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BRAIN RESEARCH

Research Report

Cardiovascular effects of angiotensin II and glutamate in the PVN of Dahl salt-sensitive rats

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ARTICLE INFO

Article history:
Accepted 24 January 2012
Available online 1 February 2012

Keywords:
Paraventricular nucleus
Glutamate
Ang II
Dahl S
Sodium
Blood pressure

ABSTRACT

Several models of chronic sympathetic hyperactivity are associated with an increase in excitatory angiotensinergic and glutamatergic activity, and a decrease in GABAergic activity in the PVN. The present study evaluated whether activation of glutamate and AT_1 receptors in the PVN contributes to the maintenance of resting BP in Dahl salt sensitive (S) rats on regular or high salt diet for 4–6 weeks. Candesartan and kynurenate were infused bilaterally into the PVN and BP and heart rate (HR) were recorded. Both candesartan and kynurenate in the PVN did not change MAP and HR in normotensive Dahl salt resistant (R) and S rats on regular salt diet or in R rats on high salt diet. In hypertensive Dahl S rats on high salt diet, candesartan decreased MAP (−14±2 mm Hg), and tended to increase HR (22±5 bpm). Kynurenate decreased both MAP (−22±3 mm Hg) and HR (−42±7 bpm) in these rats. At the peak BP decrease by candesartan, kynurenate in the PVN further decreased BP by ~50% (−14±2 mm Hg), whereas candesartan did not further decrease BP at the peak BP response to kynurenate (−4±2 mm Hg). These results indicate that activation of glutamate and AT_1-receptors in the PVN contributes to the maintenance of BP in hypertensive Dahl S rats, but not normotensive Dahl S and R rats. The increased BP response to AT_1-receptor activation in the PVN of hypertensive Dahl S appears to be mediated by enhanced local glutamate receptor activation, but another mechanism(s) appears to further enhance glutamate responses.

1. Introduction

The Dahl rat strains represent genetic models of salt-sensitive (S) versus salt-resistant (R) blood pressure (BP). Dysregulation of Na^+-homeostasis in the brain appears to play a primary role in the salt-induced hypertension in Dahl S rats (for review, see Leenen, 2010). In Dahl S rats, high salt diet increases cerebrospinal fluid (CSF) [Na^+] (Huang et al., 2004; Nakamura and

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Abbreviations: AAV, adeno-associated virus; ACE, angiotensin-converting enzyme; AUC, area under the curve; BP, blood pressure; cGMP, guanosine monophosphate; CHF, chronic heart failure; CSF, cerebrospinal fluid; Dahl R, salt resistant; Dahl S, salt sensitive; EO, endogenous ouabain; EPSC, excitatory postsynaptic currents; GABA, gamma-aminobutyric acid; GLUT1, glutamate transporter 1; HR, heart rate; ICV, intracerebroventricular; IML, intermediolateral cell column; LT, lamina terminalis; NMDA, *N*-methyl-D-aspartate; OVLT, organum vasculosum of the lamina terminalis; PVN, paraventricular nucleus; ROS, reactive oxygen species; RSNA, renal sympathetic nerve activity; RVLM, rostral ventrolateral medulla; SD, Sprague–Dawley; SFO, subfornical organ; SHR, spontaneously hypertensive rats; siRNA, small-interference RNA; SNA, sympathetic nerve activity; WKY, Wistar Kyoto

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doi:10.1016/j.brainres.2012.01.060

Cowley, 1989) and causes sympathetic hyperactivity and hypertension (Huang et al., 2004; Serino et al., 2001). An increase in CSF [Na^+] may excite Na^+ sensitive nuclei in the lamina terminalis (LT) such as the subfornical organ (SFO) (Anderson et al., 2001; Denton et al., 1996) or the organum vasculosum of the lamina terminalis (OVLT) (Vivas et al., 1990). This increase in neuronal activity can be relayed to parvocellular neurons of the paraventricular nucleus (PVN) projecting to the intermediolateral cell column (IML) or rostral ventrolateral medulla (RVLM), thereby increasing sympathetic activity and BP (Ito et al., 2003; Li et al., 2003a; McKinley et al., 2001). Pressor responses from a brief increase in [Na^+] in the CSF or directly in the PVN are both prevented by an AT_1-receptor blocker in the PVN (Gabor and Leenen, 2009), indicating that AT_1-receptors in the PVN mediate these pressor responses to [Na^+]. A chronic increase in CSF [Na^+] by intracerebroventricular (icv) infusion of Na^+ rich aCSF or by high salt diet in Dahl S rats also increases hypothalamic tissue aldosterone and endogenous ouabain (EO) (Huang et al., 2006, 2008), angiotensin-converting enzyme (ACE) and AT_1-receptor densities in cardiovascular nuclei such as the PVN and causes sympathetic hyperactivity and hypertension (Huang et al., 2006; Wang et al., 2003). Aldosterone via EO release and AT_1-receptor stimulation appears to mediate the chronic effects of [Na^+] (Huang et al., 2011; Leenen, 2010). Whether AT_1-receptor activation in the PVN contributes to the hypertension from a chronic increase in CSF [Na^+] has not yet been assessed.

In the PVN, glutamate and Ang II raise (Gabor and Leenen, 2009; Kannan et al., 1989), whereas gamma-aminobutyric acid (GABA) lowers sympathetic nerve activity (SNA), BP and HR (Akine et al., 2003). Injection of a glutamate (Li and Pan, 2007) or AT_1-receptor blocker (Chen and Toney, 2001; Gabor and Leenen, 2009) in the PVN of normotensive rats does not affect BP or sympathetic activity whereas a $GABA_A$-receptor blocker increases SNA, BP, HR and local glutamate release (Li et al., 2006). Pressor and sympathetic responses from a $GABA_A$-receptor blocker in the PVN are prevented by a glutamate (Chen et al., 2003; Li et al., 2006) or AT_1-receptor blocker (Chen and Toney, 2003) indicating that in normal physiological conditions, GABA release in the PVN tonically inhibits local glutamate release and AT_1-receptor activation. To our knowledge, no studies have yet assessed the mechanism by which GABA release inhibits AT_1-receptor activation in the PVN. However, Ang II in the PVN decreases GABA-mediated inhibition of pre-sympathetic neurons in the PVN (Li et al., 2003a) and presumably increases local glutamate release. Similar to its effects on magnocellular neurons (Latchford and Ferguson, 2004), Ang II may also increase glutamate release from glutamate interneurons to activate pre-sympathetic parvocellular neurons.

The balance of inputs in the PVN changes in several chronic models of sympathetic hyperactivity. A glutamate or AT_1-receptor blocker in the PVN decreases SNA, BP and HR in rats with chronic heart failure (CHF) (Li et al., 2003c; Zheng et al., 2009) and in spontaneously hypertensive rats (SHR) (Li and Pan, 2007). Glutamate and AT_1-receptor blockers in the PVN both decrease BP in water deprived but not replete rats (Freeman and Brooks, 2007). In contrast, increases in SNA, BP and HR by a $GABA_A$ receptor blocker in the PVN are attenuated in rats with CHF (Wang et al., 2009), renal-wrapped hypertensive rats (Martin and Haywood, 1998) and in SHR (Li and Pan, 2007). These findings suggest that conditions with chronic sympathetic hyperactivity are associated with an increase in excitatory angiotensinergic and glutamatergic inputs, and a decrease in inhibitory GABAergic input in the PVN. No studies have yet evaluated the effects of high salt diet on balance of these excitatory and inhibitory inputs in the PVN of Dahl S rats. We hypothesized that AT_1 receptor activation via increased glutamate release in the PVN also contributes to the maintenance of hypertension in Dahl S rats on high salt diet.

In the present study, we first evaluated whether increased glutamate and AT_1 receptor activation in the PVN contributes to the maintenance of elevated BP in Dahl S rats on high salt intake. We then assessed whether in the PVN of Dahl S on high salt diet the increased glutamate receptor activation is mediated by increased local AT_1-receptor activation. Accordingly, we evaluated the effects of acute blockade of glutamate receptors or AT_1-receptors in the PVN on BP and HR of Dahl S and R rats on regular or high salt intake. To assess the

Table 1 – Baseline MAP and HR levels prior to first or second bilateral infusion of vehicle, kynurenate (1.4 μg/side) or candesartan (5 μg/side) into the PVN of Dahl R and S rats on regular or high salt diet. Five to twenty-five minutes was given after end of first infusion and recording of second baseline.

Infusions in the PVN	n	First baseline before first infusion		Second baseline before second infusion	
		MAP (mm Hg)	HR (bpm)	MAP (mm Hg)	HR (bpm)
Vehicle, kynurenate in Dahl S on regular salt	4	109±3	442±4	110±2	442±5
Vehicle, kynurenate in Dahl S on high salt	4	153±8 *	435±12	150±8 *	425±11
Candesartan, kynurenate in Dahl R on reg. salt	4	106±4	408±6	104±3	409±7
Candesartan, kynurenate in Dahl R on high salt	5	112±3	421±10	110±2	425±12
Candesartan, kynurenate in Dahl S on reg. salt	4	109±2	444±7 a	111±4	459±9 a
Candesartan, kynurenate in Dahl S on high salt	5	149±3 *,a,#	454±7 a	135±4 *,a	466±10 a
Kynurenate, candesartan on high salt	5	149±4 #	444±16	128±6	410±15

Values are mean ± SEM.
* $P<0.05$ vs. regular salt.
a $P<0.05$ vs. Dahl R in same group.
# $P<0.05$ vs. second infusion.