



Title	Roles of Na <sup>+</sup> /Ca <sup>2+</sup> exchanger in regulation of intracellular Ca <sup>2+</sup> concentration in rat pancreatic islets
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## INFORMATION

Hokkaido University conferred the degree of Doctor of Philosophy (Ph. D) in Veterinary Medicine on March 25, 1999 to 18 recipients.

The titles of their theses and other information are as follows :

### Roles of $\text{Na}^+/\text{Ca}^{2+}$ exchanger in regulation of intracellular $\text{Ca}^{2+}$ concentration in rat pancreatic islets

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$[\text{Ca}^{2+}]_i$  of rat pancreatic islets was monitored by a fluorimetric method using fura-2, and the effects of lowering extracellular  $\text{Na}^+$  ( $[\text{Na}^+]_o$ ) on  $[\text{Ca}^{2+}]_i$  and those of KB-R7943, a selective inhibitor of the reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, on  $[\text{Ca}^{2+}]_i$  dynamics induced under various conditions were investigated. Total replacement of  $\text{Na}^+$  by equimolar N-methyl-D(-)-glucamine caused a rapid increase in  $[\text{Ca}^{2+}]_i$ . Partial replacement of  $\text{Na}^+$  resulted in correlative increases in  $[\text{Ca}^{2+}]_i$  in accordance with the magnitude of reduced  $[\text{Na}^+]_o$ . The increase in  $[\text{Ca}^{2+}]_i$  induced by  $\text{Na}^+$  removal was strongly inhibited in  $\text{Ca}^{2+}$ -deficient environment or by  $\text{Ni}^{2+}$ , indicating that the increase can be ascribed to  $\text{Ca}^{2+}$  influx through the plasma membrane. The  $[\text{Ca}^{2+}]_i$  increase remained almost unchanged in the presence of nifedipine of SK&F 96365, suggesting the  $\text{Ca}^{2+}$  influx induced by  $\text{Na}^+$  removal is not mediated via  $\text{Ca}^{2+}$  channels. Moreover, the result that the  $[\text{Ca}^{2+}]_i$  increase was enhanced by addition of ouabain indicated that the increase depends on the transmembrane  $\text{Na}^+$  gradient. The electrochemical gradients for  $\text{Ca}^{2+}$  ( $\Delta\mu\text{Ca}^{2+}$ ) and for  $\text{Na}^+$  ( $\Delta\mu\text{Na}^+$ ) were calculated to be 39.1 and 12.8 kJ/mol, respectively. The next series of experiments

was performed to investigate a possible contribution of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger to changes in  $[\text{Ca}^{2+}]_i$  under the membrane-depolarized condition.  $\text{Na}^+$  removal followed by  $\text{Ca}^{2+}$  reintroduction induced a transient increase in  $[\text{Ca}^{2+}]_i$  and a subsequent sustained increase under 100 or 5 mM  $\text{K}^+$  condition. The increases in  $[\text{Ca}^{2+}]_i$  were inhibited by KB-R7943. The net amount of the  $[\text{Ca}^{2+}]_i$  increases during  $\text{Na}^+$  removal ( $\Delta[\text{Ca}^{2+}]_i$ ) significantly increased when extracellular  $\text{K}^+$  was raised. Based on these findings, it is conceivable that the  $\text{Ca}^{2+}$  influx through the reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger can be enhanced by membrane depolarization in pancreatic islet cells. It is not fully understood whether  $\text{Ca}^{2+}$  influx via the reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger contributes to the biphasic increase in  $[\text{Ca}^{2+}]_i$  induced by high glucose in pancreatic islets. KB-R7943 partially inhibited the second phase of the  $[\text{Ca}^{2+}]_i$  increase rather than the first phase, suggesting that the reverse mode of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger functions after the first phase of the  $[\text{Ca}^{2+}]_i$  increase.

It is concluded that: 1) the increase in  $[\text{Ca}^{2+}]_i$  induced by lowering  $[\text{Na}^+]_o$  is mainly due to  $\text{Ca}^{2+}$  influx mediated by the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger; 2) the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger plays an

important role in maintaining  $[Ca^{2+}]_i$  at a steady state ; 3) the increase in  $[Ca^{2+}]_i$  induced by  $Na^+$  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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Original papers of this thesis appeared in "Japanese Journal of Physiology", Vol.46, 473-480 (1996), and "Japanese Journal of Physiology", Vol.49, 71-80 (1999)

## 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