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BRAIN RESEARCH

Research Report

The cardiovascular response of normal rats to dual lesion of the subfornical organ and area postrema at rest and to chronic losartan

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ABSTRACT

The subfornical organ (SFO) and the area postrema (AP), two of the sensory circumventricular organs (CVO), are known to play a role in the chronic central control of blood pressure. In previous studies in which these regions were independently lesioned, the chronic hypotensive effects of the AT_1 receptor blocker losartan (10 mg/kg/day) were attenuated by ~15 mm Hg. In the present study, we sought to investigate the effect of concurrent lesion of both the SFO and the AP on the cardiovascular effects of chronic losartan infusion in order to test the hypothesis that a greater attenuation of the hypotensive effects of losartan would be observed in rats with dual lesions. To do so, arterial pressure and heart rate responses to 10-day infusion of losartan were compared in sham rats and those with dual lesions of the AP and SFO. Two important findings resulted from this study. First, dual lesion rats exhibited a sustained and significant decrease in resting blood pressure (83±1 mm Hg vs. 104±1 mm Hg, respectively) and heart rate (356±3 bpm vs. 398±6 bpm, respectively) compared to sham animals. Secondly, rats with concurrent lesion of both the AP and the SFO demonstrated a significantly attenuated response to losartan compared to sham animals but showed no greater attenuation of losartan's chronic hypotensive effects than animals with lesion of either the SFO or the AP (~15 mm Hg). Although these results do not support the stated hypothesis, they do suggest redundancy and compensatory roles of the AP and SFO in basal cardiovascular control.

1. Introduction

The hormone Angiotensin II (AngII) has been well documented as having a prominent role in the regulation of blood pressure and pathogenesis of hypertension, although we still do not fully understand the myriad of effects of this hormone on the central nervous system. However, two of the circumventricular organs (CVO), the subfornical organ (SFO) and the area postrema (AP), have received much attention as regions in the brain central to the regulation of blood pressure and actions of AngII (Simpson, 1981, Fink et al., 1987; Ferguson and Bains, 1997, Zimmerman et al., 2004). Both of these CVO are well situated to play important roles in this regard, as they lack the blood/brain barrier (and thus are easily accessible to peptides like AngII), house a dense supply of AT1 receptors (Phillips et al., 1993; Tsutsumi and Saavedra, 1991), and have been shown to project to major CNS cardiovascular control centers such as the hypothalamic paraventricular nucleus (PVN) and the rostral ventral lateral medulla (RVLM) (Ferguson and Bains, 1996; Johnson and Gross, 1993; Osborn et al., 2007). In fact, by utilizing lesion of either the SFO or AP, we have previously characterized the roles of both of these CVO in the

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chronic hypertensive effects of AngII (Hendel and Collister, 2005; Nahey and Collister, 2007).

With regard to the effects of endogenous AngII, our lab has consistently shown a profound and slowly developing decrease in blood pressure of approximately 30 mm Hg in rats chronically administered the AT_1 antagonist, losartan (10 mg/kg/d IV) (Collister et al., 1996). This suggests a major role of the endogenous RAS in the maintenance and regulation of normal blood pressure, yet we still do not fully understand the mechanism(s) mediating this response. It seemed reasonable that, like the effects of exogenously administered AngII, the chronic hypotensive effects of losartan are similarly mediated in part via CVO, such as the SFO and AP. In that regard, our lab has demonstrated an attenuation of this chronic hypotensive effect of losartan by ~15 mm Hg in rats with lesion of either the SFO (Collister and Hendel, 2003a,b) or the AP (Collister and Osborn, 1998a,b).

Interestingly, lesion of either the AP or SFO did not completely abolish the effects of losartan but merely attenuated them. We cannot explain these results solely based on the idea of blockade of AT_1 receptors at a given CVO, as complete removal of CVO AT_1 receptors (via lesion of the CVO) should conceivably have the same effect as CVO AT_1 blockade, and although blood pressure transiently falls in animals with lesion of the AP (Collister and Osborn, 1998a,b), we do not see any long-term changes in arterial pressure in animals with lesion of either the SFO (Collister and Hendel, 2003a,b) or the AP (Collister and Osborn, 1998a,b). Indeed, we acknowledge the fact that other (non-AT1 related) mediators of the RAS such as Ang(1–7) do appear to be playing a role in this chronic response (Collister and Hendel, 2003a,b). However, the possibility remains that there could be redundant pathways involving these CVO, in that either of these CVO could compensate for the loss of the other during chronic AT_1 receptor blockade. We thus hypothesized that under conditions of chronic losartan infusion, rats with dual lesions of both the SFO and the AP would demonstrate a further attenuation, or near abolishment of the hypotensive effects of losartan compared to rats with lesion of either the SFO or the AP. To test this hypothesis, rats underwent sham or SFO/AP co-lesion surgery and MAP and HR responses were continuously measured during 10 days of losartan infusion.

2. Results

2.1. *Cardiovascular response to losartan*

As shown in Fig. 1, after dual lesion of the SFO and AP, rats demonstrated a significantly lower baseline MAP and HR compared to sham animals. The effects of chronic losartan treatment on MAP and HR are shown in Fig. 2. Animals with lesions of both the SFO and AP demonstrated an attenuated hypotensive response to losartan compared to sham animals; by day 2 of losartan infusion, MAP in SFOAPx rats had only decreased 13±1 mm Hg while MAP in SFOAPshm rats had decreased by 20±2 mm Hg. The difference in this attenuation was found to be significant and continued through the protocol, reaching −22+3 mm Hg in SFOAPx and −32+2 mm Hg in SFOAPshm rats by day 10 of treatment. When compared to their respective control data, MAP values were found to be

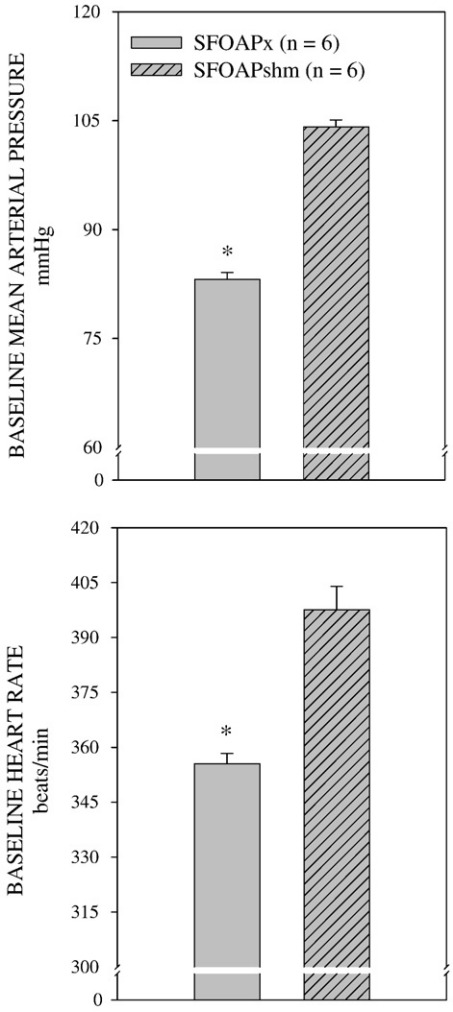

Fig. 1 – Baseline averages of mean arterial pressure (top) and heart rate (bottom) in SFOAPx and SFOAPshm rats during control period. *P<0.05 between groups.

significantly different on days 2–10 of losartan infusion in SFOAPx rats, and on all days of losartan infusion in SFOAPshm rats (statistics not shown).

With regard to the HR response, no difference was observed between sham and lesion groups during losartan infusion. There were, however, significant differences seen in both groups when comparing values during losartan infusion to baseline values (statistics not shown). Heart rate in SFOAPx rats was significantly higher during losartan than control values on days 2 through 9 of treatment, and in SFOAPshm rats on days 2, 4–6 and 10 of treatment.

2.2. *Food intake and sodium and water balance responses*

Food intake (FI) of both groups is shown in Fig. 3. Although rats with dual lesions were observed to have eaten less than sham animals throughout the experimental treatment, this difference was not significant, nor was consumption of food within groups altered compared to control values.

Sodium and water data are shown in Figs. 4 and 5, respectively. As expected with a slightly lower FI, the sodium