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Brain Research 1040 (2005) 64–72

BRAIN RESEARCH

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Research report

Effect of the activation of central 5-HT_{2C} receptors by the 5-HT_{2C} agonist mCPP on blood pressure and heart rate in rats

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Accepted 19 January 2005
Available online 11 March 2005

Abstract

In the present study we investigated the role of central 5-HT_{2C} receptors in the control of blood pressure and heart rate in non-stressed and stressed, adult, male, Wistar rats. Third ventricle injections of the 5-HT_{2C} agonist mCPP elicited a significant increase in blood pressure in non-stressed animals. The initial period of this hypertensive response (10–30 min after mCPP administration) was accompanied by baroreflex-mediated bradycardia, while after this period the coexistence of hypertension and tachycardia was observed. These cardiovascular effects promoted by the central administration of mCPP were blocked by pretreatment with the 5-HT_{2C} antagonist, SDZ SER 082. The administration of SDZ SER 082 alone induced no significant changes in blood pressure or heart rate. The pharmacological stimulation of central 5-HT_{2C} receptors by mCPP did not change the hypertensive or tachycardic responses induced by restraint stress. Conversely, the blockade of central 5-HT_{2C} receptors by SDZ SER 082 blunted stress-induced hypertension without modifying stress-induced tachycardia. It is concluded that the activation of central 5-HT_{2C} receptors induces hypertension in non-stressed rats and that the normal function of these receptors is essential for the rise in blood pressure that occurs in the course of restraint stress.

Theme: Endocrine and autonomic regulation
Topic: Cardiovascular regulation

Keywords: mCPP; Serotonin; Blood pressure; Stress; 5-HT_{2C} receptors

1. Introduction

A large number of behavioral and visceral responses are regulated by the brain serotonin circuitries, a complex system of mesencephalic origin that reaches many brain areas in which serotonin exerts its effects by coupling to a large family of membrane receptors [5]. Among the complex interactive systems that contribute to the central regulation of cardiovascular function there are many areas that are under the direct influence of serotoninergic pathways or that contain a dense array of serotonergic interneurons [31].

Selective manipulation of the central serotoninergic pathways has shown that brain serotonin seems to exert significant control over cardiovascular function by acting on distinct serotonin receptors [18,31]. Some data in the literature show that the nature of brain serotonin actions on cardiovascular regulation may vary depending on the central area and serotonin receptor subtype studied [31,35]. Indeed, both blood pressure and heart rate may be substantially increased or decreased by the activation of distinct brain serotonin receptors. Most of these central serotoninergic influences on cardiovascular function are exerted by a significant positive or negative modulation

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doi:10.1016/j.brainres.2005.01.054

of the autonomic nervous system status by different serotonin receptor subtypes.

We have recently demonstrated that the pharmacological activation of central 5-HT_3 receptors evokes a significant hypotensive effect in rats. In this previous paper we have also shown that these receptors seem to exert an endogenous, constant, negative drive that is important in maintaining blood pressure within its physiological range since the blockade of these receptors by selective antagonist results in a significant increase in blood pressure [16]. This negative drive exerted by serotonin actions on central 5-HT_3 receptors seems to depend on a sympathoinhibitory-related mechanism and does not appear to rely on any significant influence on vagal tone. We have also demonstrated that the hypotensive drive exerted by central 5-HT_3 receptors is probably overwhelmed by the central neurochemical components that normally trigger and sustain stress-induced hypertensive response [16].

In the central nervous system, the 5-HT_2 receptor family also seems to participate in cardiovascular regulation. Indeed, activation of 5-HT_2 receptors in the lateral hypothalamus [26] and in the paraventricular nucleus [6] increases blood pressure and heart rate. Conversely, in the nucleus of the solitary tract, these same receptors seem to modulate a hypotensive and bradycardic response [36]. In the present study, we have investigated the role of central 5-HT_{2C} receptors in the regulation of blood pressure both in non-stressed and stressed rats.

2. Methods

2.1. Animals

Male Wistar rats (300 ± 20 g), kept under controlled light (lights on from 5 AM to 7 PM) and temperature (24 ± 2 °C) conditions, were used in the experiments. They had free access to tap water and laboratory chow (Nuvital Nutrientes, Curitiba, Brazil).

2.2. Surgical procedures

Third ventricles were cannulated under sodium pentobarbital anesthesia (50 mg/kg ip) 6 days before the experimental sessions. Briefly, after positioning the rat in a stereotaxic apparatus (David Kopf Instruments, USA), a chronic 28-gauge guide cannula was implanted. The following coordinates were used: anteroposterior = 0.5 mm behind the bregma; lateral = 0.0 mm; vertical = 8.0 mm below the skull. To avoid lesions to the brain regions involved in the control of cardiovascular and body fluid homeostasis, the animals were fixed to the stereotaxic apparatus with the head inclined upwards (+2.0 mm). The cannulas were fixed to the skull bone by two screws embedded in dental acrylic. The animals were housed in individual cages after surgery. The day before the experimental sessions, a catheter (PE50) filled with heparinized saline solution (1000 U/ml) was inserted into the left carotid artery under pentobarbital anesthesia and exteriorized at the nape of the animal's neck to permit blood pressure recording. After the experimental sessions, the position of the cannulas was verified. The animals were sacrificed by CO_2 inhalation and a Blue Evans dye injection was given through the cannula in order to confirm whether its tip was in the proper place. Only the data from animals whose cannulas were strictly inside the third ventricle were considered.

2.3. Drugs and microinjections

The following drugs were used: mCPP (1-(3-chlorophenyl)piperazine), a 5-HT_{2C} agonist (34), and SDZ SER 082 (+)-*cis*-4,5,7a,8,9,10,11,11a-octahydro-7H-10-methylindolo(1,7-bc)(2,6)-naphthyridine], a selective 5-HT_{2C} receptor antagonist [21], were purchased from Tocris Cookson, Inc. Ballwin, MO. All drugs were dissolved in sterile isotonic saline solution. A total volume of 2 μl was slowly injected (60 s) into the third ventricle using a Hamilton microsyringe connected to a 30-gauge injector through polyethylene tubing. There was no significant damage to the regions participating in cardiovascular regulation following third ventricle cannulation and injections. Indeed, in the present study, control third-ventricle-cannulated animals presented normal, stable blood pressure levels and their stress-induced hypertensive response was fully preserved. This demonstrates that third ventricle cannulation did not disrupt the central mechanisms that maintain blood pressure and trigger its enhancement following recognized stressful stimulus.

2.4. Blood pressure recording

Arterial pressure was continuously monitored through the carotid catheter connected to a blood pressure transducer (World Precision Instruments) whose signal was amplified and digitally recorded using an analog-to-digital interface (AqDados—application for data acquisition, Lynx Tecnologia Eletrônica Ltda, São Paulo, Brazil, version 5.0) and recorded (1 kHz) on a microcomputer for later analysis. Mean arterial pressure (MAP) was calculated from systolic and diastolic pressures, and heart rate (HR) was determined from the pulsation of arterial pressure using the AcqKnowledge software, version 3.5.7, developed by Biopac Systems, California, USA.

2.5. Restraint stress

In order to induce restraint stress, the animals were placed within plastic (PVC) tubes specially designed to