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学 位 論 文 の 要 約 (研 究 成 果 の ま と め)

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学位論文名 ラット唾液腺におけるプロサポシンとその受容体の雌雄差

学位論文の要約

Saliva, a watery substance in the mouth, is secreted from the salivary glands by double autonomic sympathetic and parasympathetic innervation [1]. The secretory activities of salivary glands are modulated mainly by nutrient metabolism and neuroendocrine system, including sex and stress hormones. Dysregulation of salivary secretion causes various oral diseases. For example, xerostomia, or dry mouth disease, is a condition of severe hyposalivation due to aging, systemic disease (diabetes and Sjögren syndrome), or radiotherapy [2]. The prevalence rates of xerostomia and Sjögren's syndrome differ between the sexes, as postmenopausal women have a higher prevalence than men [3], indicating that salivary functions are altered with age and sex.

The salivary glands produce various neurotrophins those are thought to regulate salivary function during normal and pathological conditions [4]. Prosaposin (PSAP), a saposin precursor, is a potent neurotrophin found in several tissues and various biological fluids [5, 6]. Although PSAP is a clinically significant and potent neurotrophin with a postulated role regulating salivary function, little is known about its localisation and distribution in salivary glands. Accordingly, this study examined whether PSAP and its receptors, G protein-coupled receptor 37 (GPR37) and GPR37L1, are expressed in the major salivary glands, submandibular gland (SMG) and sublingual gland (SLG), of rats. As the functions of salivary glands vary based on age and sex, this study also examined whether sex and age affect expression of PSAP and its receptors in salivary glands. To clarify this, the present study used male and female Wistar rats at different ages from young adult to postmenopausal (2, 6, 18 and 27 months old).

Histopathological results of the SMG revealed the presence of serous and granular convoluted tubule (GCT) cells at different age points. At the age of 2 months, most of the cells in the SMG were serous in male and female rats, although a few GCT cells, primarily in male rats, were visible. Prominent changes in the size and shape of GCT cells were observed in both sexes of older aged rats. In quantitative analysis, the number of GCT cells in the SMG of male and female rats did not differ at any age in this study, except at 2 month of age when the male rats had significantly higher number GCT cells than female rats. On the other hand, the SLG was predominantly mucous and no prominent changes in the size, shape and number of cells were observed in both sexes at any age points.

Immunohistochemical analysis provide evidence that the immunoreactivity of PSAP and its GPR37 and GPR37L1 receptors is detectable in the major salivary glands of rats, suggesting that the PSAP originating from the salivary glands might be functioning in an autocrine fashion. The immunohistochemical analysis also revealed that the expression of PSAP and its receptors were varied considerably based on the type of gland, acinar cells, age, and sex. In fact, PSAP, GPR37, and GPR37L1 were predominantly expressed in GCT cells of the SMG, and the intensity of their immunoreactivity was higher in young adult female rats than age-matched male rats, which was more prominent at menopause. On the other hand, weak PSAP, GPR37, and GPR37L1 immunoreactivity was observed mainly in basal layer of mucous cells of the SLG. Triple label immunofluorescence analysis revealed that PSAP, GPR37, and GPR37L1 were co-localised in the basal layer of acinar cells in the major salivary glands, although immunoreactivities varies between male and female rats. In addition to acinar cells, a widespread staining of PSAP and its receptors were observed in the ductal system of both SMG and SLG. PSAP immunoreactivity in ductal system shows a very similar distribution pattern to other neurotrophins, i.e., exclusive localization in the secretory granules of ducts [4], suggesting that the PSAP and other neurotrophins might be functioning as exocrine factors, or endocrine factors after reabsorption.

As PSAP is a glycoprotein and is differentially expressed in the SMG of male and female rats, it is possible that sex-related changes in saliva biochemistry, particularly salivary glycoproteins in males, might be different from those in females. Therefore, it is possible that sex-related differences in the release of PSAP and/or neurotrophin-like molecules those are more abundant in female glands might play a role in the changes in saliva biochemistry causing oral discomfort, particularly in cases where sex and age are affected unequally, such as xerostomia and Sjögren's syndrome.

In conclusion, the present study found sex- and age-dependent differences in the expression of PSAP and its GPR37 and GPR37L1 receptors in the major salivary glands of rats. The identification of PSAP and its receptors is the first step toward further studies to identify the specific roles of this potent neurotrophic factor in the regulation of salivary functions in normal and pathological conditions.

All above data are involved the main published paper:

Main Paper : Farzana Islam, Sakirul Islam Khan, Hiroaki Nabeka, Shouichiro Saito, Xuan Li, Tetsuya Shimokawa, Kimiko Yamamiya, Naoto Kobayashi, Seiji Matsuda. Prosaposin and its receptors are differentially expressed in the salivary glands of male and female rats. *Cell and Tissue Research* 2018 DOI: 10.1007/s00441-018-2835-9