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Author(s)	WINARTO, Adi
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## INFORMATION

Hokkaido University conferred the degree of Doctor of Philosophy (Ph. D) in Veterinary Medicine from December, 2000 to March, 2001 to 17 recipients.

The titles of theses and other information are as follows :

### Involvement of KATP channels in development and survival of pancreatic islet cells in mice

Adi Winarto

*Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan*

The involvement of ATP-sensitive potassium channels (KATP channels) in development and survival of pancreatic islet cells in mice has been studied by using Kir 6.2-knockout mice. The aim of present study is to investigate the morphological changes of pancreatic islet in relation to the loss of KATP channel function in order to get better understanding on the role of KATP channel in the homeostasis of pancreatic islets. Furthermore, this study is purposed to find out the cellular distribution of a calcium-binding protein (CaBP) in pancreatic islet cells to obtain direct evidence on its buffering function in normal and KATP channel-deficient mice.

The KATP channel is an essential ion channel involved in glucose-induced insulin secretion. The KATP channel is composed of an inwardly rectifying potassium channel, Kir 6.2, and the sulfonylurea receptor (SUR 1), and in the pancreas it is reported to be shared by all endocrine cell types. A previous study by our research group showed that Kir 6.2-knockout mice lacked KATP channel activities and failed to secrete insulin in response to glucose, but displayed normal blood glucose levels and only mild impairment in glucose tolerance in younger ages. In aged knockout

mice, however, obesity and hyperglycemia were recognizable. The first part of this study aimed to reveal morphological changes in pancreatic islets of Kir 6.2-knockout mice throughout life. At the day of birth, there were no significant differences in the islet cell arrangement between the knockout mice and controls. At 14 postnatal weeks glucagon cells appeared in the central parts of islets, and this image became more pronounced with aging. In animals older than 50 weeks insulin cells showed decreased numbers and intensity of insulin immunoreactivity; most islets in 70- and 80-week-old mice were predominantly composed of glucagon cells and peptide YY (PYY)-containing cells. Staining of serial sections and double staining of single sections from these old mice demonstrated frequent coexpression of glucagon and PYY, which is a phenotype for the earliest progenitor cells of pancreatic endocrine cells. These findings suggest that the KATP channel is important for insulin cell survival and also regulates the differentiation of islet cells.

The first part of study showed the different changes caused by lack of the KATP channel between  $\alpha$  and  $\beta$  cells which share the channel:  $\beta$  cells decreased in number and the

immunoreactivity for insulin, while  $\alpha$  cells increased in number. The second part of the study aimed to elucidate the difference, with respect to the existence of a CaBP, which is known to buffer  $\text{Ca}^{2+}$  rises following stimulation. Calbindin-D 28 k is a predominant calcium-binding protein contained in the pancreatic islets. It can buffer  $\text{Ca}^{2+}$  rises following stimulation and thereby protect cells against calcium toxicity.

The immunoreactivity for calbindin-D 28 k was localized only in  $\alpha$  cells in normal mice, but not present in  $\beta$  cells. This finding held true in islet cells of the KATP channel-

deficient mice. An immunohistochemical survey using six rodents including the mouse showed that calbindin-D 28 k was preferentially localized in  $\alpha$  cells in the rat and guinea pig, while in the hamster both  $\alpha$  and  $\beta$  cells were rich in calbindin-D 28 k. None of the  $\alpha$  and  $\beta$  cells in the squirrel or gerbil pancreas were immunoreactive for calbindin-D 28 k. This finding may explain how  $\alpha$  cells but not  $\beta$  cells in the knockout mice could escape from the calcium toxicity, and shows that the cellular localization of calbindin-D 28 k in the islets differs even among rodents.

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Original papers of this thesis appeared in " Arch. Histol. Cytol. " Vol. 64 : 59-67 (2001) , " Biomed. Res. " Vol. 21 : 305-313 (2000).

### The cellular distribution of estrogen receptor $\alpha$ (ER $\alpha$ ) and $\beta$ (ER $\beta$ ) mRNAs in the reproductive organs of the rat : an *in situ* hybridization study

Chishimba Nathan Mowa

Laboratory of Anatomy, Department of Biomedical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo 060-0818, Japan

This study thoroughly mapped the cellular distribution of estrogen receptor (ER)  $\alpha$  and ER  $\beta$  mRNAs in the reproductive organs of the female and male rats by *in situ* hybridization technique in order to elucidate the roles of estrogen in the reproductive events.

In the adult female rat, expression of ER  $\alpha$  and ER  $\beta$  mRNAs was predominant in the reproductive tract and ovary, respectively. ER  $\alpha$  mRNA had the most pronounced expression in epithelial cells and subepithelial stromal cells from the oviduct to the vagina, while in the ovary it was moderately detected in only the theca folliculi and interstitial glands. The oviduct showed a region-dependent expres-

sion pattern of ER  $\alpha$  mRNA : the isthmus had the most intense signals while the infundibulum revealed a low intensity of expression. Signals for ER  $\beta$  mRNA in the ovary were most intense in the granulosa cells of healthy follicles whereas degenerating follicles lacked any significant expression. Less intense signals for ER  $\beta$  mRNA were localized in the theca folliculi and corpus luteum. Detectable levels of ER  $\beta$  mRNA were observed in the subepithelial stromal cells from the oviduct to the vagina.

In the developing female reproductive organs, diffuse signals of ER  $\alpha$  and  $\beta$  mRNAs were coexpressed in the fetal ovary ; they