

**Larsson L-I & Rehfeld J F.** Localization and molecular heterogeneity of cholecystokinin in the central and peripheral nervous system. *Brain Res.* 165:201-18, 1979. [Institute of Medical Biochemistry, University of Aarhus, Aarhus, Denmark]

The data document that cholecystokinin (CCK) immunoreactive nerves are widespread in the central and peripheral nervous systems and contain multiple different CCK components. [The *SCI*® indicates that this paper has been cited in more than 475 publications.]

## Cholecystokinin Nerves

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In the mid-1970s many peptides were found to occur both in nervous and endocrine tissues. In 1975, J.J. Vanderhaeghen and coworkers reported that immunoreactive gastrin could be detected in the brain.<sup>1</sup> As the localization of gastrin to endocrine cells represented the subject of my thesis in 1975, I also wanted to localize the hormone in brain tissue. I was aided in this by antibodies provided by Jens F. Rehfeld, working in the same department. Although it seemed a simple-enough project, no positive results ensued, except when antibodies directed to the C-terminal gastrin tetrapeptide were used. The explanation for this came with Graham J. Dockray's paper in 1976, showing that Vanderhaeghen's peptide really represented cholecystokinin (CCK).<sup>2</sup> Gastrin and CCK are related hormones with a possible common ancestry.<sup>3</sup> Their biological activities reside in identical C-terminal regions, and anti-

bodies to these do not distinguish the hormones. Jens made detailed investigations of CCK forms in the brain using radioimmuno-analysis, and I mapped the distribution of CCK immunoreactive nerves in the nervous system by immunocytochemistry. This work resulted in several papers (see references 4-6), of which this 1979 *Brain Research* paper apparently fared well in terms of citations.

The reasons for the frequent citations may be that the paper is the first rather extensive report on CCK nerve distribution and, in addition, characterizes the multiple CCK components that occur in tissues. In addition, it draws attention to hippocampal CCK fibers.

Much interest has been devoted to CCK because of its abundant presence in the cerebral cortex and its possible role as a satiety signal. CCK forms may also modulate opiate binding sites. Some years ago, we found that snails showed inverse ageand season-dependent variations in the content of neuronal CCK and opioid peptide immunoreactivity.<sup>7</sup> At that time, such plasticity was evident only at the peptide level. With refined in situ hybridization tools and quantitation, we now address such problems at higher levels.<sup>8</sup> It is a tantalizing thought that epigenetic controls may regulate the types of transmitters in individual neurons.

The CCK mapping studies were conducted at night by the fluorescence microscope. In many settings, scientists are prevented from doing scientific work during the day, interrupted as they are by administration, meetings, teaching, visitors, etc. As before, most of my scientific work is still conducted outside office hours, but now at home in a comfortable microscopy room.

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2. **Dockray G J.** Immunochemical evidence of cholecystokinin-like peptides in brain. *Nature* 264:568-70, 1976. (Cited 485 times.)
3. **Larsson L-I & Rehfeld J F.** Evidence for a common evolutionary origin of gastrin and cholecystokinin. *Nature* 269:335-8, 1977. (Cited 175 times.)
4. **Uvnäs-Wallensten K, Rehfeld J F, Larsson L-I & Uvnäs B.** Heptadecapeptide gastrin in the vagal nerve. *Proc. Nat. Acad. Sci. USA* 74:5707-10, 1977. (Cited 100 times.)
5. **Larsson L-I & Rehfeld J F.** A peptide resembling COOH-terminal tetrapeptide amide of gastrin from a new gastrointestinal endocrine cell type. *Nature* 277:575-8, 1979. (Cited 55 times.)
6. -----. Pituitary gastrins occur in corticotrophs and melanotrophs. *Science* 213:768-70, 1981. (Cited 55 times.)
7. **Gesser B P & Larsson L-I.** Changes from enkephalin-like to gastrin/cholecystokinin-like immunoreactivity in snail neurons. *J. Neurosci.* 5:1412-7, 1985.
8. **Larsson L-I, Traasdahl B & Hougaard D M.** Quantitative non-radioactive in situ hybridization. Model studies and studies on pituitary proopiomelanocortin cells after adrenalectomy. *Histochemistry* 95:209-15, 1991.  
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