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BRAIN RESEARCH

Research Report

Involvement of central 5-HT$_7$ receptors in modulation of cardiovascular reflexes in awake rats

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ABSTRACT

This study evaluated the role of 5-HT$_7$ receptors within the central nervous system in modulating cardiovascular responses to the activation of chemo-, baro- and cardiopulmonary reflexes and in the regulation of mean arterial pressure and heart rate, using intracisternal (i.c.) application of the selective 5-HT$_7$ receptor antagonist SB-269970 in awake rats. Experiments were performed on male Wistar rats (300–320 g). At 4 days before the experiment, rats were anesthetized and placed in a stereotaxic frame implantation of a guide cannula in the direction of the cisterna magna to be used for microinjection of saline or SB-269970 (100 μg/kg). On the day before the experiments a femoral artery and vein were cannulated to record arterial pressure and heart rate and to inject drugs to activate cardiovascular reflexes, respectively. The chemo-, baro- and cardiopulmonary reflexes were activated in different experimental groups before and after i.c. injection of saline or SB-269970. The antagonism of 5-HT$_7$ receptors reduced: (a) the pressor (50±4 vs. 19±9 mm Hg) and bradycardic (−247±13 vs. −69±27 bpm) responses to chemoreflex activation; (b) the fall in MAP (−54±4 vs. −20±6 mm Hg) and the bradycardia (−294±12 vs. −98±34 bpm) in response to cardiopulmonary reflex activation; and (c) the gain of the baroreflex (−2.3±0.1 to −0.9±0.2 bpm/mm Hg). Intracisternal application of SB-269970 increased significantly baseline MAP in those rats previously submitted to the activation of a cardiovascular reflex but in naïve rats produced no changes in the baseline MAP were observed. The fact that cardiovascular responses to all reflexes tested were attenuated by the antagonism of 5-HT$_7$ receptors suggests that brainstem 5-HT$_7$ receptors brainstem facilitate the processing of the autonomic responses to cardiovascular reflex activation and that a 5-HT-containing pathway to the brainstem provides a normalizing input during challenges produced by cardiovascular reflex activation which seems to be mediated by 5-HT$_7$ receptors.

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1. Introduction

Neurons containing 5-hydroxytryptamine (5-HT, serotonin) play an important modulatory role in the reflex activation of parasympathetic outflow in several species (see Ramage, 2001). Central 5-HT pathways are known to innervate areas involved in cardiovascular regulation, especially the nucleus tractus solitarius (NTS), which receives dense innervation by 5-HT-containing neurons from nodose ganglia (Nosjean et al., 1990) and raphe nuclei (Schaffar et al., 1988; Steinbusch, 1981).

There is evidence that different 5-HT receptors are involved in cardiovascular regulation (Ramage, 2001). Of the 14 different 5-HT receptor subtypes, 5-HT_{1A}, 5-HT_3 and 5-HT_7 receptors are those that have received more attention in terms of the modulation of the autonomic activity to the cardiovascular system (Callera et al., 1997; see Ramage, 2001; Jordan, 2005; Kellett et al., 2005). Microinjection of 5-HT_{1A} receptor agonists into the dorsal motor nucleus of vagus increases vagal activity and produces hypotension (Sporton et al., 1991) and intracisternal injections of 5-HT_{1A} receptor antagonists in anesthetized rabbits attenuates the cardiovascular responses to baroreflex and cardiopulmonary reflex, but not to chemoreflex activation (Skinner et al., 2002). Moreover, bilateral microinjection of 5-HT_3 receptor agonists into the NTS of awake rats significantly increases the basal mean arterial pressure and attenuates bradycardia and hypotension in response to activation of cardiopulmonary reflex (Leal et al., 2001) and the bradycardic response to baro- and chemoreflexes activation (Callera et al., 1997).

Blockade of supraspinal but not spinal 5-HT_7 receptors attenuate the micturition reflex (i.e. parasympathetic outflow to the bladder) in anesthetized rats (Read et al., 2003), while the blockade of 5-HT_7 receptors within the central nervous system in anesthetized rats, using the selective 5-HT_7 receptor antagonist SB-269970 (Hagan et al., 2000), attenuated cardiovascular responses evoked by the activation of chemo-, baro- and cardiopulmonary reflexes (Kellett et al., 2005).

The aim of the present study was to evaluate the contribution of brainstem 5-HT_7 receptors in the central regulation of arterial pressure and heart rate and its involvement in modulation of autonomic activity to the cardiovascular system in response to the activation of chemo-, baro- and cardiopulmonary reflexes, using intracisternal injection of the selective 5-HT_7 receptor antagonist SB-269970 in unanesthetized rats. These experiments were performed in awake rats to avoid any possible distorting effect of the anesthetics on this neuromodulatory system at the brainstem level.

2. Results

2.1. *Effect of 5-HT_7 receptor antagonist on the baseline mean arterial pressure and heart rate*

Baseline MAP and HR were quantified in all experimental groups before and after the intracisternal injection of the 5-HT_7 receptor antagonist (SB-269970) or vehicle (saline), in rats in which cardiovascular reflexes had been activated, and in naïve rats in which no cardiovascular reflexes had been stimulated.

Intracisternal microinjection of SB-269970 had no significant effects on baseline HR in any of the experimental groups. A statistically significant increase in baseline MAP was observed when SB-269970 was injected in rats in which chemo-, baro- or cardiopulmonary reflexes were tested previously. Mean arterial pressure had increased 5 min after injection of SB-269970 and returned to the baseline within 30 min. SB-269970 injection in naïve rats produced no significant changes in the baseline MAP and microinjection of the saline (vehicle) produced negligible cardiovascular changes in all experimental groups (Table 1).

2.2. *Effect of 5-HT_7 receptor antagonist on the cardiovascular responses to chemoreflex activation*

Intracisternal injection of SB-269970 (100 μg/kg) significantly attenuated the cardiovascular responses to chemoreflex activation. Fig. 1 shows tracings of one rat, representative of the group, which was submitted to chemoreflex stimulation before and after microinjection of SB-269970. In the group of 10 animals it significantly reduced the bradycardia (−247±13 vs. −69±27 bpm) and the pressor response (50±4 vs. 19±9 mm Hg) in response to chemoreflex activation within 5 min of injection (Fig. 2). Whilst the pressor and bradycardic responses returned to control within 30 min.

Injection of saline (n=7) had no significant effect on the bradycardic (−251±23 vs. −234±21 bpm) or pressor responses (55±7 vs. 52±6 mm Hg) to chemoreflex activation.

2.3. *Effect of 5-HT_7 receptor antagonist on the cardiovascular response to cardiopulmonary reflex activation*

Following intracisternal injection of SB-269970 there was a significant reduction in the cardiovascular responses to cardiopulmonary reflex activation. Fig. 3 shows tracings

Table 1 – Basal mean arterial pressure (MAP) before (control) and after (5, 10 and 30 min) intracisterna magna injection of 5-HT_7 receptor antagonist (SB-269970, 100 μg/kg, 5 μl) or vehicle (saline, 5 μl) in rats previously submitted to chemoreflex activation (KCN), to cardiopulmonary reflex activation (5-HT) and to baroreflex activation (PHE) and also in naïve rats without any previous cardiovascular reflexes activation

Groups	N	MAP before reflex test	MAP after i.c. injections		
			5 min	10 min	30 min
KCN+saline	7	100±2	101±4	105±5	104±4
KCN+SB-269970	10	97±2	113±4[a,b]	108±3[a,b]	103±3
5-HT+saline	7	99±3	101±3	102±4	103±2
5-HT+SB-269970	9	100±3	113±4[a,b]	112±4[a,b]	105±2
PHE+saline	7	101±1	104±2	104±2	101±2
PHE+SB-269970	10	100±2	110±3[a,b]	109±2[a,b]	107±2
Naïve+SB-269970	7	103±1	104±2	104±1	106±2

[a] $P<0.05$ compared to control responses.
[b] $P<0.05$ compared to response to SB-269970 in naïve rats.