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Effect of arginine vasopressin on the cortex edema in the ischemic stroke of Mongolian gerbils

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ABSTRACT

Brain edema formation is one of the most important mechanisms of ischemia-evoked cerebral edema. It has been demonstrated that arginine vasopressin (AVP) receptors are involved in the pathophysiology of secondary brain damage after focal cerebral ischemia. In a well-characterized animal model of ischemic stroke of Mongolian gerbils, the present study was undertaken to clear the effect of AVP on cortex edema in cerebral ischemia. The results showed that (1) occluding the left carotid artery of Mongolian gerbils not only decreased the cortex specific gravity (cortex edema) but also increased AVP levels in the ipsilateral cortex (ischemic area) including left prefrontal lobe, left parietal lobe, left temporal lobe, left occipital lobe and left hippocampus for the first 6 hours, and did not change of the cortex specific gravity and AVP concentration in the right cortex (non-ischemic area); (2) there were many negative relationships between the specific gravity and AVP levels in the ischemic cortex; (3) intranasal AVP (50 ng or 200 ng), which could pass through the blood–brain barrier to the brain, aggravated the focal cortex edema, whereas intranasal AVP receptor antagonist-D(CH_2)$_5$Tyr(ET)DAVP (2 μg) mitigated the cortex edema in the ischemic area after occluding the left carotid artery of Mongolian gerbils; and (4) either intranasal AVP or AVP receptor antagonist did not evoke that edema in the non-ischemic cortex. The data indicated that AVP participated in the process of ischemia-evoked cortex edema, and the cerebral AVP receptor might serve as an important therapeutic target for the ischemia-evoked cortex edema.

1. Introduction

Arginine vasopressin (AVP), a nonapeptide posterior hormone of the pituitary, is mainly synthesized and secreted in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). This hormone, combined with an apparent carrier protein (neurophysin), is transported along the hypothalamo-hypophyseal pathway to the neurohypophysis, where it is stored for subsequent release (Antunes and Zimmerman, 1978). The remarkable functions of AVP include body fluid homeostasis, hormone regulation, cardiovascular control, learning and memory (McEwen, 2004), depression (Yang et al., 2012b), stress (Bao et al., 2014), influence and pain modulation (Yang et al., 2006a, 2006b, 2007b, 2007c, 2009b, 2012a).

Brain edema formation is one of the most important mechanisms of ischemia-evoked cerebral damage. It has been demonstrated that AVP receptors are involved in the pathophysiology of secondary brain damage after focal cerebral ischemia (Kleindienst et al., 2013; Liu et al., 2010; Vakili et al., 2005). Experimental cerebral ischemia increased plasma AVP levels (Chang et al., 2006). The brain edema following experimental stroke was modulated by V_1, specially V_{1a} but not V_2 receptor (Kleindienst et al., 2013; Liu et al., 2010). Ischemia-evoked cerebral edema was attenuated in AVP-deficient rats (Dickinson and Betz, 1992) and V_1 receptor antagonist treatment (Kleindienst et al., 2006; Rauen et al., 2013; Shuiab et al., 2002). V_{1a} receptor antagonism has been consistently associated with attenuated secondary brain edema in experimental stroke models. The role of the V_2 receptor remains unclear, but perhaps it is involved in a positive feedback loop for AVP expression (Ameli et al., 2014).

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The diameter was slim and the function was poor in Willis' circle artery communication of Mongolian gerbils, although there were several types, especially the posterior communicating artery (Yang et al., 2007a). So occluding the carotid artery of Mongolian gerbils is usually used for a good cerebral ischemia model. In a well-characterized animal model of ischemic stroke of Mongolian gerbils (Dodson et al., 1977; Ito et al., 1975; Mrsulja et al., 1975), the present study was undertaken to clear the effect of AVP on the edema of cortex including prefrontal lobe, parietal lobe, temporal lobe, occipital lobe and hippocampus in the cerebral ischemia.

2. Materials and methods

2.1. Animals

Adult male Mongolian gerbils weighing 60–70 g were used in all experiments (Hubei Research Center of Experimental Animals, Wuhan, China). Animals were housed in a colony room under controlled temperature, humidity and a 12 hours light/dark cycle (light on at 6:00 AM), with food and water available *ad libitum*. All procedures were conducted according to the guidelines of the International Association for the Study of Pain (Zimmermann, 1983), and approved by the Ethics Committee of Hubei Research Center of Experimental Animals and the Animal Committee of Xinxiang Institute for New Medicine.

Because Mongolian gerbil, which does not like the other types of rats or mice, has poor Willis' circle artery communication, the ipsilateral brain ischemic stroke is established easy and the other brain hemisphere shows normal relatively after occluding the carotid artery of Mongolian gerbil (Dodson et al., 1977; Ito et al., 1975; Mrsulja et al., 1975).

2.2. Materials

AVP and D(CH_2)$_5$Tyr(ET)DAVP (a peptide drug, an antagonist for V_{1a}, V_{1b} and V_2 receptor) were obtained from Peninsula Laboratories, San Carlos, CA, USA. ^{125}Iodine was from Amersham Pharmacia, Buckinghamshire, UK. The other chemicals were from Sigma Co., St. Louis, MO, USA.

Rabbit anti-arginine vasopressin (AVP) serum was made by Department of Neurobiology, Second Military Medical University, Shanghai, China. The specificity of the antiserum was 100% cross-reactivity with AVP and no cross-reactivity with oxytocin, vasotocin, lysine-vasopressin, vasoactive intestinal peptide, neurotensin, leucine-enkephalin, methionine-enkephalin, β-endorphin and dynorphin A_{1-13}. The dilution of the antiserum was more than 1:40,000 for radioimmunoassay.

2.3. Cerebral ischemia model

All operations were carried out under sterile conditions. The etherized animal was fixed to the operating table. The left carotid artery was revealed carefully by isolating skins and subcutaneous tissues, and occluded with surgical sutures. The right carotid artery was not occluded. Then the isolating subcutaneous tissues and skins were sutured.

For demonstrating the effect of cerebral ischemia, some of the animals were decapitated in 30 min after the left carotid artery occluded. Their brain were taken out and cut into the coronal slices (2 mm/slice). The brain slices are shown in Fig. 1 after 2,3,5-Triphenyl tetrazolium chloride (TTC) staining. The ischemic area (left cerebral hemisphere) showed no TTC straining, whereas the non-ischemic area (right cerebral hemisphere) showed TTC straining.

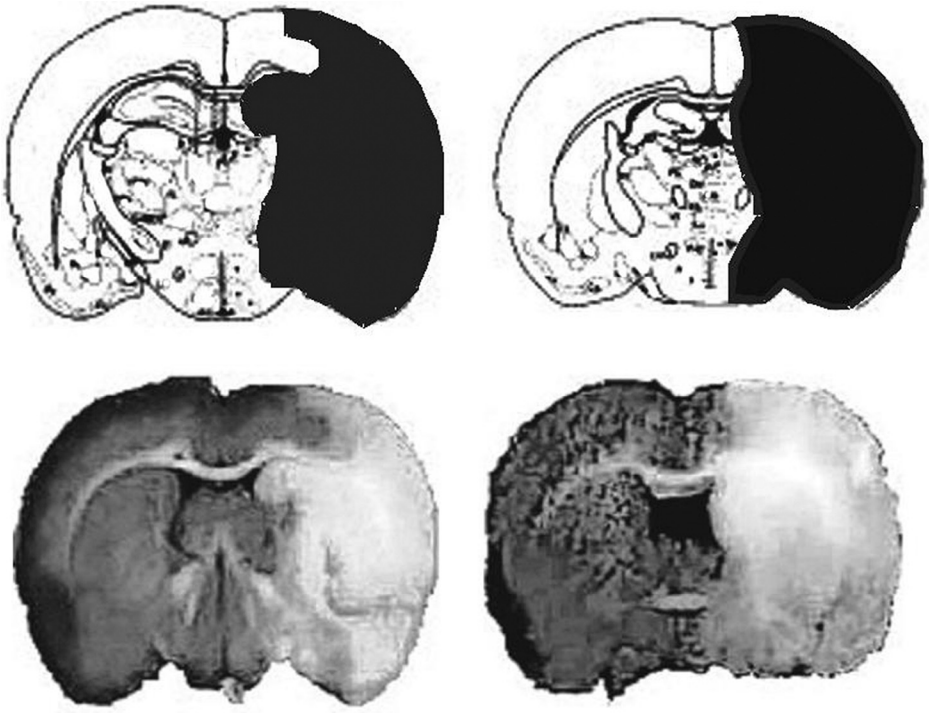

Fig. 1. Brain slices after 2,3,5-triphenyl tetrazolium chloride (TTC) staining. The ischemic area (left cerebral hemisphere) showed no TTC straining, whereas the non-ischemic area (right cerebral hemisphere) showed TTC straining.