The Role of Brain Glutathione in Blood Pressure Regulation

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The sympathetic nervous system plays an important role in the control of blood pressure (BP). Posterior hypothalamus (PH) is considered to be the higher center affecting the tone of sympathetic nervous system. It is known that hypothalamus projects the descending pathways to the nuclei in the brain stem. The nuclei regulates the sympathetic tone. However, little information is available on the chemical substance released from hypothalamic neuron to activate the vasomotor center in the brain stem.

We report in this paper the significance of brain glutathione in regulating BP.

I. Isolation and characterization of a brain oligopeptide for blood pressure regulation

We compared the oligopeptide pattern extracted from brain stem of PH stimulated-rats with that of sham control rats, using reversed-phase high performance liquid chromatography (RPLC). Male Wister rats (250 g) were anesthetized with urethane (1 g/Kg). PH stimulation was performed to deliver 50–150 μA currents for 2 hours through the electrode in order to achieve a BP above 150 mmHg in animal. The RPLC was performed using LKB 2-Pump system equipped with TSK gel ODS-120T column (4.6 mm x 25 cm, Toyo-Soda). A linear gradient elution system from 0 to 10% of acetonitrile was used at a flow rate of 0.3 ml/min for 30 min. Column effluents were monitored by measuring absorbance at 206 nm.

One of the peaks obtained from the peptide pattern was reduced remarkably after electrical PH stimulation. A fraction of this peptide was purified to determine the chemical structure. The result from amino acid analysis indicated that this peptide contained equivalent moles of 3 amino acids, glutamic acid, cysteine and glycine. The spectrum of this peptide from fast bombardment mass spectrometry showed that the isolated peptide was glutathione disulfide.

II. The effect of central administration of glutathione on BP and sympathetic nerve activity

The brain is rich in glutathione, presented in 2 forms, reduced form (GSH) and oxidized form (glutathione disulfide, GSSG). However, no information on the role of glutathione in BP regulation is available.

The role of glutathione in the central nervous system in regulating BP and sympathetic nerve activity (SNA) was investigated in urethane anesthetized male Wistar rats (250 g). The SNA was recorded by the spike counts from abdominal plexus. Intracerebroventricular (ICV) administration of GSSG (1.7–33 nmol) resulted in a dose-dependent increase in BP (Δmean BP: 17 ± 1 mmHg, n = 7, for 33 nmol dose) together with a marked increase in SNA (163 ± 13 to 672 ± 70 spikes/10 sec, n = 7, p < 0.001). The ICV injection of GSH (33 nmol) produced a vasodepressor response (Δmean BP: −9 ± 2 mmHg, n = 6) accompanied by a corresponding decrease in SNA (192 ± 15 to 54 ± 22 spikes/10 sec, n = 6, p < 0.01). These responses were not due to a leakage in the systemic circulation, since intravenous injection of GSSG (33 nmol) or GSH (33 nmol) did not show any cardiovascular effects.

The results from this study indicate that...
GSSG has a stimulatory control over the sympathetic nervous system while GSH has an inhibitory effect on SNA. GSSG and GSH may act within the central nervous system to modulate the tone of the sympathetic nervous system.

III. Brain glutathione metabolism in hypertensive animals

We studied the role of brain glutathione metabolism in 2 models of hypertension, namely spontaneously hypertensive rats (SHR) and deoxycorticosterone acetate (DOCA)-salt hypertensive rats.

Male SHR at 4, 10 and 22 weeks of age and the age-matched Wistar Kyoto rats (WKY) were used. Male Wistar rats (8 weeks of age) were made hypertensive by uninephrectomy, subcutaneous injections of DOCA, 20 mg/week and 1% NaCl solution to drink for 8 weeks. The normotensive control rats for DOCA-salt hypertensive rats were prepared by uninephrectomy and by drinking tap water. The amounts of GSSG and GSH, and glutathione reductase (GR) activity in the hypothalamus and in the brain stem were compared between SHR and WKY and between DOCA-salt hypertensive rats and normotensive control rats.

In SHR, GSSG content (4 weeks old; 16 ± 4 μg/g tissue, n = 11, 22 weeks old; 48 ± 6 μg/g tissue, n = 9) and GSSG/GSH ratio (4 weeks old; 5.6 ± 1.0%, n = 11, 22 weeks old; 21.1 ± 2.4%, n = 9, in the hypothalamus) were always significantly (p < 0.05) higher and hypothalamic GR activity (4 weeks old; 1.1 ± 0.1 U/g tissue, n = 11, 22 weeks old; 1.0 ± 0.1 U/g tissue, n = 9) was significantly (p < 0.05) lower than those of age-matched WKY from prehypertension (4 weeks of age) to established hypertension (10 and 22 weeks of ages). DOCA-salt hypertensive rats also had greater values of GSSG content (60 ± 6 μg/g tissue, n = 8) and lower GR activity (1.0 ± 0.0 U/g tissue, n = 8) in the hypothalamus than normotensive control rats. There were no significant differences in these values in the brain stem between hypertensive rats and normotensive controls.

These results suggest that the increased GSSG/GSH ratio in the hypothalamus due to reduced activity of GR may have an important role in the development of hypertension of SHR and DOCA-salt hypertensive rats (Fig. 1).

IV. Conclusion

Firstly, we developed a new method to detect biologically active peptide regulating BP by coupling RPLC with an electrical stimulation of central nervous nuclei. Secondly, we provided physiological evidence that GSSG and GSH may act within the central nervous system to modulate the tone of sympathetic nervous system, resulting in the regulation of BP control. Thirdly, we showed that the increased ratio of GSSG/GSH from reduced activity of GR in the hypothalamus might contribute to the elevation of BP in hypertensive animals.

REFERENCES


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