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Acute effects of antipsychotic drugs on cardiovascular responses to stress

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Abstract

The effect of acute treatment with clozapine, risperidone and haloperidol on cardiovascular response to open field novelty stress was investigated in rats using radio-telemetry and video-tracking analysis. Pretreatment with clozapine dose-dependently inhibited the pressor response, tachycardia and increase in dP/dt and caused a marked reduction of exploratory locomotor activity. Similar effects were observed after risperidone treatment. Haloperidol treatment markedly reduced locomotor activity but its cardiovascular effects were limited to a more rapid return of heart rate towards baseline levels. These data suggest that particularly the atypical antipsychotic drugs, clozapine and risperidone, but not the typical antipsychotic, haloperidol, reduce cardiovascular stress responses, an effect that could reflect their anxiolytic action. Such anxiolytic effects could contribute to the beneficial clinical effects of atypical antipsychotic drugs in patients with schizophrenia.

Keywords: Clozapine; Haloperidol; Risperidone; Stress; Blood pressure; Heart rate; Behaviour

1. Introduction

Several studies have suggested that stress may precipitate psychotic symptoms in sensitive individuals or induce relapse in patients with schizophrenia (Goldstein, 1987; Kuipers and Bebbington, 1988; Malla et al., 1990). Treatment with antipsychotic drugs appears to protect against the effects of stress by raising the threshold for stressful life events to induce relapse (Nuechterlein et al., 1994). Behavioural therapy of both patients and carers has been suggested to reduce the risk of relapse (Goldstein, 1987; Linszen et al., 1996). Also, treatment with anxiolytic drugs, such as diazepam, has been found to reduce early symptoms of schizophrenia (Carpenter et al., 1999; Jaspert and Ebert, 1994) and a high number of patients with schizophrenia are co-medicated or abuse benzodiazepine anxiolytics (Pecknold, 1993; Stimmel, 1996).

There is conflicting evidence on possible anxiolytic properties of typical and atypical antipsychotic drugs themselves. This may be due to the wide variety of animal models used and to motor side-effects of the drugs that could interfere with the outcome of the tests (Costall and Naylor, 1995; Inoue et al., 1996). However, overall, the evidence would suggest that atypical antipsychotics, such as clozapine and risperidone, but not typical antipsychotics, such as haloperidol and chlorpromazine, exert moderate anxiolytic effects in animal models predictive of such action. For example, clozapine, but not haloperidol and chlorpromazine, increased responding in a conflict procedure suggesting anxiolytic effects (Wiley et al., 1993). Similarly, clozapine and risperidone, but not haloperidol and chlorpromazine, increased social interactions in rodents (Corbett et al., 1993).

While the anxiolytic effects of atypical antipsychotics could contribute to their superior therapeutic effect compared to typical antipsychotics, little is known about the effect of antipsychotic drugs on physiological responses to stress. We recently developed an experimental stress model in rats that combines the measurement of autonomic parameters with analysis of locomotor behaviour (Van den Buuse et al., 2001a,b). Rats are instrumented with radio-telemetry transmitters, allowing measurement of blood pressure and heart rate while the animals are freely moving (Brockway et al., 1991; Van den Buuse, 1994). The rats are placed in a brightly lit 'open field', from which there is no escape, and behaviour is analyzed by automated video-tracking (Van den Buuse et al., 2001a,b). The 'large' open field is a

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classical model to test fear and anxiety responses to novelty (Denenberg, 1969; Ramos and Mormede, 1998), a more naturalistic stress than widely used methods such as restraint. In the open field, rats showed increases in blood pressure and heart rate (Van den Buuse et al., 2001a,b), cardiac contractility (Van den Buuse, 2002) and body temperature (Van den Buuse et al., 2002). The increase in blood pressure was mediated by increased sympathetic vasomotor tone, while the tachycardia was mediated by increased cardiac sympathetic activity (Van den Buuse, 2002; Van den Buuse et al., 2001b).

Using this model, we found a clear separation of locomotor responses and autonomic responses to novelty. For example, repeated exposure of the rats to the open field resulted in reduced exploratory locomotor activity (Van den Buuse et al., 2001b), suggesting habituation (Ramos and Mormede, 1998). In contrast, pressor responses and tachycardia were similar on four consecutive days of open field exposure (Van den Buuse et al., 2001b), arguing against habituation. Pretreatment with diazepam almost completely abolished the pressor response to open field exposure and reduced the tachycardia, but had only minor effects on overall locomotor activity (Van den Buuse et al., 2001b). Our present study revealed marked effects of clozapine and risperidone on cardiovascular stress responses unrelated to their behavioural effects.

2. Materials and methods

2.1. Animals and surgery

Ten male Fischer 344 rats weighing 380–420 g were anaesthetised with pentobarbitone (Nembutal, 60 mg/kg intraperitonerally) and instrumented with TA11PA-C40 telemetry transmitters (Data Sciences Intl., St. Paul, MN, USA). Briefly, through a midline abdominal incision, the abdominal aorta was exposed and clamped off. A small hole was punctured in the wall of the aorta just rostral of the iliac bifurcation and the flexible tip of the transmitter cannula was inserted and fixed in place with a drop of tissue glue (Loctite 401 Instant Adhesive, Delware, USA). The body of the transmitter was sutured to the inside abdominal wall and all incisions were suture closed. After surgery, the rats were given a subcutaneous injection of 5 mg/kg of Carprofen (Zenecarp® Injection, UK) and allowed to recover in a warm box until they had completely recovered from anesthesia. From then on, the rats were housed individually under standard laboratory conditions with food and tap water ad libitum. Experiments were performed at least 10 days after surgery.

2.2. Open field telemetry

The open field consisted of a black 90 cm circular arena with a wall of approximately 30 cm high. Two 60W lights approximately 1 m above the open field floor provided lighting. Eight RLA 1010 receivers (Data Sciences) were placed under the floor and connected to a receiver multiplexer (RMX10, Data Sciences) and one channel on the system's consolidation matrix (BCM100, Data Sciences). The Dataquest Labpro (version 3.01) data acquisition system (Data Sciences) was used to obtain data for systolic, diastolic and mean blood pressure, heart rate, and gross locomotor activity every 12 s while each rat was in the open field (Van den Buuse et al., 2001a,b).

2.3. Video tracking analysis

A video camera, mounted on the ceiling above the open field, was used to record the rats' behaviour while it was in the open field. Video recordings were later analyzed using the Noldus Ethovision video tracking system (version 3.0). We determined distance moved and velocity of movements per min (Van den Buuse et al., 2001b). After antipsychotic treatment, the rats showed a high degree of inactivity, variably interrupted by bouts of exploratory locomotor activity. Because this lead to a large variability in the time-course of behavioural activity scores, only total 15-min scores are presented here.

2.4. Experimental protocol

Individual rats were placed in their home-cage on a single telemetry receiver in order to record pre-injection baseline values of blood pressure, heart rate and dP/dt. Fifteen minutes later, using a randomized crossover design, the animals were injected intraperitoneally (1 ml/kg) with either saline, 1.5 mg/kg or 5 mg/kg of clozapine (B. Dent Global, New Zealand), 0.05 mg/kg of haloperidol (*Haldol*, Searle, NSW, Australia), or 0.1 mg/kg of risperidone (*Risperdal*, Janssen-Cilag, NSW, Australia). These doses were based upon literature reports and preliminary experiments (not shown). Clozapine was dissolved in 0.1 N HCl, diluted with saline and pH neutralized. For haloperidol and risperidone, commercial solutions were diluted with saline to the appropriate dose. After injection, and still in their home-cage, the rats were placed on a second receiver to allow recording of post-injection baseline values during 15 min, the last 5 min of which are presented here. The rats were then gently transferred from their home cage to the open field, where they remained for 15 min. Blood pressure, heart rate, dP/dt and behavioural activity counts were recorder every 20 s by the telemetry system. The dP/dt here refers to the maximum rate of rise of the blood pressure wave (dP/dt_{max}).

After the experiment, the rats were returned to their home-cage and used again after a 3–4-day wash-out period.

2.5. Statistical analysis

All data is expressed as mean ± standard error of the mean (S.E.M.). Cardiovascular telemetry data were calculated as 1- or 15-min averages. Telemetry locomotor activity

counts were expressed as cumulative 15-min counts. Distance moved and velocity of movements, obtained from video tracking analysis, were expressed as cumulative 15-min values or 15-min averages, respectively. Time courses and differences between treatments were analysed using analysis of variance (ANOVA) with repeated measures, using the Systat 9.0 statistical software package. The Greenhouse–Geisser correction was applied when calculating P values from F values in the ANOVAs. Differences were considered statistically significant when $P<0.05$.

Preliminary analysis with one-way ANOVA with repeated measures on the entire data set showed significant differences between the five treatments for changes in blood pressure, heart rate and dP/dt (data not shown). In order to isolate which treatments caused significant changes from control responses, subsequent analysis compared responses seen after one particular drug treatment with those seen after saline injection.

3. Results

3.1. Baseline data

Intraperitoneal injection of saline did not induce any significant changes in mean arterial pressure, heart rate, or dP/dt (Table 1). In contrast, injection of both 1.5 and 5 mg/kg of clozapine caused a significant increase in resting heart rate and reduction of dP/dt. In addition, the high dose of clozapine also induced a significant reduction of basal blood pressure (Table 1). While haloperidol treatment did not cause any significant changes in baseline parameters, in rats treated with risperidone basal blood pressure and dP/dt were significantly reduced and resting heart rate tended to be increased ($P=0.07$).

3.2. Cardiovascular responses in the open field

After being placed in the open field, the rats showed a rapid rise in blood pressure, heart rate and dP/dt (Figs. 1 and 2). The increase in blood pressure peaked at 2–4 min after the rats were placed in the open field, with little return towards baseline values during the entire 15 min open field exposure. Pretreatment with 1.5 mg/kg of clozapine had no significant effect on the pressor response to open field novelty stress (Fig. 1). In contrast, after pretreatment with 5 mg/kg of clozapine, the pressor response was completely absent ($F(1,8)=14.5$, $P=0.005$) and clozapine-treated rats showed a gradually developing depressor response which paralleled blood pressure in saline-treated controls (effect of Time $F(14,112)=4.8$, $P=0.024$). Haloperidol pretreatment had no significant overall effect on the pressor response or its time-course (Fig. 2). In contrast, pretreatment with risperidone not only induced a significant overall attenuation of the stress-induced pressor response ($F(1,9)=17.7$, $P=0.002$), but blood pressure gradually fell rather than increased (effect of Time $F(14,126)=4.3$, $P=0.006$; Treatment × Time interaction $F(14,126)=2.9$, $P=0.030$).

The increase in heart rate showed a peak at 2–4 min after the rats were placed in the open field, followed by a gradual decline towards baseline values (Figs. 1 and 2). Pretreatment with 1.5 mg/kg of clozapine caused a significant overall attenuation of the tachycardia ($F(1,9)=8.3$, $P=0.018$), but did not influence the time-course of heart rate changes (effect of Time $F(14,126)=23.5$, $P<0.001$). Pretreatment with 5 mg/kg of clozapine similarly inhibited

Table 1
Baseline blood pressure, heart rate and dP/dt of male Fischer 344 rats before and 10–15 min after injection of saline or antipsychotic drugs

Treatment	Before injection	After injection	Change	In open field	Change
Mean arterial pressure (mm Hg)					
Saline	130 ± 3	126 ± 4	NS	140 ± 4*	14.1 ± 3.7
Clozapine 1.5 mg/kg	128 ± 4	134 ± 5	NS	141 ± 5*	6.7 ± 2.6
Clozapine 5 mg/kg	131 ± 5	116 ± 6*	− 13.6 ± 3.4	110 ± 8	NS
Haloperidol 0.05 mg/kg	129 ± 4	133 ± 4	NS	144 ± 5*	10.6 ± 1.5
Risperidone 0.1 mg/kg	129 ± 5	120 ± 5*	− 8.6 ± 3.3	117 ± 6	NS
Heart rate (beats/min)					
Saline	346 ± 8	332 ± 11	NS	425 ± 7*	93 ± 16
Clozapine 1.5 mg/kg	330 ± 10	376 ± 11*	51 ± 8	428 ± 8*	52 ± 8
Clozapine 5 mg/kg	349 ± 14	396 ± 15*	47 ± 15	417 ± 17*	21 ± 8
Haloperidol 0.05 mg/kg	338 ± 12	342 ± 6	NS	404 ± 8*	62 ± 9
Risperidone 0.1 mg/kg	336 ± 9	369 ± 12	NS	396 ± 16*	27 ± 10
dP/dt					
Saline	1.79 ± 0.13	1.70 ± 0.12	NS	2.04 ± 0.10*	0.34 ± 0.08
Clozapine 1.5 mg/kg	1.74 ± 0.14	1.51 ± 0.12*	− 0.27 ± 0.08	1.81 ± 0.13*	0.30 ± 0.04
Clozapine 5 mg/kg	1.89 ± 0.17	1.58 ± 0.14*	− 0.31 ± 0.07	1.81 ± 0.17*	0.23 ± 0.06
Haloperidol 0.05 mg/kg	1.80 ± 0.14	1.74 ± 0.13	NS	1.85 ± 0.13	NS
Risperidone 0.1 mg/kg	1.71 ± 0.11	1.40 ± 0.09*	− 0.32 ± 0.04	1.76 ± 0.13*	0.36 ± 0.05

NS = Not significant. Data are mean ± S.E.M.

* $P<0.05$ for difference with pre-injection values (post-injection data) or post-injection values (open field data).

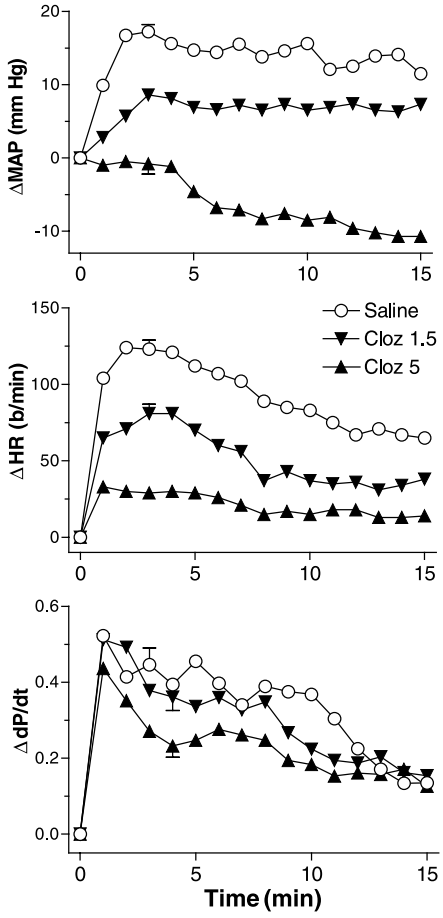


Fig. 1. Changes in blood pressure (top panel), heart rate (middle panel) and dP/dt (bottom panel) in Fischer 344 rats during 15 min in an open field. Rats were pretreated randomly with saline (○), 1.5 mg/kg of clozapine (Cloz 1.5, ▼) or 5 mg/kg of clozapine (Cloz 5, ▲).

the tachycardia ($F(1,8)=13.1$, $P=0.007$) and also significantly depressed the time-course of heart rate changes (effect of Time $F(14,112)=22.9$, $P<0.001$; Treatment × Time interaction $F(14,112)=11.3$, $P<0.001$). Pretreatment with haloperidol caused a significant overall attenuation of the tachycardia observed in the open field ($F(1,9)=9.4$, $P=0.013$). After haloperidol treatment, the rats initially showed a similar rapid rise in heart rate as saline-treated controls, followed by a more rapid return to baseline (effect of Time $F(14,126)=56.2$, $P<0.001$; Treatment × Time interaction $F(14,126)=3.6$, $P=0.014$). A similar, although more pronounced effect was seen after risperidone treatment. Again there was a significant overall reduction of the tachycardia ($F(1,9)=13.4$, $P=0.005$) and a more rapid return of heart rate values towards baseline (effect of Time $F(14,126)=25.3$, $P<0.001$; Treatment × Time interaction $F(14,126)=5.0$, $P=0.006$).

The increase in dP/dt was maximal at peak at 1 min after the rats were placed in the open field, followed by a gradual decline towards baseline values (Figs. 1 and 2). Neither dose of clozapine significantly influenced the increase in dP/dt or its time-course (Fig. 2). Pretreatment with haloperidol significantly reduced the increase in dP/dt when compared to saline-treatment ($F(1,8)=13.7$, $P=0.006$). After haloperidol treatment, the rats initially showed a similar rapid rise in dP/dt, followed by a more rapid return to baseline (effect of Time $F(14,112)=21.0$, $P<0.001$; Treatment × Time interaction $F(14,112)=4.7$, $P=0.003$). Risperidone treatment did not significantly influence dP/dt (Fig. 2).

A comparison of average changes blood pressure, heart rate and dP/dt after all treatments (Fig. 3) revealed that the average pressor response in the open field was significantly reduced by pretreatment with 5 mg/kg of clozapine and with risperidone. The average heart rate response was furthermore reduced by all pretreatments although the high dose of clozapine and risperidone had the most pronounced effect (Fig. 3). The increase in dP/dt in the open field was significantly reduced by haloperidol pretreatment only (Fig. 3).

3.3. Behavioural responses in the open field

Pretreatment with clozapine dose-dependently reduced locomotor activity in the open field (Fig. 3). Distance moved was significantly reduced after pretreatment with

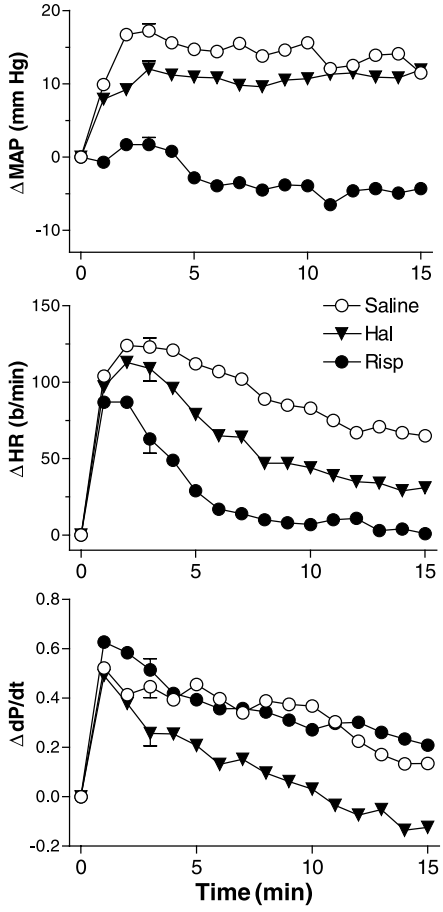
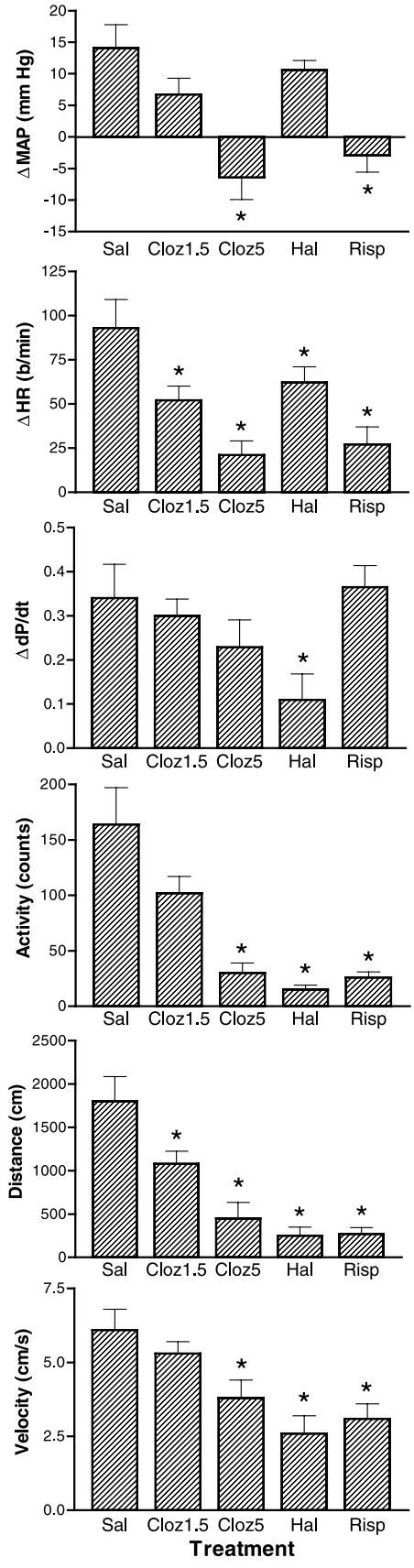


Fig. 2. Changes in blood pressure (top panel), heart rate (middle panel) and dP/dt (bottom panel) in Fischer 344 during 15 min in an open field. Rats were pretreated randomly with saline (○), 0.05 mg/kg of haloperidol (Hal, ▼), or 0.1 mg/kg of risperidone (Risp, ●).



either dose of clozapine, although the effect of 1.5 mg/kg was of borderline significance ($P = 0.04$). Only the highest dose of clozapine reduced velocity of movements (Fig. 3). Distance moved was markedly reduced by pretreatment with haloperidol and risperidone. Similarly, both haloperidol and risperidone significantly decreased velocity of movements (Fig. 3). These behavioural changes were reflected in the activity counts produced by the telemetry system. While pretreatment with 5 mg/kg of clozapine, haloperidol and risperidone markedly reduced locomotor activity counts, the decrease observed after pretreatment with 1.5 mg/kg of clozapine was of borderline significance ($P = 0.06$).

4. Discussion

The present results show pronounced effects of clozapine on cardiovascular responses to novelty stress in rats. The increase in blood pressure, observed when the animals were put in an open field, was completely abolished, whereas the tachycardia was markedly inhibited. These effects of clozapine were dose-dependent and similar effects were seen after treatment of the rats with risperidone, but not haloperidol. Although full dose–response studies are needed to confirm and extend the present findings, the results suggest marked anxiolytic effects of atypical antipsychotic drugs, such as clozapine and risperidone, but not typical antipsychotics, such as haloperidol. While these data confirm earlier studies in rats suggesting such effects (Corbett et al., 1993; Costall and Naylor, 1995; Wiley et al., 1993), our study is the first to focus on the cardiovascular effects of stress.

Cardiovascular regulation has received relatively little attention in experimental and clinical schizophrenia studies. Unmedicated patients with schizophrenia showed elevated resting levels of blood pressure and heart rate in some studies (Volz et al., 1994; Zahn et al., 2001), although this was not observed in other studies (Nielsen et al., 1988; Van Valkenburg and Winokur, 1984). Cardiovascular reactivity to physiological stimuli was exaggerated in schizophrenia (Olbrich et al., 2001) and this hyperreactivity was reversed by neuroleptic treatment (Nielsen et al., 1988) or after symptomatic remission (Olbrich et al., 2001). On the other hand, other investigators found cardiovascular reactivity to mild stress to be either reduced (Dawson et al., 1994; Zahn et al., 2001) or unchanged in patients with schizophrenia (Gispen-de Wied, 2000). The effects of antipsychotic treatment on cardiovascular responses to stress in patients with schizophrenia has been suggested to differ according to the anticholinergic properties of the drugs (Zahn et al., 2001).

Fig. 3. Average 15-min values for the pressor response (top panel), tachycardia (second panel), increase in dP/dt (third panel), activity counts (fourth panel), distance moved (fifth panel), and velocity of movements (bottom panel) observed in Fischer 344 rats in the open field. The rats were pretreated with 1.5 or 5 mg/kg of clozapine (Cloz), haloperidol (Hal), or risperidone (Risp). *$P < 0.05$ for difference with saline-pretreatment.

Our study also reveals marked differences in the effect of antipsychotic treatment on cardiovascular stress responses. While haloperidol, clozapine and risperidone had similar effects on behaviour, only the atypical antipsychotics blocked cardiovascular stress responses. A number of conclusions can be drawn from these differential effects. Firstly, the differential effects of antipsychotic drugs in our study cannot be explained simply by their action on exploratory locomotor activity. It could be argued that the high levels of locomotor activity indirectly cause blood pressure and heart rate to increase, rather than these effects being a direct stress-induced effect. Clozapine, risperidone and haloperidol had comparable effects on exploratory locomotor activity in the open field, despite having differential effects on cardiovascular responses.

Secondly, dopamine receptor blockade of the drugs tested are unlikely to be the mechanism solely responsible for the apparent anxiolytic effects in our model. If so, haloperidol, with its relatively high affinity for dopamine D_2 and D_1 receptors, would have been equally or more effective than clozapine and risperidone, which have moderate affinity for these receptors (Bymaster et al., 1999; Hartman et al., 1996; Janssen and Awouters, 1994) (see Table 2). Stress increases dopamine release from mesolimbic projections, including in the frontal cortex and nucleus accumbens (Finlay and Zigmond, 1997; Kalivas and Duffy, 1995; Roth et al., 1988). We have previously shown that activation of dopaminergic neurons in the ventral tegmental area modulates cardiovascular regulation (Cornish and Van den Buuse, 1995) and that administration of dopamine D_2 receptor agonists causes rapid increases in blood pressure (Van den Buuse, 1992; Van den Buuse et al., 1996). Thus, while these previous data suggest that novelty stress-induced changes in blood pressure and heart rate are at least partly mediated by central dopamine release, the lack of effect of haloperidol on these parameters in our model would argue against this possibility. The dose of haloperidol we used was clearly effective as it induced the most prominent decrease of exploratory locomotor activity of the three drugs.

Table 2
Summary of receptor binding affinities (K_i, nM) of haloperidol, clozapine and risperidone for dopaminergic and non-dopaminergic receptors

Receptor	Clozapine	Haloperidol	Risperidone
Dopamine D_1	85	25	75
Dopamine D_2	125	1	1.5
Dopamine D_3	84	5	6.7
Dopamine D_4	47	1.6	–
Dopamine D_5	85	12	–
$5HT_{1A}$	770	7930	16
$5HT_{2A}$	6.5	58	0.6
Muscarinic M_1	1.9	1475	>3000
α_1-Adrenoceptor	7	46	2
α_2-Adrenoceptor	8	360	3
β_1-Adrenoceptor	>10,000	>10,000	>10,000
$GABA_A$	>10,000	>10,000	>10,000

Data obtained from studies by Bymaster et al. (1999) and Hartman et al. (1996).

While haloperidol treatment did not attenuate either the maximum pressor response or tachycardia, it was not totally devoid of cardiovascular effects. Unexpectedly, haloperidol treatment significantly inhibited the later phase of the increase in heart rate and dP/dt caused by novelty stress, an effect not seen with clozapine and risperidone. Further studies with other antipsychotics are needed to investigate whether this effect of haloperidol reflects a generalized difference between typical and atypical antipsychotics. At this point we can only speculate about the mechanism of action of haloperidol. It is however unlikely that α-adrenergic, β-adrenergic or muscarinic effects are involved as the affinity of haloperidol for these receptors is low or negligible (see Table 2). Dopamine D_2 receptors have been found on sympathetic nerve endings and both D_2 and D_4 receptors have been located in the heart (Amenta et al., 1993; O'Malley et al., 1992). The high affinity of haloperidol for these receptors makes them a target for its action on heart rate and contractility. Alternatively, the effect of haloperidol is centrally mediated and reflects a selective inhibition of the increased cardiac sympathetic activity normally associated with this stress. This effect could thus be a compensatory mechanism, as the initial increase in heart rate and dP/dt in haloperidol-treated rats was similar as that seen in controls, unlike in animals treated with a β-adrenoceptor blocker (Van den Buuse et al., 2001b) or clozapine. Haloperidol treatment then facilitates return of increased cardiac sympathetic activity to baseline levels, suggesting that prolonged stress-induced dopamine release in the forebrain is involved in cardiac sympathetic activation, but in its maintenance rather than the initial response. Future studies using other selective dopamine receptor antagonists are needed to test this hypothesis.

One shortcoming of this study is that only the acute effects of antipsychotics were investigated and future studies will have to address whether the apparent anxiolytic effects are also observed after chronic treatment. Furthermore, peripheral effects of the antipsychotic drugs on cardiovascular regulation could have influenced the results of our study. Both clozapine and risperidone have physiologically relevant affinity for a number of receptors involved in peripheral regulation of blood pressure and heart rate (Table 2) (Bymaster et al., 1999; Hartman et al., 1996). For example, both clozapine and risperidone, but not haloperidol, have significant affinity for α_1-adrenoceptors (Table 2) (Bymaster et al., 1999; Hartman et al., 1996). This is probably the mechanism behind the reduction of baseline blood pressure observed after treatment with these drugs (Table 1). Blockade of vascular α_1-adrenoceptors could also be involved in the attenuation of the stress-induced pressor response. Muscarinic receptor blockade by clozapine could be responsible for the significant increase in resting heart rate in rats (Table 1) as has been suggested in humans (Agelink et al., 2001; Zahn and Pickar, 1993). In contrast, muscarinic

blockade is unlikely to play a role a major role in the effect of this drug on the stress-induced tachycardia seen in rats in the open field. We have previously shown that muscarinic blockade by treatment with methyl-atropine has little effect on the tachycardia, whereas treatment with the β-adrenoceptor antagonist atenolol virtually eliminated this effect (Van den Buuse, 2002; Van den Buuse et al., 2001b). Both clozapine and risperidone have negligeable affinity for β-adrenoceptors, making it unlikely that peripheral blockade of these receptors is the mechanism by which these drugs inhibit the stress-induced tachycardia. Consequently, this suggests that the inhibition of cardiovascular changes induced by open field stress cannot be explained solely by peripheral mechanisms and make it likely that a central action is involved in the effects of atypical antipsychotics on both the pressor response and tachycardia.

Changes in baseline blood pressure, heart rate and dP/dt after treatment with clozapine or risperidone could have influenced subsequent cardiovascular changes when the rats are placed in the open field. Particularly the significant elevation of baseline heart rate after clozapine treatment could have limited the subsequent tachycardia in the open field. This would seem unlikely, however, as the increase in baseline heart rate was similar with both doses of clozapine, but the high dose inhibited the tachycardia more markedly than the low dose. Similarly, the small fall in baseline blood pressure caused by 5 mg/kg of clozapine and by risperidone did not cause enhanced pressor responses, but after these treatments rather the opposite was observed, a blockade of the pressor response.

In conclusion, our experimental model, combining telemetric measurements of cardiovascular responses and video analysis of behaviour, provides a way to study the central and systemic mechanisms involved in the possible anxiolytic action of antipsychotic drugs. For example, future studies could address the action of other typical and atypical drugs with varying receptor-binding profiles on behavioural and cardiovascular effects of stress. Further studies could also include central administration of these drugs to analyse the brain regions involved in their effect. These studies could shed more light on the mechanisms involved in the beneficial anxiolytic effects of atypical antipsychotic drugs.

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