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Involvement of serotonin$_{1A}$ receptors in cardiovascular responses to stress: a radio-telemetry study in four rat strains

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Abstract

We studied the effect of treatment with the serotonin-1A (5-HT$_{1A}$) receptor ligands buspirone, 8-hydroxy-di-propyl-aminotetralin (8-OH-DPAT), and (8-[2-(2,3-dihydro-1,4-benzodioxin-2-yl-methylamino)ethyl]-8-azaspiro[4,5]decane-7,9-dione methyl sulphonate (MDL73,005EF) on blood pressure and heart rate increases to open field stress. We compared Spontaneously Hypertensive Rats (SHR), Fawn–Hooded (FH) rats, Wistar–Kyoto (WKY) rats, and Sprague–Dawley (SD) rats instrumented with radio-telemetry probes. Buspirone treatment reduced the blood pressure increase in SHR, FH rats, and WKY rats and heart rate increase in FH rats and WKY rats. 8-OH-DPAT treatment reduced the blood pressure increase in FH rats and WKY rats, but had no effect in SHR and enhanced the pressor response in SD rats. This treatment reduced the heart rate increase in FH rats and WKY rats only. Similarly, MDL73,005EF treatment reduced the blood pressure increase in FH rats and WKY rats, but had no effect in SHR and enhanced this response in SD rats. Little effect of this treatment was seen on heart rate changes. For comparison, diazepam treatment abolished the pressor response in SD rats and reduced it in FH rats and WKY rats, but not SHR. Differential effects of the treatments were also seen between strains for locomotor activity in the open field, although behavioural changes could not explain the effects of the drugs on cardiovascular responses. These data suggest that 5-HT$_{1A}$ receptors are involved in cardiovascular stress responses; however, the extent of this involvement differs between rat strains and the drugs used. These results could be important for our understanding of possible anxiolytic properties of antipsychotic drugs with affinity for the 5-HT$_{1A}$ receptor.

Keywords: 5-HT$_{1A}$ receptor; Stress; Blood pressure; Heart rate; Anxiolytic; Strain difference

1. Introduction

Stress is a risk factor in many illnesses, including mental disorders, such as schizophrenia (Gispen-de Wied, 2000; Norman and Malla, 1993). In this illness, stress may induce relapse or aggravations of symptoms. Psychosocial treatments, such as behavioural therapy, and medication with anxiolytic drugs in addition to antipsychotic medications may help to reduce these risks (Gispen-de Wied, 2000; Norman and Malla, 1993).

There is increasing interest in the role of serotonin (5-HT) in the development and symptoms of schizophrenia and the action of antipsychotic drugs (Breier, 1995; Meltzer, 1999). While much of the early research has focused on the 5-HT$_{2A}$ receptor, there is increasing interest in the potential role of 5-HT$_{1A}$ receptors as well. Several of the second generation and newer antipsychotic drugs, including clozapine, aripiprazole, and ziprasidone, display high affinity for the 5-HT$_{1A}$ receptor (Bantick et al., 2001; Li et al., 2004). Amongst other brain areas, 5-HT$_{1A}$ receptors are located on glutamatergic pyramidal neurons in the cortex and hippocampus and on serotonergic cell bodies in the raphe nuclei (Duncan et al., 1998; Hall et al., 1997). Postmortem studies revealed a significant increase in the density of 5-HT$_{1A}$ receptors in the frontal cortex of subjects with schizophrenia

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(Burnet et al., 1996; Simpson et al., 1996). 5-HT_{1A} receptor density was decreased in the amygdala of patients with schizophrenia (Yasuno et al., 2004), which is particularly interesting in view of the role this brain areas plays in anxiety and stress responses (Davis and Whalen, 2001). Several experimental or clinically used anxiolytic drugs display (partial) agonist activity at the 5-HT_{1A} receptor, e.g., buspirone (Apter and Allen, 1999; Moser et al., 1990), flesinoxan (Groenink et al., 2000), and (8-[2-(2,3-dihydro-1,4-benzodioxin-2-yl-methylamino)ethyl]-8-azaspiro[4,5]-decane-7,9-dione methyl sulphonate (MDL73,005EF; Moser et al., 1990), and it is likely that at least some of these effects are mediated via the amygdala (Groenink et al., 2000; Schreiber and De Vry, 1993).

Animal models of anxiety and stress usually involve recording differential behavioural responses of rodents to aversive or conditioned situations (Belzung and Le Pape, 1994; Van Gaalen and Steckler, 2000). However, stress is accompanied by a complex set of autonomic changes, including changes in blood pressure, heart rate and cardiac output, body temperature, and regional blood flow (Hjemdahl, 2000), and the role of central serotonergic mechanisms and effect of serotonergic anxiolytics on these parameters has been little studied. In rats, we developed a model of mild psychological novelty stress using freely moving rats equipped with radio-telemetry transmitters (Van den Buuse et al., 2001b). When placed in a wide open-field, the animals display a marked increase in blood pressure, heart rate, dP/dt, and body temperature (Van den Buuse, 2002; Van den Buuse et al., 2002), in addition to exploratory locomotor activity. Treatment with the prototypical benzodiazepine anxiolytic, diazepam, almost completely blocked cardiovascular stress responses in this model (Van den Buuse et al., 2001b). Interestingly, also the administration of the atypical antipsychotic drugs, clozapine and risperidone, inhibited these responses (Van den Buuse, 2003), suggesting these drugs may have anxiolytic properties that contribute to their favourable clinical profile.

In view of the abovementioned role of 5-HT_{1A} receptors in mental illnesses, such as schizophrenia, changes in stress sensitivity in this illness, and the effect of stress on the autonomic nervous system, the focus of the present study was the effect of different drugs with high affinity for the 5-HT_{1A} receptor on cardiovascular responses to stress. We compared the prototypical 5-HT_{1A} receptor agonist 8-hydroxy-di-propyl-aminotetralin (8-OH-DPAT) and the partial agonists buspirone and MDL 73,005EF (Moser et al., 1990). Fawn–Hooded rats (FH-rats) have been used widely as an animal model of alcohol preference and of depression and anxiety (Overstreet et al., 1992; Rezvani et al., 2002). The density of 5-HT_{1A} receptors was found to be increased in the hippocampus of these animals, together with other alterations in serotonergic markers in the brain (Chen and Lawrence, 2000; McBride et al., 1994). SHR were chosen because of their markedly increased cardiovascular stress responsivity (Van den Buuse et al., 2001a) and because studies have suggested altered density of 5-HT_{1A} receptors in the brains of these rats (Huguet and Brisac, 1991). Wistar–Kyoto rats (WKY rats) are usually used as controls for both FH rats and SHR; however, studies have suggested that this strain displays behavioural changes and may be an animal model for depression (Lahmame and Armario, 1996). We therefore also included Sprague–Dawley rats (SD rats) in our study.

2. Material and methods

Male SD rats, WKY rats, SHR, and FH rats of approximately 6 months of age were anaesthetised with an isoflurane/oxygen mixture and instrumented with TA11PA-C40 telemetry transmitters (Data Sciences Intl., St. Paul, MN, USA) as described previously (Van den Buuse, 1994, 2003). 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, DE, USA). The body of the transmitter was sutured to the inside abdominal wall and all incisions were suture closed. The rats were given a subcutaneous injection of 5 mg/kg of Carprofen (Zenecarp ® Injection, UK) to reduce postoperative discomfort. After surgery, 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.

The open field consisted of a black 90-cm circular arena with a wall of approximately 30 cm high (Van den Buuse, 1994, 2003; Van den Buuse and De Jong, 1988). Two 60-W lights approximately 1 m above the open-field floor provided lighting. Six 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 20 s while each rat was in the open field (Van den Buuse, 2003; Van den Buuse et al., 2001a,b).

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 minute (Van den Buuse et al., 2001a,b).

Individual rats were placed in their home cage on a single telemetry receiver in order to record preinjection baseline values of blood pressure and heart rate. Thirty minutes later,

using a randomized crossover design, the animals were injected intraperitoneally (1 ml/kg) with either saline, 0.05 mg/kg or 0.25 mg/kg of 8-OH-DPAT, 0.1 mg/kg or 0.5 mg/kg of buspirone, 1 mg/kg of MDL 73,005EF, or 2.5 mg/kg of diazepam. Thus, all animals received all treatments in a randomized sequence. All drugs were obtained from Sigma and dissolved in saline immediately prior to the experiments. After injection, and still in their home cage, the rats were placed on a second receiver to allow recording of postinjection baseline values during 30 min, the last 10 min of which is presented here. The rats were then gently transferred from their home cage to the open field, where they remained for 30 min. Blood pressure, heart rate, and behavioural activity counts were recorded every 20 s by the telemetry system. After the experiment, the rats were returned to their home cage and used again after a 3–4 day washout period.

All data were expressed as mean±standard error of the mean (S.E.M.), and statistical comparisons were made using analysis of variance (ANOVA) with repeated measures where appropriate (Systat 9 statistical software, SPSS, USA). Preinjection blood pressure and heart rate values obtained in the home cage during each of the experimental sessions were considered as baseline values and analyzed using Strain as between-group factor and Session as within-group, repeated measures factor (Figs. 1 and 2). The effect of different drugs and drug doses on baseline blood pressure and heart rate was analyzed by combining preinjection values and postinjection values with Strain as the between-group factor and Treatment as the within-group factor. Similarly, the effects of different drugs and drug doses on blood pressure and heart rate values in the open-field were analyzed by combining postinjection values with Strain as the between-group factor and Treatment as the within-group factor. In the latter analysis, Time was also used as within-group, repeated factor. Data for distance moved and velocity of movement obtained from Ethovision analysis were summed and averaged, respectively, for the entire 30 min in the open-field. Group differences were analyzed with Strain as between-group factor and Treatment as within-group factor. Data were considered significantly different if $P<0.05$.

3. Results

3.1. Baseline blood pressure and heart rate

There were marked strain differences in baseline blood pressure. Blood pressure was highest in SHR, ranging from 154 to 166 mm Hg between sessions, and FH rats, ranging from 153 to 166 mm Hg. Blood pressure was lowest in SD rats, ranging from 116 to 126 mm Hg between sessions, and WKY rats, ranging from 115 to 123 mm Hg. Analysis of all preinjection blood pressure values showed a main effect of Strain [$F(3,24)=8.9$, $P<0.001$]; however, there were no differences within each strain in basal blood pressure values between the seven experiments the animals were subjected to.

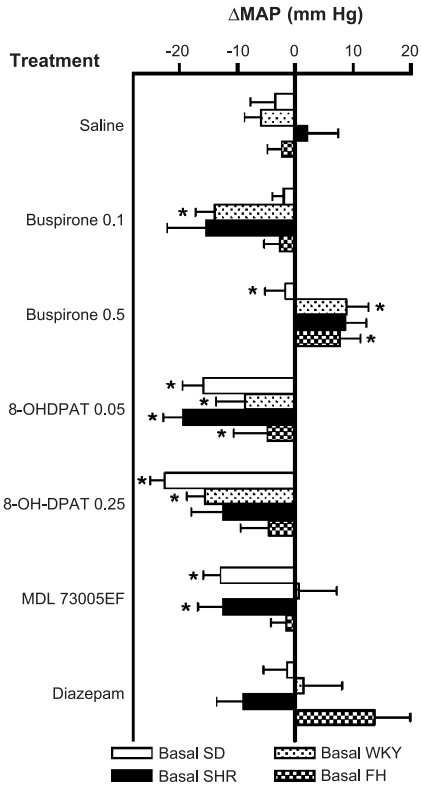

Fig. 1. Changes in baseline mean arterial pressure (MAP, mm Hg) in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats after treatment with saline, 0.1 or 0.5 mg/kg of buspirone, 0.05 or 0.25 mg/kg of 8-OH-DPAT, 1 mg/kg of MDL 73,005EF, or 2.5 mg/kg of diazepam. Baseline MAP was measured for 30 min in the home cage by radio-telemetry.

Analysis of baseline, preinjection heart rate values also showed a main effect of Strain [$F(3,25)=10.0$, $P<0.001$] and no difference between sessions. Baseline heart rate was highest in SD rats, ranging from 337 to 355 b/min between sessions, and lowest in WKY rats, ranging from 275 to 291 b/min. Heart rate values were intermediate in SHR, ranging from 283 to 310 b/min between sessions, and FH rats, ranging from 303 to 328 b/min.

3.2. Treatment effects on basal blood pressure and heart rate

Analysis of preinjection and postinjection blood pressure values from all strains revealed significant differences between the various treatments [main effect of Drug $F(6,144)=3.5$, $P=0.003$; main effect of Time $F(1,24)=20.3$, $P<0.001$; interaction of Drug×Time $F(6,144)=10.6$, $P<0.001$] and between strains [main effect of Strain $F(3,24)=11.2$, $P<0.001$; interaction of Time×Strain $F(3,24)=4.1$, $P=0.018$; interaction of Drug×Time×Strain $F(18,144)=1.7$, $P=0.046$].

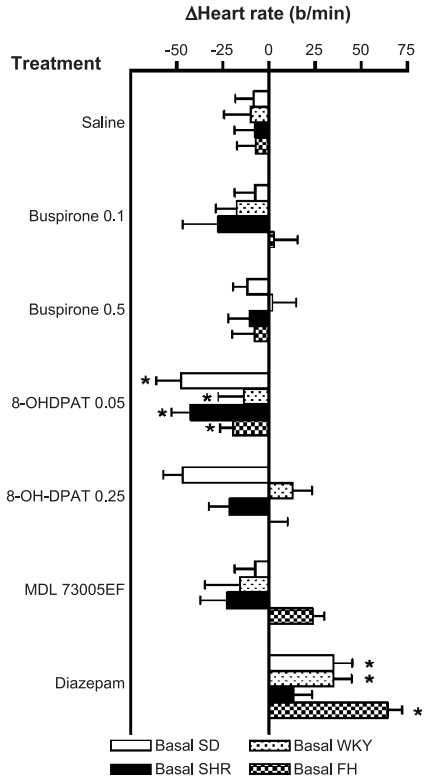

Fig. 2. Changes in baseline heart rate (b/min) in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats after treatment with saline, 0.1 or 0.5 mg/kg of buspirone, 0.05 or 0.25 mg/kg of 8-OH-DPAT, 1 mg/kg of MDL 73,005EF, or 2.5 mg/kg of diazepam. Baseline heart rate was measured for 30 min in the home cage by radio-telemetry.

Further comparison of the effect of treatment with individual drugs and doses on basal blood pressure in all cases showed the expected main effect of Strain (not shown). Saline treatment did not significantly affect baseline blood pressure. Treatment with 0.1 mg/kg of buspirone caused a significant fall in blood pressure [main effect of Treatment $F(1,24)=15.5$ $P=0.001$], which tended to be different between strains [interaction of Strain×Treatment $F(3,24)=2.8$, $P=0.059$]. Paired t-test analysis of responses in individual strains revealed a significant reduction of baseline blood pressure in WKY rats, but not in SD rats or FH rats. Blood pressure tended to be decreased in SHR after treatment with 0.1 mg/kg of buspirone; however, this was not significant (Fig. 1). Analysis of blood pressure responses to treatment with 0.5 mg/kg of buspirone yielded a main effect of Treatment [$F(1,24)=9.5$, $P=0.005$) with no indication of a strain difference, although inspection of the data (Fig. 1) shows a tendency for blood pressure to increase after this treatment in WKY rats, SHR, and FH rats, but not SD rats. Treatment with 0.05 mg/kg of 8-OH-DPAT caused a significant reduction of baseline blood pressure [main effect of Treatment $F(1,24)=22.4$, $P<0.001$], which also was not different between strains (Fig. 1). Analysis of blood pressure responses to treatment with 0.25 mg/kg of 8-OH-DPAT showed a significant reduction [main effect of Treatment $F(1,24)=34.3$, $P<0.001$] which tended to be different between strains [interaction of Strain×Treatment $F(3,24)=2.5$, $P=0.082$]. The effect of this dose of 8-OH-DPAT was significant in SD rats and WKY rats, but not SHR and FH rats (Fig. 1). Analysis of blood pressure responses to treatment with MDL73,005EF also showed a significant reduction [main effect of Treatment $F(1,24)=8.6$, $P=0.007$], which again tended to be different between strains [interaction of Strain×Treatment $F(3,24)=2.5$, $P=0.087$]. The effect of this drug was significant in SD rats and SHR, but not WKY rats and FH rats (Table 1). Treatment with diazepam caused no significant effect on blood pressure in any of the strains (Fig. 1).

Analysis of preinjection and postinjection heart rate values from all strains revealed significant differences between the various treatments [main effect of Drug $F(6,150)=4.9$, $P<0.001$; interaction of Drug×Time $F(6,150)=13.8$, $P<0.001$] in addition to the expected main effect of Strain [$F(3,25)=14.4$, $P<0.001$].

Further comparison of the effect of treatment with individual drugs and doses on basal heart rate in all cases showed the expected main effect of Strain (not shown). Saline treatment did not significantly affect basal heart rate. Similarly, treatment with either 0.1 mg/kg or 0.5 mg/kg of buspirone did not affect basal heart rate in any of the strains (Fig. 2). Furthermore, while treatment with 0.05 mg/kg of 8-OH-DPAT caused a significant reduction of basal heart rate [$F(1,25)=25.4$, $P<0.001$], which was not significantly different between strains, treatment with 0.25 mg/kg of 8-OH-DPAT or MDL 73,005EF did not have a significant effect (Fig. 2). On the other hand, diazepam treatment markedly increased baseline heart rate [main effect of Treatment $F(1,25)=74.5$, $P<0.001$], and this effect was different between strains [interaction of Strain×Treatment $F(3,25)=6.4$, $P=0.002$]. Analysis with paired t-test showed a significant increase in heart rate in SD rats, WKY rats, and FH rats, but not SHR (Fig. 2).

3.3. Strain differences in blood pressure and heart rate changes in the open field

After placement of the rats in the open-field, blood pressure increased rapidly, generally peaking in the first 5–10 min (Fig. 3). There were marked differences in the magnitude of blood pressure changes between strains [$F(3,24)=8.9$, $P<0.001$] and strain-related differences in the time course of the pressor response [main effect of Time $F(5,120)=6.2$, $P<0.001$; Time×Strain interaction $F(15,120)=3.1$, $P<0.001$]. Blood pressure changes in the open-field were smallest in SD rats, followed by FH rats and WKY rats. In SHR, blood pressure increases were much more prolonged than in the other strains (Figs. 3 and 4).

Similar to blood pressure, heart rate increased rapidly after the rats were placed in the open-field (Fig. 3) and there were marked strain differences in the magnitude of the tachycardic response [main effect of Strain $F(3,25)=9.9$,

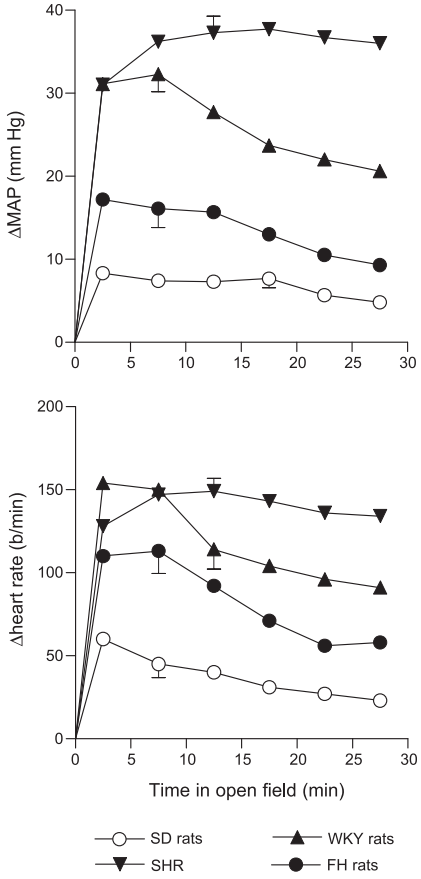

Fig. 3. Comparison of changes in mean arterial pressure (MAP, top panel) and heart rate (bottom panel) in saline-treated Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats. The animals were placed in the open-field for 30 min, and MAP and heart rate changes were detected by radio-telemetry.

$P<0.001$) and its time course [main effect of Time $F(5,125)=16.6$, $P<0.001$; interaction of Time×Strain $F(15,125)=3.1$, $P<0.001$]. Heart rate changes in the open field were smallest in SD rats, followed by WKY rats and FH rats. As with blood pressure changes, the increase in heart rate was more prolonged in SHR than in the other strains (Figs. 3 and 5).

3.4. Effect of treatments on blood pressure changes in the open field

Analysis of the changes in blood pressure from all strains and all drug treatments revealed a main effect of Strain [$F(3,24)=23.8$, $P<0.001$] and of Treatment [$F(6,144)=8.9$, $P<0.001$], as well as an interaction between these two factors [$F(18,144)=1.9$, $P=0.024$], indicating differential effects of the drugs between strains. There were also a main effect of Time [$F(5,120)$, $P=2.9$, $P=0.017$], a Time× Treatment interaction [$F(30,720)=6.9$, $P<0.001$], a Time× Strain interaction [$F(15,120)=4.3$, $P<0.001$], and a Time×Strain×Treatment interaction [$F(90,720)=1.4$, $P=0.008$], confirming that the time course of blood pressure changes was also influenced by the drug treatments and strains.

To further unravel the effects of the different drugs in the different strains (Figs. 4 and 6), subsequent ANOVAs were done comparing the pressor response after treatment with saline with that after different individual drugs in different individual strains. While after treatments in many cases still a significant increase in blood pressure was seen when the animals were placed in the open-field (Fig. 6), individual treatments differentially altered the magnitude or time course of this response (Fig. 4). Generally, main effects of Time were observed (not shown). Treatment with 0.1 mg/kg of buspirone did not significantly affect the blood pressure increase in any of the strains. Treatment with 0.5 mg/kg of buspirone similarly had no significant effect in SD rats but virtually abolished the pressor response in WKY rats [$F(1,6)=40.2$, $P=0.001$], SHR [$F(1,6)=8.0$, $P=0.029$] and FH rats [$F(1,7)=25.2$, $P=0.002$]. In addition, the increase in blood pressure was shortened in WKY rats and SHR [interaction of Time× Treatment $F(5,30)=7.1$, $P<0.001$ and $F(5,30)=3.5$, $P=0.013$, respectively; Fig. 4].

Treatment with 0.05 mg/kg of 8-OH-DPAT significantly reduced the pressor response in WKY rats [main effect of Treatment $F(1,6)=6.6$, $P=0.043$] and FH rats [$F(1,7)=12.0$, $P=0.011$] and altered the time course of the blood pressure changes in WKY rats [interaction of Time×Treatment $F(5,30)=7.2$, $P<0.001$]. In contrast, this dose of 8-OH-DPAT had no significant effect in SHR and caused a late *enhancement* of the pressor response in SD rats [interaction of Time×Treatment $F(5,20)=3.1$, $P=0.031$]. Treatment with 0.25 mg/kg of 8-OH-DPAT also reduced the pressor response in WKY rats [$F(1,6)=11.7$, $P=0.014$] and FH rats [$F(1,7)=11.2$, $P=0.012$] and altered the time course in both strains [interaction of Time×Treatment $F(5,30)=35.8$, $P<0.001$ and $F(5,35)=12.4$, $P<0.001$]. Inspection of the data (Fig. 4) revealed that the pattern of an early peak followed by a gradual decline of the pressor response was altered into a suppression of the early peak followed by a plateau (WKY rats) or even a gradual slight increase (FH rats). In SHR, a similar effect was seen, although this only reached trend level [main effect of Treatment $F(1,6)=5.0$, $P=0.067$; Time×Treatment interaction $F(5,30)=2.2$, $P=0.079$]. In SD rats, similar to the lower dose, this treatment caused a gradual enhancement of the pressor response [interaction of Time×Treatment $F(5,20)=6.0$, $P=0.002$; Fig. 4].

Treatment with MDL73,005EF caused a small, but significant reduction of the pressor response in WKY rats [main effect of Treatment $F(1,6)=7.2$, $P=0.036$; Time× Treatment interaction $F(5,30)=4.3$, $P=0.004$] and FH rats [main effect of Treatment $F(1,7)=5.6$, $P=0.050$; Fig. 4]. There was no effect of MDL73,005EF in SHR; however, in SD rats, this treatment altered the time course of the pressor response [interaction of Time×Treatment $F(5,20)=3.5$,

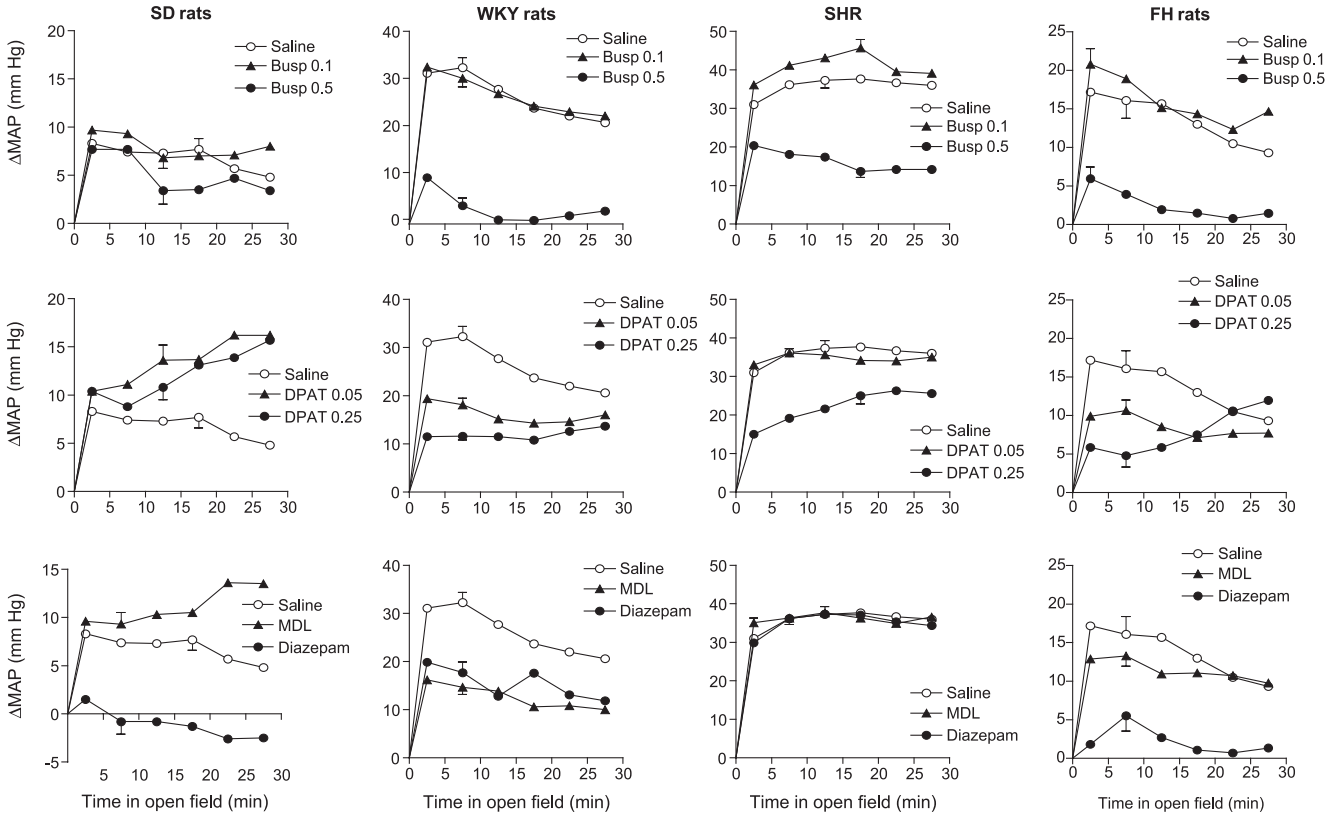

Fig. 4. Changes in mean arterial pressure (MAP) in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats. The animals were treated with 0.1 or 0.5 mg/kg of buspirone (top panels), 0.05 or 0.25 mg/kg of 8-OH-DPAT (middle panels), 1 mg/kg of MDL73,005EF (MDL, bottom panel), or 2.5 mg/kg of diazepam (bottom panel) in a randomized cross-over design. At 30 min after injection, the rats were placed in the open-field for 30 min, and MAP changes were detected by radio-telemetry. Note the differences in scales on the vertical axes. Data are mean±average within-animal standard error of the mean (S.E.M.) of n=8–9 rats per group.

P=0.019], such that, similar to the effect of 8-OH-DPAT in this strain, the pattern of an early peak followed by a gradual decline was altered into a late enhancement of the pressor response (Fig. 4). Treatment with diazepam markedly reduced the pressor response in SD rats [main effect of Treatment $F(1,4)=26.7$, $P=0.007$], WKY rats [$F(1,6)=11.3$, $P=0.015$], and FH rats [$F(1,7)=21.2$, $P=0.002$]; however, there was no effect in SHR.

3.5. Effect of treatments on heart rate changes in the open field

Analysis of the changes in heart rate from all strains and all drug treatments revealed a main effect of Strain [$F(3,25)=40.5$, $P<0.001$] and of Treatment [$F(6,150)=8.6$, $P<0.001$]. There were also a main effect of Time [$F(5,125)$, $P=85.1$, $P<0.001$], a Time×Treatment interaction [$F(30,750)=2.9$, $P<0.001$], and a Time×Strain interaction [$F(15,125)=6.1$, $P<0.001$], suggesting that the time course of heart rate changes was influenced both by the drug treatments and strains (Fig. 5).

Subsequent ANOVAs were done comparing the effect of saline injection with that of different individual drugs in different individual strains. As with blood pressure, while after treatments in many cases still a significant increase in heart rate was seen when the animals were placed in the open-field (Figs. 5 and 7), individual treatments differentially altered the magnitude or time course of this response (Fig. 5). Generally, main effects of Time were observed (not shown). Treatment with 0.1 mg/kg of buspirone did not significantly affect the heart rate increase in any of the strains, although a trend towards a reduction was seen in FH rats [Fig. 5; main effect of Treatment $F(1,7)=5.4$, $P=0.053$; Time×Treatment interaction $F(5,35)=2.5$, $P=0.051$]. Treatment with 0.5 mg/kg of buspirone had no significant effect in SD rats, in contrast to a significant reduction of the tachycardic response in WKY rats [$F(1,6)=37.6$, $P=0.001$] and FH rats [$F(1,7)=11.8$, $P=0.011$]. The only effect this treatment had in SHR was to slightly alter the time course of the heart rate changes [Time×Treatment interaction $F(5,35)=20.3$, $P<0.001$], such that the prolonged time course was now changed into an early peak followed by a gradual decline, similar to that seen in other strains (Fig. 5).

Treatment with either 0.05 or 0.25 mg/kg of 8-OH-DPAT had no significant effect on the heart rate increase in SD rats. In WKY rats and FH rats, treatment with the lower dose significantly reduced and shortened the response [main effect of Treatment $F(1,6)=11.5$, $P=0.015$

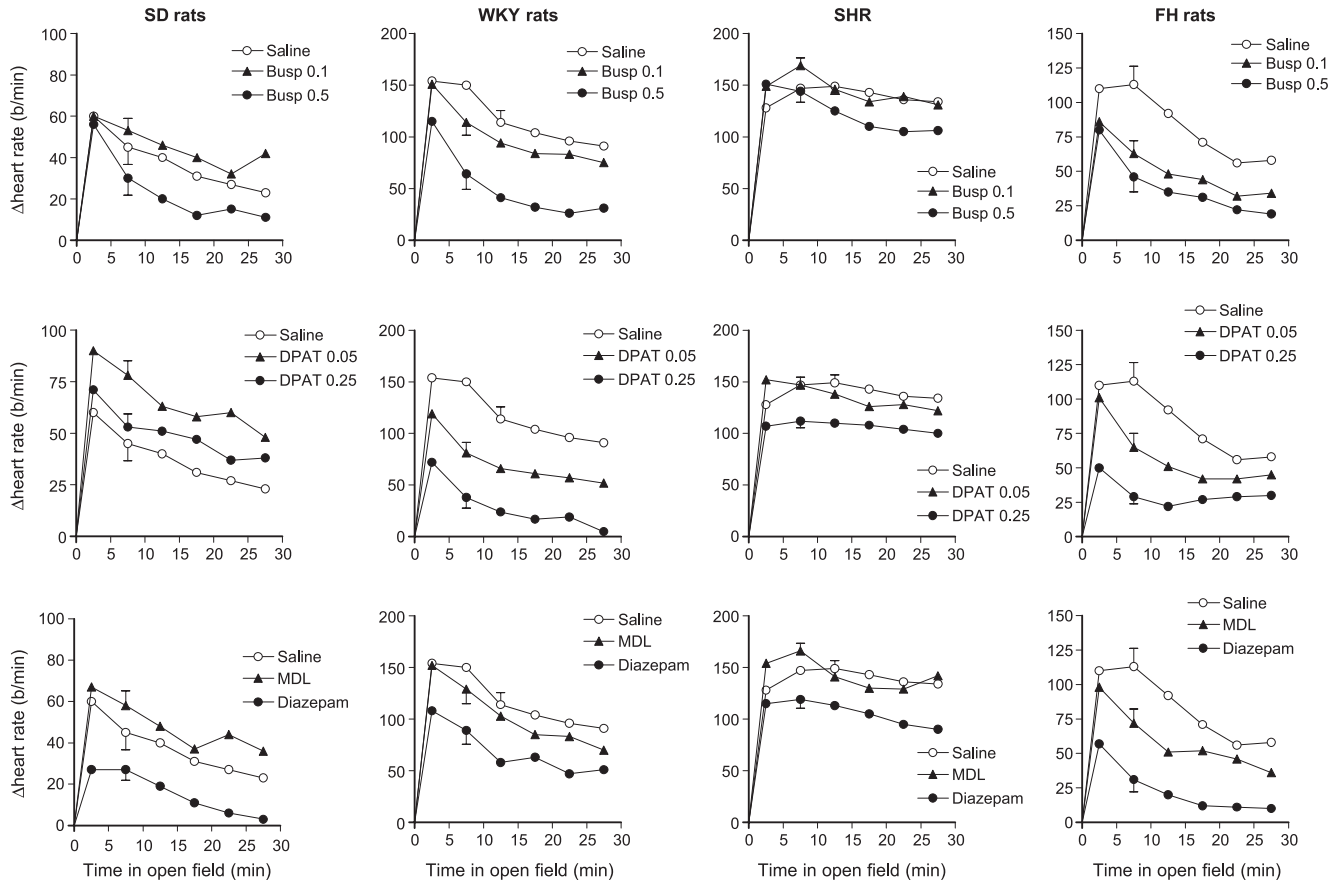

Fig. 5. Changes in heart rate in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats. The animals were treated with 0.1 or 0.5 mg/kg of buspirone (top panels), 0.05 or 0.25 mg/kg of 8-OH-DPAT (middle panels), 1 mg/kg of MDL73,005EF (MDL, bottom panel), or 2.5 mg/kg of diazepam (bottom panel) in a randomized cross-over design. At 30 min after injection, the rats were placed in the open-field for 30 min, and heart rate changes were detected by radio-telemetry. Note the differences in scales on the vertical axes. Data are mean±average within-animal standard error of the mean (S.E.M.) of n=8–9 rats per group.

and $F(1,7)=4.9$, $P=0.062$, respectively; Time×Treatment interaction $F(5,30)=3.5$, $P=0.014$ and $F(5,35)=3.6$, $P=0.010$, respectively]. In SHR, similar to the effect of buspirone, 0.05 mg/kg of 8-OH-DPAT altered the time course of the heart rate changes [Time×Treatment interaction $F(5,35)=3.4$, $P=0.013$] so that the prolonged response now had an early peak followed by a gradual decline (Fig. 5). Treatment with 0.25 mg/kg of 8-OH-DPAT also reduced and shortened the heart rate response in WKY rats [main effect of Treatment $F(1,6)=82.9$, $P<0.001$; Time×Treatment interaction $F(5,30)=2.6$, $P=0.045$] and in FH rats [$F(1,7)=13.7$, $P=0.008$ and $F(5,35)=7.8$, $P<0.001$, respectively]. The effect of 0.25 mg/kg tended to be greater than that of 0.05 mg/kg of 8-OH-DPAT (Figs. 5 and 7). There was no effect of 0.25 mg/kg of 8-OH-DPAT in SHR (Figs. 5 and 7).

Treatment with MDL73,005EF had no effect on the heart rate responses in SD rats, WKY rats, or FH rats (Figs. 5 and 7). In SHR, it altered the time course of the heart rate changes similarly to buspirone and 8-OH-DPAT [see above; interaction of Time×Treatment $F(5,35)=3.7$, $P=0.009$]. Treatment with diazepam tended to reduce the heart rate response in SD rats, although this did not reach statistical significance (Fig. 5). In WKY rats and FH rats, there was a significant reduction of the heart rate response [$F(1,6)=19.8$, $P=0.004$ and $F(1,7)=14.6$, $P=0.006$, respectively]. In SHR, again there was only a change in the time course of the heart rate response [Time×Treatment interaction $F(5,35)=2.6$, $P=0.044$].

3.6. Effect of treatments on behavioural activity in the open field

Analysis of the values for distance moved in the open field from all strains and all drug treatments revealed a main effect of Strain [$F(3,27)=32.2$, $P<0.001$] and of Treatment [$F(6,162)=9.8$, $P<0.001$] and a Strain×Treatment interaction [$F(18,162)=3.7$, $P<0.001$], suggesting differential effects of the drugs on behaviour between the different strains (Table 1). Baseline activity of the different strains, in terms of distance moved after saline treatment, was significantly higher in both SHR and FH rats compared to either SD rats or WKY rats, but no other strain differences were found (Table 1). Further analysis of drug effects was done in individual strains, comparing with values found after saline treatment (Table 1).

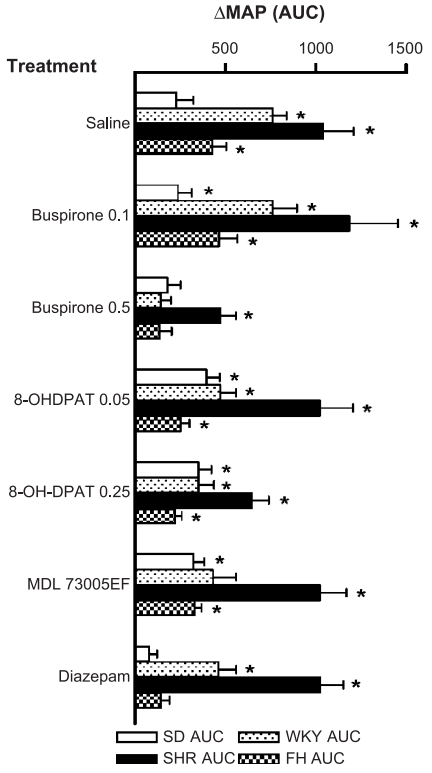

Fig. 6. Changes in mean arterial pressure (MAP), expressed as area under the curve (AUC) in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats. The animals were treated with 0.1 or 0.5 mg/kg of buspirone, 0.05 or 0.25 mg/kg of 8-OH-DPAT, 1 mg/kg of MDL73,005EF, or 2.5 mg/kg of diazepam. At 30 min after injection, the rats were placed in the open-field for 30 min, and MAP changes were detected by radio-telemetry. Data are mean±S.E.M. of n=8–9 rats per group.

No significant effect of either dose of buspirone was found on distance moved, except in SHR that showed a slight reduction in activity after treatment with the 0.5 mg/kg dose [$F(1,7)=5.6$, $P=0.049$].

In SD rats, treatment with 8-OH-DPAT caused an increase in distance moved, with a strong trend after the 0.05 mg/kg dose [$F(1,6)=4.8$, $P=0.07$] and a highly significant effect after the 0.25 mg/kg dose [$F(1,6)=21.2$, $P=0.004$]. 8-OH-DPAT treatment was less effective in WKY rats and FH rats [0.25 mg/kg dose: $F(1,6)=6.6$, $P=0.042$ and $F(1,8)= 6.7$, $P=0.033$, respectively], whereas there was no effect of either dose in SHR (Table 1).

Treatment with MDL 73,005EF caused a reduction of distance moved in WKY rats [$F(1,6)=8.8$, $P=0.025$] but had no effect in the other strains (Table 1). Treatment with diazepam had no effect in SD rats and caused a reduction of distance moved in WKY rats and FH rats [$F(1,6)=20.1$, $P=0.004$ and $F(1,8)=25.5$, $P=0.001$, respectively]. In contrast, this treatment caused a significant increase in open field distance moved in SHR [$F(1,7)=18.0$, $P=0.004$].

Generally, for velocity of movements, the same trends were seen as for distance moved. Thus, again there were significant main effects of Strain [$F(3,27)=34.4$, $P<0.001$] and of Treatment [$F(6,162)=9.4$, $P<0.001$] and a Strain× Treatment interaction [$F(18,162)=3.6$, $P<0.001$]. Baseline activity of the different strains, in terms of velocity of movements after saline treatment, was significantly higher in SHR compared to either SD rats ($P<0.001$), WKY rats ($P<0.001$), or FH rats ($P=0.044$). In addition, velocity was higher in FH rats compared to SD rats ($P=0.001$) and WKY rats ($P=0.007$; Table 1). Further analysis of drug effects was done in individual strains, comparing with values found after saline treatment (Table 1).

No significant effect of either dose of buspirone was found on velocity of movements, except again in SHR that showed a slight reduction of this parameter after treatment with the 0.5 mg/kg dose [$F(1,7)=5.6$, $P=0.049$].

In SD rats, treatment with 8-OH-DPAT caused an increase in velocity, again with a strong trend after the 0.05 mg/kg dose [$F(1,6)=4.8$, $P=0.07$] and a highly significant effect after the 0.25 mg/kg dose [$F(1,6)=21.2$, $P=0.004$]. In WKY rats and FH rats, 0.25 mg/kg of 8-OH-DPAT caused slight increases in velocity of movements [$F(1,6)=6.6$, $P=0.043$ and $F(1,8)= 6.7$, $P=0.033$, respectively], whereas there was no effect in SHR (Table 1).

Treatment with MDL 73,005EF caused a reduction of velocity in WKY rats [$F(1,6)=8.7$, $P=0.026$] but had no effect in the other strains (Table 1). Velocity of movements

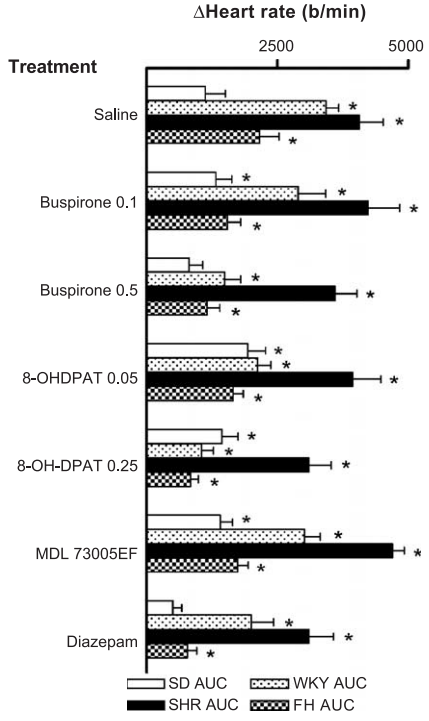

Fig. 7. Changes in heart rate, expressed as area under the curve (AUC) in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats. The animals were treated with 0.1 or 0.5 mg/kg of buspirone, 0.05 or 0.25 mg/kg of 8-OH-DPAT, 1 mg/kg of MDL73,005EF, or 2.5 mg/kg of diazepam. At 30 min after injection, the rats were placed in the open-field for 30 min, and heart rate changes were detected by radio-telemetry. Data are mean±S.E.M. of n=8–9 rats per group.

Table 1
Average values of distance moved and velocity of movement in Sprague–Dawley (SD) rats, Wistar–Kyoto (WKY) rats, Spontaneously Hypertensive rats (SHR), and Fawn–Hooded (FH) rats after treatment with saline, 0.1 or 0.5 mg/kg of buspirone, 0.05 or 0.25 mg/kg of 8-OH-DPAT, 1 mg/kg of MDL 73,005EF, or 2.5 mg/kg of diazepam

	SD rats	WKY rats	SHR	FH rats
Distance moved (cm)				
Saline	2066±537	2583±357	7829±673	5589±629
Buspirone 0.1	2812±648	1738±222	7458±648	4703±514
Buspirone 0.5	2934±642	1979±324	6229±615	5006±958
8-OH-DPAT 0.05	3277±563	2733±443	6985±897	6031±1031
8-OH-DPAT 0.25	4794±581[a]	4944±1017[a]	8859±1016	9624±1205[a]
MDL73,005EF 1	3513±919	1607±210[a]	7015±527	5714±755
Diazepam 2.5	2011±519	1741±280[a]	11480±1243[a]	3993±591[a]
Velocity (cm/s)				
Saline	1.15±0.30	1.44±0.20	4.40±0.39	3.11±0.35
Buspirone 0.1	1.56±0.36	0.97±0.12	4.15±0.36	2.61±0.29
Buspirone 0.5	1.66±0.38	1.10±0.18	3.47±0.34[a]	2.79±0.53
8-OH-DPAT 0.05	1.82±0.31	1.52±0.25	3.89±0.50	3.35±0.57
8-OH-DPAT 0.25	2.67±0.32[a]	2.75±0.57[a]	4.93±0.56	5.35±0.67[a]
MDL73,005EF 1	1.95±0.51	0.89±0.12[a]	3.91±0.29	3.27±0.39
Diazepam 2.5	1.12±0.29	0.97±0.16[a]	6.39±0.69[a]	2.22±0.33

Data are mean±S.E.M. of eight to nine rats per group. Values were obtained during 30 min of recordings while the animal was in the open field.
[a] $P<0.05$ for difference with saline-treatment values.

showed no effect of treatment with diazepam in SD rats or FH rats, a significant reduction in WKY rats [$F(1,6)=20.0$, $P=0.004$] and a significant increase in SHR [$F(1,7)=19.3$, $P=0.003$].

4. Discussion

The main effects of this study are summarized in Table 2. There were marked differences between the effects of the various drugs and between responses in different strains. In general, treatment with 0.5 mg/kg of buspirone markedly reduced the increase in blood pressure and heart rate seen in the open-field, with the exception of SD rats where, although the same trend was seen, the effect did not reach statistical significance. In SHR, the effect of buspirone on the tachycardia was only expressed as a change of the time course (Table 2). The cardiovascular effects of buspirone could not be explained by sedation, as no consistent effect was seen on locomotor activity in the open-field. These results are consistent with the well-known anxiolytic properties of buspirone in behavioural tests for anxiety, such as the elevated plus maze, punished drinking, and the black–white transition test (Carli et al., 1989; Moser et al., 1990). Furthermore, in one previous study, administration of a very much higher dose of buspirone (10 mg/kg) also

Table 2
Summary of drug effects on the increase in mean arterial pressure (MAP) and heart rate and on distance moved in the open field

Treatment		SD rats	WKY rats	SHR	FH rats
Buspirone 0.1	MAP	No effect	No effect	No effect	No effect
	Heart rate	No effect	No effect	No effect	Trend reduction
	Activity	No effect	No effect	No effect	No effect
Buspirone 0.5	MAP	No effect	Abolished and shortened	Reduced and shortened	Abolished
	Heart rate	No effect	Reduced	Time course change	Reduced
	Activity	No effect	No effect	Trend reduction	No effect
8-OH-DPAT 0.05	MAP	Late enhancement	Reduced and flattened	No effect	Reduced
	Heart rate	No effect	Reduced and shortened	Time course change	Reduced and shortened
	Activity	Trend increased	No effect	No effect	No effect
8-OH-DPAT 0.25	MAP	Late enhancement	Reduced and flattened	No effect	Early reduction
	Heart rate	No effect	Reduced and shortened	No effect	Reduced and shortened
	Activity	Increased	Increased	No effect	Increased
MDL73,005EF 1	MAP	Late enhancement	Reduced and flattened	No effect	Reduced
	Heart rate	No effect	No effect	Time course change	No effect
	Activity	No effect	Reduced	Trend reduction	No effect
Diazepam 2.5	MAP	Abolished	Reduced	No effect	Abolished
	Heart rate	Trend reduction	Reduced	Time course change	Reduced
	Activity	No effect	Reduced	Increased	Reduced

Summary is based upon statistical analysis and inspection of the data (Figs. 4–7; Table 1).

suppressed stress-induced increases in blood pressure and heart rate (Taylor et al., 1989), consistent with our results. Early studies have suggested that the effects of buspirone are mediated by the (partial) agonist properties of this drug on 5-HT_{1A} receptors (Carli et al., 1989; Taylor, 1988). One conclusion of these results could then be, that the data shows that stimulation of 5-HT_{1A} receptors results in inhibition of cardiovascular stress responses reflecting a beneficial anxiolytic role of these receptors in the receptor binding spectrum of new antipsychotic treatments (see Introduction). However, our other results do not support such a straightforward role of 5-HT_{1A} receptor stimulation.

Administration of the prototypical 5-HT_{1A} receptor agonist, 8-OH-DPAT, did not fully mimic the effects of buspirone. This was most noticeable in SD rats where, instead of a trend to an inhibition of cardiovascular responses, 8-OH-DPAT treatment caused a late enhancement of the pressor response. Also in other rat strains was the time course of the changes in blood pressure altered compared to that seen after saline treatment or buspirone treatment. This suggests either that additional mechanisms are involved in the action of buspirone on stress responses or that 5-HT_{1A} receptor stimulation has multiple effects on cardiovascular control, differing between rat strains. The former explanation is supported by the suggestion that buspirone may have effects on alpha-2 adrenoceptors, most likely through metabolism to 1-(2-pyrimidyl)piperazine (Gower and Tricklebank, 1988; Moser et al., 1990). Interestingly, we have previously shown that a low dose of the alpha-2 receptor agonist, clonidine, caused a reduction of the stress-induced tachycardia in the open field (Van den Buuse et al., 2001b). Thus, the effect of buspirone may be a combination of 5-HT_{1A} receptor stimulation and alpha-2 receptor stimulation. Further evidence for such a dual mode of action comes from the results with MDL73,005EF. This compound shares several features with buspirone, with the important exception that it is not metabolized to 1-(2-pyrimidyl)piperazine (Moser et al., 1990). In our experiments, treatment with MDL73,005EF produced effects similar to 8-OH-DPAT on blood pressure in SD rats (i.e., a late enhancement of the pressor response) and WKY rats (i.e., a small reduction of the pressor response). However, in SHR, MDL73,005EF had no significant effect. In any case, the effects of buspirone were markedly different from those of MDL73,005EF, suggesting that metabolism of buspirone could have played a role in its marked effects on cardiovascular stress responses.

The other possibility to explain the involvement of 5-HT_{1A} receptor stimulation in blood pressure responses to stress is suggested by the differential time course of the effects seen in different strains. We postulate that 5-HT_{1A} receptors are involved in both pressor responses and depressor responses and that, depending on the rat strains used and time after the onset of stress, either of these could predominate. There are several possibilities to explain this dual mechanism. First, the overall effect of 8-OH-DPAT could be the sum of effects of activation of 5-HT_{1A} receptors on many positions in the central nervous system cardiovascular control axis. 5-HT_{1A} receptors are found in many brain regions (Duncan et al., 1998; Hall et al., 1997), several of which have some involvement in cardiovascular control. In addition, 5-HT_{1A} receptors have been demonstrated in the spinal cord (Marlier et al., 2004) where they could be involved in regulation of sympathetic outflow. Treatment with 8-OH-DPAT reduces resting blood pressure (Buisson-Defferier and Van den Buuse, 1992; Di Francesco et al., 1988), as was seen in the present study as well. Nevertheless, it caused sympathoexcitation in some vascular beds (Anderson et al., 1992), and this regionalized stimulation of sympathetic tone could be enough in some strains (i.e., SD rats in our study) and some situations (e.g., stress) to result in an increase rather than a decrease of blood pressure. It should be noted, that the inhibitory effects of 5-HT_{1A} receptor stimulation on blood pressure cannot explain the effects seen on the cardiovascular changes in the open field (compare (Figs. 1 and 2 with 6 and 7)). Thus, it is more likely that the cardiovascular modulation of open field responses reflects anxiolytic properties of the treatments rather than nonspecific effects on sympathetic outflow.

One other possibility to explain the enhancement of the pressor response in the open field in SD rats or the alterations of the time course of this effect in other strains, could be the induction of hormone release by stimulation of 5-HT_{1A} receptors, particularly vasopressin. However, it has been shown that administration of 8-OH-DPAT to rats does not result in an increase in vasopressin release (Jorgensen et al., 2003). Alternatively, central 5-HT_{1A} receptor stimulation has been shown to activate the hypothalamus–pituitary–adrenal axis through activation of central corticotropin-releasing factor (CRF) receptors (Owens et al., 1990), which could have influenced the stress-induced pressor response (Van den Buuse et al., 2002). These effects could be at the level of the blood vessels or by modulating sympathetic vasomotor tone, as a similar enhancement of the heart rate changes in the open field was never observed.

There were several other strain differences in the effects of the various drugs on blood pressure and heart rate. This shows that caution is needed when generalizing findings from studies where only one rat strain was used. It is not clear what mechanism lies behind these marked strain differences. At this point, strain differences in pharmacokinetics or pharmacodynamics cannot be excluded, although these factors are unlikely to explain the differences in time course between the strains. Another possibility is strain differences in 5-HT_{1A} receptor densities in the brain. Few studies have systematically compared central 5-HT_{1A} receptor levels in different rat strains. 5-HT_{1A} receptor density was increased in the medulla of SHR compared to WKY rats (Huguet and Brisac, 1991), which would appear to be at odds with our finding, that SHR generally were *less* responsive to 5-HT_{1A} receptor stimulation than WKY rats

and other strains. We recently observed, that SHR responded similarly than WKY rats and SD rats to the action of 8-OH-DPAT on prepulse inhibition (Van den Buuse, 2004). In studies on the anxiolytic and cardiovascular effects of 5-HT_{1A} receptor ligands, SHR may be less useful than the other strains in this study. On the other hand, FH rats, compared to WKY rats and SD rats, showed enhanced sensitivity to the disrupting effect of 8-OH-DPAT on prepulse inhibition (Martin et al., 2004). FH rats showed higher 5-HT_{1A} receptor densities in cortical regions and hippocampus when compared to WKY rats (Chen and Lawrence, 2000). However, no evidence was observed in the present study for a similar enhanced sensitivity as FH rats and WKY rats showed essentially the same responses. Prepulse inhibition is a behavioural model for sensorimotor gating, which is impaired in schizophrenia and other mental illnesses (Geyer and Markou, 1995; Van den Buuse et al., 2003).

In conclusion, administration of buspirone, 8-OH-DPAT, and MDL 73,005EF in different rat strains produced differential effects on cardiovascular responses to stress. Overall, these treatments tended to reduce stress responses, although with clear exceptions, such as in SHR. Nevertheless, these results could reflect a role of 5-HT_{1A} receptors in stress responses, as was suggested also by behavioural studies using anxiety models (see Introduction). Our results could indicate that antipsychotic drugs with 5-HT_{1A} receptor modulating activity have anxiolytic properties in addition to their antipsychotic action, as we have recently suggested (Van den Buuse, 2003). Further studies are needed to confirm this idea, for example, by assessing if the apparent anxiolytic action of antipsychotic drugs can be blocked by 5-HT_{1A} receptor antagonists. Development of new antipsychotic drugs could be targeted to include (partial) agonist activity at 5-HT_{1A} receptors so as to include these beneficial anxiolytic properties in their mode of action.

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