important role in maintaining $[Ca^{2+}]_i$ at a steady state ; 3) the increase in $[Ca^{2+}]_i$ induced by $Na^+o$ removal may be enhanced when plasma membrane is depolarized ; and 4) consequently, the $Ca^{2+}$ influx through the reverse mode of the $Na^+/Ca^{2+}$ exchanger may partially contribute to the glucose-induced $[Ca^{2+}]_i$ dynamics in rat pancreatic islets.

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# REGULATION OF PERIPHERAL CYTOKINE EXPRESSION BY THE BRAIN IN RODENTS, WITH REFERENCE TO THE MECHANISM OF STRESS-INDUCED IMMUNOMODULATION

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Much growing evidence has revealed that the brain alters peripheral immune functions in non-inflammatory stress situations, in a different manner from inflammation. It has been demonstrated that both the endocrine and/or the autonomic nervous systems such as the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal-medullary axis (SAM) affect the activity of immune cells directly through their own receptors. However, it is difficult to delineate the complicated neuroimmunomodulation by this direct mechanism alone. Recently, some reports indicated that the circulating level of interleukin (IL-)6 is elevated in various stress situations. Because immune cytokines such as IL-6, IL-1, and tumor necrosis factor (TNF) have numerous effects on immune cells, the brain may 'indirectly' modulate the peripheral immune responses through these cytokine syntheses. However, little is known about the regulatory mechanism of peripheral cytokines by the brain and also in non-inflammatory stress situations. In this study, using mice and rats, I examined the expression of some cytokines in peripheral organs under immobilization stress and compared the results with those under inflammation. Then, I elucidated the role of brain IL-1 and sympathetic nervous system in the stress-induced peripheral cytokine production. Finally, possible existence of novel stress-related molecules was explored in the brain using an RNA arbitrarily primed-polymerase chain reaction (RAP-PCR) technique.

1) The effects of non-inflammatory stress on the peripheral IL-6 production were examined in mice, and compared with those of inflammatory stimulus. When mice were subjected to restriction of movement in a small cage (immobilization stress), the serum IL-6 level rose in 1 h, following increased expression of IL-6 mRNA in both the liver and spleen. The IL-6 mRNA induction was much greater in the liver than in the spleen when compared on a whole-organ basis. Intraperitoneal injection of bacterial lipopolysaccharide (LPS), a stimulant of systemic inflammation, also increased IL-6 mRNA expression in these organs, but more preferentially in the spleen. Immunohistochemical examinations of

liver tissue using an antibody against murine IL-6 revealed that immobilization stress induced IL-6 mainly in hepatic parenchymal cells, whereas LPS injection did so only in sinusoidal mononuclear cells. These results indicate that immobilization stress induces IL-6 production in the liver, especially in hepatic parenchymal cells, probably by a different mechanism from that for IL-6 induction by LPS.

2) Recently, growing evidence has accumulated that IL-1 produced in the brain participates various stress responses, including activation of HPA and SAM. To clarify a role of brain IL-1 in the stress-induced IL-6 production, the effects of intracerebroventricular (icv) injection of human recombinant IL-1 $\beta$ on mRNA expression of IL-6 in the liver and spleen were examined in rats. Icv injection of IL-1 produced a rapid rise of the tissue mRNA levels of IL-6 in both organs in parallel with an increase in its serum level. Peripheral IL-1 and TNF were also induced by icv IL-1 injection. Pretreatment with chlorisondamine, a ganglionic blocking agent, repressed the IL-6 and IL-1 responses, while it influenced little the TNF responses. The cytokine responses to icv IL-1 injection were not attenuated, but much exaggerated in adrenalectomized rats. The results prove that brain IL-1 induces peripheral production of IL-6 and IL-1, but not of TNF, through the sympathetic nerve activation.

3) To find novel molecules being involved in stress and inflammatory responses, brain mRNA of mice subjected to immobilization stress or systemic inflammation by LPS was examined by RAP-PCR analysis using 151 sets of primers. Apparent effects of immobilization and/or LPS were found in the mRNA levels of 45 out of 1,500 genes : 11 genes by immobilization and 10 genes by LPS injection. The remainder was affected by the both situations. A gene, 142.5, induced only by LPS injection in the brain was also increased in a wide variety of peripheral organs, especially in immunocompetent organs including the spleen. Although 142.5 was not induced by immobilization stress in the brain, the mRNA levels of 142.5 in the spleen and liver were increased by either immobilization or intracranial injection of IL-1. Similarly to TNF response, the increase of 142.5 mRNA by centrally given IL-1 was not affected by ganglionic blockade. Thus, the peripheral expression of 142.5 may be regulated by the brain in the same or similar manner to TNF. It was suggested that 142.5 seems to participate in immune-associated functions, and to be a key molecule for the neuroimmune interaction.

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