

SECRETORY AND ANTI-INFLAMMATORY ACTIONS OF SOME GASTRO-INTESTINAL HORMONES IN SALIVARY GLANDS

Akademisk avhandling

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av

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The thesis is based on the following papers:

- I. **Çevik Aras H, Ekström J.** Cholecystokinin- and gastrin-induced protein and amylase secretion from the parotid gland of the anaesthetized rat. *Reg Pept* 2006; 134: 89-96.
- II. **Çevik Aras H, Ekström J.** Pentagastrin-induced nitric oxide-dependent protein secretion from the parotid gland of the anaesthetized rat. *Exp Physiol* 2006; 91: 977-982.
- III. **Çevik Aras H, Ekström J.** Pentagastrin-induced protein synthesis in the parotid gland of the anaesthetized rat, and its dependence on CCK-A and -B receptors and nitric oxide generation. *Exp Physiol* 2006; 91: 673-679.
- IV. **Ekström J, Çevik Aras H.** Parasympathetic non-adrenergic, non-cholinergic transmission in rat parotid glands: Effects of cholecystokinin-A and -B receptor antagonists on the secretory response. *Reg Pept* 2008; 146: 278-284.
- V. **Çevik Aras H, Ekström J.** Melatonin-evoked in vivo secretion of protein and amylase from the parotid gland of the anaesthetised rat. *J Pineal Res* 2008; 45: 413-421.
- VI. **Darnell M, Çevik Aras H, Magnusson B, Ekström J.** Lipopolysaccharide induced-in vivo increases in β -defensins of the rat parotid gland. *Arch Oral Biol* 2006; 51: 769-774.
- VII. **Çevik Aras H, Ekström J.** Anti-inflammatory effects of cholecystokinin and melatonin in the lipopolysaccharide-exposed rat parotid gland as indicated by myeloperoxidase activity. *In manuscript.*



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ABSTRACT

Secretory and anti-inflammatory actions of some gastro-intestinal hormones in salivary glands

Textbooks generally state that the secretory activity of salivary glands is solely regulated by nerves. This view is challenged in the present *Thesis*, using the parotid gland of the anaesthetized rat as experimental *in vivo* model. By changing focus from secretion of fluid to secretion of protein and of acinar amylase a secretory role was found not only for gastrin and cholecystokinin but also for the non-traditional gastro-intestinal hormone melatonin. Neither intravenous infusion of the hormone-analogues pentagastrin and desulfated cholecystokinin-8 nor of melatonin evoked any overt fluid secretion from the duct-cannulated gland. However, a subsequent intravenous wash-out injection of the secretagogue methacholine revealed protein/amylase secretion in response to the infusion of the hormone/hormone-analogues. The hormone/hormone-analogues exerted their effect directly on the gland cells: it persisted in the presence of α - and β -adrenoceptor antagonists, after disconnecting the gland from its peripheral ganglia and after evisceration. The gland protein synthesis increased to pentagastrin. Cholecystokinin(CCK) -A and CCK-B receptor types as well as the melatonin receptors, MT1 and MT2, were expressed in the gland. By the use of hormone-receptor antagonists, protein secretion was shown to involve mainly the CCK-A receptors and the MT2 receptors, whereas both types of cholecystokinin receptors were involved in the protein synthesis. The secretion of protein/amylase and the synthesis of protein to the hormone/ hormone-analogues were partially dependent on nitric oxide generated by the activity of neuronal type NO-synthase, probably of parenchymal origin. Cholecystokinin may occur as a transmitter in the peripheral nervous system and, hypothetical, cholecystokinin might belong to the group of parasympathetic non-adrenergic, non-cholinergic transmitters that upon stimulation of the parasympathetic auriculo-temporal nerve evokes secretion of fluid and, in particular, secretion of protein/amylase. However, the stimulation of the parasympathetic innervation, in the presence of cholecystokinin receptor antagonists, gave no support for a transmitter role for cholecystokinin in the gland. Lipopolysaccharide injected intraductally towards the parotid gland induced inflammation, as shown by neutrophil infiltration and increased myeloperoxidase activity in the gland, and mobilization of β -defensins, being a part of the oral defense mechanism. Melatonin and cholecystokinin (sulfated CCK-8) administered intraperitoneally exerted anti-inflammatory actions in the inflamed gland as judged by reduced levels of the elevated activity of myeloperoxidase. The effect of melatonin was non-receptor mediated, while that of sulfated CCK-8 was partially dependent on CCK-A receptors. The inflammatory response involved NO generated from inducible NO-synthase and neuronal type of NO-synthase as shown by selective NO-synthase inhibitors, the neuronal type being most likely of parenchymal origin, since it was activated also in the chronically denervated gland. In conclusion, the secretory activity of salivary glands seems not only to be regulated by a cephalic phase of nervous activity but also by a gastric phase and an intestinal phase of endocrine activity. Circulating melatonin and cholecystokinin/gastrin may not only influence the secretory activity but may also protect the salivary glands from inflammation. The present findings have implications for salivary gland dysfunction/dry mouth and its treatment.

Keywords: Salivary glands, protein secretion, synthesis, inflammation, β -defensins, myeloperoxidase, cholecystokinin, gastrin, melatonin, nitric oxide, nerve stimulation.