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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,