragastric intubation (p.o.) in a volume of 10 ml/kg body weight. Due to experimental circumstances (see below) olanzapine was administered by subcutaneous injection (s.c.).

The studies were performed as follows: groups of 4–5 rats were treated once daily for 21 days with risperidone (dose range: 0.024–6.1 μmol/kg/day corresponding to 0.01–2.5 mg/kg/day), olanzapine (dose range: 7.8–32 μmol/kg/day corresponding to 2.5–10 mg/kg/day), seroquel (dose range: 23–91 μmol/kg/day corresponding to 10–40 mg/kg/day), ziprasidone (dose range: 0.024–12 μmol/kg/day corresponding to 0.01–5 mg/kg/day) or amperozide (dose range: 2.9–23 μmol/kg/day corresponding to 1.25–10 mg/kg/day).

Two doses of risperidone (0.39 and 1.5 μmol/kg/day) were tested twice ($n = 9$). A higher dose of olanzapine was administered (64 μmol/kg/day corresponding to 20 mg/kg/day, p.o. and s.c.) but the experiment was terminated due to severe side-effects (i.e. diarrhea and decreased body weight). Furthermore, subcutaneous administration caused necrosis at the injection site.

The dosages were chosen based on effects in behavioural experiments in rats (personal communication, J. Arnt).

The control group ($n = 19$) received saline (p.o.) for 21 days. The rats received the last saline or drug dose 2 h before start of surgery.

2.4. Statistics

In order to verify the statistical significance of changes in the number of spontaneously active dopamine neurons in ventral tegmental area or substantia nigra pars compacta compared with those in a population of saline-treated control animals, the data were analyzed by comparing the number of active dopamine neurons in the drug-treated groups and in the control group (i.e. each dose versus the control

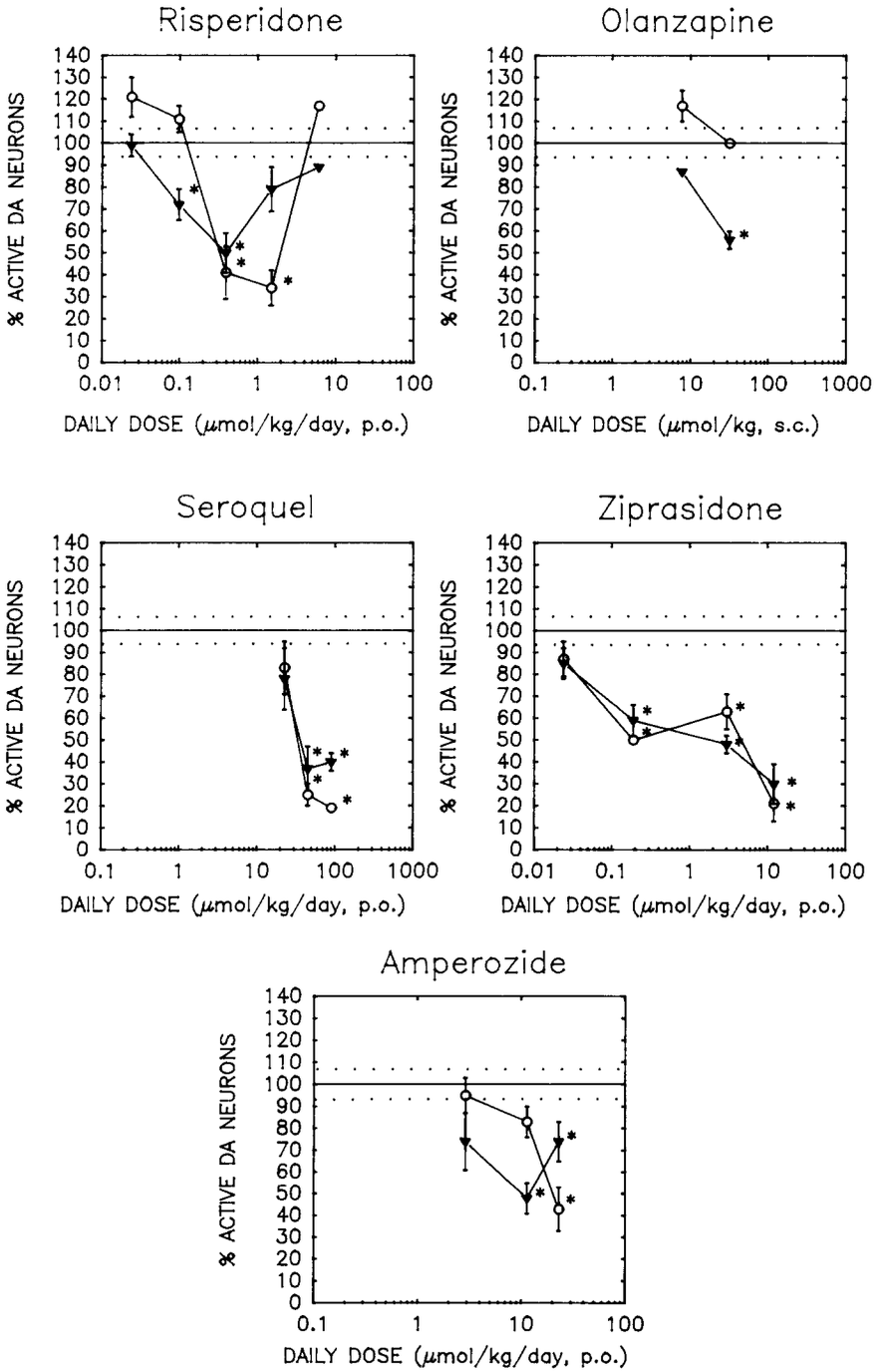

Fig. 1. Changes in the number of spontaneously active dopamine neurons in ventral tegmental area (filled triangles) and substantia nigra pars compacta (open circles) after repeated treatment (21 days) with risperidone (upper left panel), olanzapine (upper right panel), seroquel (middle left panel), ziprasidone (middle right panel) and amperozide (lower panel) in rats. The horizontal lines indicate the mean (solid) and S.E.M. (dotted) value of the controls ($n = 19$). All values are expressed as means ± S.E.M. Except for two doses of risperidone (see section 2.3) four or five rats were used for each dose. Asterisks indicate a significant ($P < 0.05$) decrease in the number of active dopamine neurons compared to the control values.

value) using the non-parametric Mann-Whitney U-test. A P value less than 0.05 was considered statistically significant.

3. Results

3.1. Effect on active dopamine neurons in ventral tegmental area and substantia nigra pars compacta

The 19 saline-treated controls provided the reference levels of spontaneous activity in ventral tegmental area and substantia nigra pars compacta. In the ventral tegmental area the number of active dopamine neurons was 0.86 ± 0.028 (mean $\pm$ S.E.M.) cells per track while in the substantia nigra pars compacta the activity was 0.81 ± 0.030 (mean $\pm$ S.E.M., $n = 19$) cells per track.

Treatment with risperidone induced a biphasic response with maximum effect at 0.39 μmol/kg/day (corresponding to 0.16 mg/kg) (Fig. 1, upper left panel). Only a single dose (0.098 μmol/kg/day) was selective in the ventral tegmental area versus the substantia nigra pars compacta.

Subcutaneous administration of olanzapine (32 μmol/kg/day) selectively decreased the number of spontaneously active dopamine neurons in the ventral tegmental area (Fig. 1, upper right panel). Both seroquel and ziprasidone reduced the number of spontaneously active dopamine neurons in both areas (Fig. 1, middle panel).

Amperozide selectively inhibited dopamine activity in the ventral tegmental area at one particular dose (11 μmol/kg/day), whereas a higher dose (23 μmol/kg/day) inhibited dopamine activity in the substantia nigra pars compacta (Fig. 1, lower panel).

4. Discussion

Recently, risperidone was introduced as an antipsychotic compound. In vivo the primary action of risperidone is 5-HT_2 receptor blockade but, in addition, risperidone produces potent dopamine D_2 receptor blockade (Janssen et al., 1988; Megens et al., 1994). Besides, risperidone has an affinity for both adrenoceptors (α_1-and α_2-adrenoceptors) and histamine receptors (Leysen et al., 1993). Clinical studies with risperidone (2–16 mg, b.i.d.) have shown antipsychotic efficacy (Chouinard et al., 1993, Borison et al., 1992; Češková and Švestka, 1993). In addition, risperidone induces extrapyramidal side-effects at dosages just above the recommended clinical dose (4–5 mg, b.i.d.) (Risperdal, Product Monograph, 1993).

Risperidone showed a U-shaped dose-response curve which is in accordance with clinical observations as risperidone possessed less antipsychotic efficacy at dosages above 6 mg b.i.d. (Chouinard et al., 1993). The reason for the reduction in effect in both areas at higher doses is unknown.

Recently, olanzapine was described as a novel antipsychotic agent with high affinity for 5-HT_2, histamine H_1, dopamine D_1 and D_2 receptors and α_1-adrenoceptors in vitro (Moore et al., 1993).

In open-label and double-blind studies in schizophrenic and schizophreniform patients olanzapine has shown efficacy to reduce positive symptoms with a low propensity for causing extrapyramidal side-effects (Beasley et al., 1993; Harrison et al., 1994). In accordance with this, Rasmussen and Stockton (1993) showed a selective decrease in the number of active dopamine neurons in ventral tegmental area vs. substantia nigra pars compacta after repeated administration (21 days, via osmotic minipumps) of olanzapine (Rasmussen and Stockton, 1993).

The present results support a selective effect of olanzapine on the active dopamine neurons in the ventral tegmental area. Rasmussen and Stockton (1993) also reported that olanzapine increased the number of spontaneously active dopamine neurons in the substantia nigra pars compacta, but this finding was not confirmed.

Seroquel, described as a predominantly α_1-adrenoceptor antagonist with low affinity for dopamine D_2 and 5-HT_2 receptors (Saller and Salama, 1993), induces catalepsy in rats treated with 40–80 mg/kg, i.p. At 80 mg/kg the magnitude of the catalepsy was the same as that with haloperidol at 4 mg/kg and the liability for causing extrapyramidal side-effects in schizophrenic patients was greater than that of clozapine (Migler et al., 1993). In addition, dyskinetic reactions in haloperidol-sensitized cebus monkeys were reported after treatment with 5–20 mg/kg, p.o. of seroquel (Migler et al., 1993).

A previous study with seroquel (20 mg/kg, p.o. for 28 days, corresponding to 45 μmol/kg/day) showed a decrease in the number of spontaneously active dopamine neurons in the ventral tegmental area, while the activity in the substantia nigra pars compacta was left unaffected (Goldstein et al., 1993). However, the current study showed clearly that seroquel decreased the number of active dopamine neurons in both areas, indicating an antipsychotic potential but also implying that seroquel possesses a high liability for causing extrapyramidal side-effects. The reason for the discrepancy between the previously reported selective action of seroquel and the result of the present study is not known. Seroquel is under evaluation for treatment of schizophrenia and the published data indicate that high dosages (750 mg, b.i.d.) are needed in order to obtain an antipsychotic effect (Hirsch, 1994). The incidence of extrapyramidal side-effects was not reported.

Ziprasidone has been described as a compound with a receptor profile predicting potential anti-psychotic with low extrapyramidal side-effect liability. Ziprasidone has a high affinity for serotonergic 5-HT_2 as well as for 5-HT_{1A} and 5-HT_{1C} receptors (Seeger et al., 1993; Zorn et al., 1993). Positron emission tomography (PET) (Wagner et al., 1983) studies in human volunteers suggest that ziprasidone possesses a high dopamine D_2 receptor occupancy (> 80%) after a single oral dose (60 mg, b.i.d.) (Bench et al., 1993) but data showing antipsychotic efficacy in schizophrenic patients are so far not available. The present electrophysiological experiments showed that ziprasidone decreased the number of spontaneously active dopamine neurons in both ventral tegmental area and substantia nigra pars compacta. Therefore, ziprasidone is expected to be categorized as a classical neuroleptic, i.e. inducing extrapyramidal side-effects in clinical studies.

Previous biochemical and behavioral findings have suggested that amperozide, a selective 5-HT_2 receptor antagonist (Meltzer et al., 1992), possesses a limbic site of action (Christensson and Gustafsson, 1985; Gustafsson and Christensson, 1990). According to Grenhoff et al. (1990) amperozide selectively affects the electrical activity (i.e. firing rate and regularization of burst firing) of dopamine neurons in the ventral tegmental area while leaving the dopamine neurons in the substantia nigra pars compacta unaffected. Amperozide has been tested for antipsychotic efficacy in a 4-week open study in 10 schizophrenic patients (Axelsson et al., 1991). Psychiatric assessments during the study suggested that amperozide possesses an antipsychotic profile, but in addition, induces extrapyramidal side-effects (i.e. tremor). The clinical profile of amperozide is consistent with the present electrophysiological findings, since amperozide inhibited the number of spontaneously active dopamine neurons in both areas.

The biochemical profile of the compounds does not indicate any correlation to the effect observed on the active dopamine neurons after repeated treatment. Amperozide and olanzapine are predominantly 5-HT_2 receptor antagonists, and yet, olanzapine showed selectivity for inhibiting the number of active dopamine neurons in the ventral tegmental area (after a single dose, only), whereas amperozide inhibited the activity in both areas. It is interesting that seroquel, an α_1-adrenoceptor antagonist, and amperozide, a 5-HT_2 receptor antagonist, are able to influence the activity of spontaneously active dopamine neurons. Several papers from Svensson and co-workers have described the effect of different receptor-specific compounds on dopamine neurons in the ventral tegmental area. Ritanserin, a 5-HT_2 receptor antagonist, blocks the effect of pre-frontal cortical inactivation of the dopamine neurons in the ventral tegmental area (Svensson et al., 1989), whereas phencyclidine (Pawlowski et al., 1990) and clonidine, an α_2-adrenoceptor agonist, caused regularization of dopamine cell firing in the ventral tegmental area (Grenhoff and Svensson, 1989). Based on experimental as well as clinical data, compelling evidence suggests that the activity of the mesolimbic dopamine neurons can be modulated (i.e. inducing an antipsychotic effect) by means other than direct dopamine receptor blockade. This is of special interest since the absence of dopamine receptor blockade might reduce the extrapyramidal side-effect liability.

Recently, Skarsfeldt and Perregaard (1990) reported that sertindole, a potent and long-acting antagonist at central 5-HT_2 receptors with relatively weaker peripheral α_1-adrenoceptor blockade in vivo (Sánchez et al., 1991), selectively reduced the number of active dopamine neurons in the ventral tegmental area, but had no significant effect in the substantia nigra pars compacta. In accordance with this, a double-blind clinical study has confirmed that this compound – without nigrostriatal dopamine blockade in vivo – possesses an antipsychotic profile without the liability to induce extrapyramidal side-effects (Martin et al., 1994). Based on the clinical profile of the novel compounds it seems to be possible to develop new research strategies (i.e. antipsychotic activity without dopamine blockade) for treatment of schizophrenic symptoms.

In summary, the present study has shown that both risperidone and olanzapine at a particular dose do show some selectivity for decreasing dopamine activity in the ventral tegmental area in comparison to dopamine activity in the substantia nigra par compacta. However, it is not possible to make predictions as to the likelyhood that these compounds tend to induce extrapyramidal side-effects, as risperidone showed a U-shaped dose-response curve and only one active dose of olanzapine was examined. No evidence was obtained to suggest that seroquel, ziprasidone and amperozide show selectivity for dopamine neurons in the ventral tegmental area.

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