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BRAIN RESEARCH

Research Report

Mechanism of glutamate receptor for excitation of medial vestibular nucleus induced by acute hypotension

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ABSTRACT

In the vestibular nuclei, acute hypotension induces excitation of electrical activity and expression of c-Fos protein and phosphorylated extracellular signal-regulated kinase (pERK). Expression of c-Fos protein and pERK is mediated by the excitatory neurotransmitter, glutamate. We investigated the signaling pathway of glutamate and its receptors in the vestibular nuclei following acute hypotension in conscious rats. Glutamate release and the expression of c-Fos protein in the medial vestibular nuclei (MVN) were measured by microdialysis and immunohistochemical analysis, respectively. We compared the responses of rats with unilateral labyrinthectomy to unaltered controls. Acute hypotension was induced by infusing sodium nitroprusside (SNP) into the femoral vein. In the control group, glutamate release and the expression of c-Fos protein increased in the bilateral MVN following acute hypotension. In the unilateral labyrinthectomy group, glutamate release and the expression of c-Fos protein increased in the MVN contralateral to the lesion, but did not change in the ipsilateral MVN following acute hypotension. Microinjection of NMDA or AMPA into the lateral ventricle increased the expression of c-Fos protein in the bilateral MVN of conscious intact labyrinthine rats. However, after intracerebroventricular microinjection of MK-801 or CNQX little c-Fos protein was expressed in the bilateral MVN of these rats following acute hypotension. These results suggest that in response to acute hypotension, excitatory afferent signals from the peripheral vestibular receptors release glutamate into postsynaptic neurons in the vestibular nuclei. These excitatory signals are transmitted through the NMDA receptors and AMPA receptors of glutamate in the vestibular system.

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1. Introduction

The vestibular system is involved in the control of posture, movement through the vestibulo-ocular, and vestibulo-spinal reflexes (Wilson and Jones, 1979). It also influences sympathetic outflow and blood pressure through the vestibulo-autonomic reflex (Yates, 1992). The medial vestibular nucleus (MVN) is one of the most important nuclei in the vestibular nucleus complex of the brainstem (Lin and Carpenter, 1993). It is the main nucleus through which information from the peripheral vestibular input is transmitted to the central pathways. Although many studies have focused on the vestibulo-ocular and vestibulo-spinal reflexes, few have focused on the vestibulo-autonomic reflex. The MVN is an important relay station of the vestibulo-autonomic reflex. Stimulation of the vestibular apparatus may evoke nausea, vomiting, vertigo, and tachycardia, and the vestibular apparatus is itself influenced by blood pressure (Jauregui-Renaud et al., 2003).

Recent studies have demonstrated that acute hypotension produces expression of c-Fos protein and extracellular signal-regulated kinase (ERK) 1/2 in the vestibular nuclei of anesthetized rats (Kim et al., 2003, 2004). However, acute hypotension does not produce changes in electrical activity and c-Fos protein expression in rats with impaired labyrinthine function (Kim et al., 2003, 2004; Park et al., 2001). These studies indicate that peripheral vestibular receptors may respond to decreases in blood pressure. It is well known that expression of c-Fos or phosphorylated extracellular signal-regulated kinase (pERK) is mediated through activation of the ERK signal pathway. ERK, one family of mitogen-activated protein kinases (MEK), is involved in a complex intracellular signaling cascade (Grewal et al., 1999; Orban et al., 1999). Depolarization in neurons, induced by electrical stimulation or glutamate release, increases the intracellular Ca^{2+} concentration, which induces activation of an intracellular secondary signal pathway.

Glutamate is required for the transmission of excitatory afferent signals from peripheral vestibular receptors to central vestibular neurons, as well as for excitatory synaptic input from vestibular commissural fibers (Choi et al., 2008; Yamanaka et al., 1997). We previously observed that glutamate release increased in the MVN following acute hypotension in anesthetized and conscious rats (Li et al., 2010; Yu et al., 2006). We postulated that glutamate receptors modulate the expression of c-Fos protein and pERK in the vestibular nuclei following acute hypotension. However, the signaling pathway of glutamate and its receptors following acute hypotension are not fully understood.

Therefore, in order to investigate the signaling pathway of glutamate and its receptors in the vestibular nuclei following acute hypotension, we measured the expression of c-Fos protein in the MVN of conscious rats using immunohistochemistry.

2. Results

The resting mean blood pressure before SNP infusion was 105.6±6.8 mm Hg in the control group. SNP infusion decreased the arterial blood pressure, beginning within 1 min of initiation of the infusion and lasting for the remainder of the 3 min infusion period. After a SNP infusion of 15 μg/kg·min, the mean arterial blood pressure was 75.3±5.9 mm Hg, a 30% decrease.

2.1. Glutamate release following acute hypotension

In the control group, acute hypotension induced by SNP increased Glu release. The amount of Glu release increased to 148.2%±8.0% and 149.1%±7.3% of the mean basal level in the MVN at 20 and 30 min after SNP infusion, respectively ($p<0.01$). In addition, Glu release returned to the basal level 50 min after SNP infusion. In UL animals, the amount of Glu release increased to 147.5%±7.5% in the MVN contralateral to the lesion 30 min after SNP infusion ($p<0.01$) and returned to the basal level 50 min after SNP infusion. The pattern of Glu release in the contralateral MVN of UL animals after acute hypotension was similar to that of the control group. However, acute hypotension induced by SNP infusion did not change the amount of Glu released in the MVN ipsilateral to the lesion (Fig. 1).

2.2. c-Fos protein expression following acute hypotension

In the control group, intravenous administration of saline at the same volume and rate as SNP infused into the experimental group did not induce significant expression of c-Fos protein in the MVN. There was significantly greater expression of c-Fos protein bilaterally in the MVN of experimental rats 30 min (28.50±0.93), 60 min (60.70±1.59), and 120 min (39.73±0.98) after acute hypotension than in the MVN of controls ($p<0.001$; Figs. 2, 3). Expression of c-Fos protein peaked 60 min after SNP injection.

In UL rats, little c-Fos protein was expressed in the MVN ipsilateral to the lesion following SNP-induced acute hypotension. However, there was significant expression of c-Fos protein in the MVN contralateral to the lesion 30 min, 60 min and 120 min following SNP-induced acute hypotension. Thirty

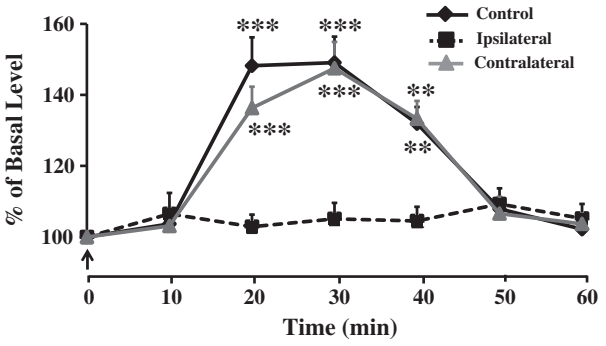

Fig. 1 – Effect of acute hypotension on glutamate content in the dialysate of MVN in conscious rats. Control, MVN of rats with intact labyrinths; Ipsilateral, ipsilateral MVN of rats with unilateral labyrinthectomy; Contralateral, contralateral MVN of rats with unilateral labyrinthectomy; arrow indicates infusion of 15 μg/kg·min sodium nitroprusside. There were 8 rats in each group. *Significant difference from basal level. $^{**}p<0.01$, $^{***}p<0.001$.