

Larsson L-I, Fahrenkrug J, Schaffalitzky de Muckadell O, Sundler F, Håkanson R & Rehfeld J F. Localization of vasoactive intestinal polypeptide (VIP) to central and peripheral neurons. *Proc. Nat. Acad. Sci. USA* 73:197-200, 1976.

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The vasoactive intestinal polypeptide (VIP), a candidate gut hormone, was demonstrated to be present in a widespread system of gastrointestinal and cerebral nerves. VIP immunoreactive endocrine cells were detected in gastric mucosa and in tumors associated with the "pancreatic cholera" syndrome. The findings underlined the concept that the endocrine and nervous system shared messengers and that VIP could be important for local blood regulation. [The SC<sup>®</sup> indicates that this paper has been cited in more than 595 publications.]

## Peptides in Nerve Cells

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In the early 1970s, we were both working at the Department of Histology at the University of Lund. We had close collaboration with two Danish scientists, Jens F. Rehfeld and Flemming Stadil, who had developed highly sensitive and specific radioimmunoassays (RIA) for gastrin. Their group included Jan Fahrenkrug and Ove Schaffalitzky de Muckadell, who developed a radioimmunoassay for the new peptide VIP (vasoactive intestinal polypeptide).

VIP had been isolated by Sami I. Said and Viktor Mutt in Viktor's laboratory at Karolinska Institutet, where many important peptides had been purified.<sup>1</sup> This peptide displayed strong vasoactive properties and had previously been reported in a system of gastrointestinal endocrine cells. Supplied with several antibodies from Fahrenkrug and Muckadell, we embarked on localizing VIP. The results turned out to be very different from the ones we expected. Apart from the few endocrine cells in the stomach

epithelium and in tumors, VIP appeared to occur in a widespread system of gastrointestinal and cerebral nerves. Many of the nerves contacted blood vessels, suggesting that neuronally released VIP could control blood flow. The immunocytochemical controls were negative and Fahrenkrug's and Muckadell's RIA analysis further attested to its specificity. Ulf von Euler, the discoverer of substance P—another peptide with a dual endocrine and neuronal localization—kindly agreed to submit the paper for us.

We believe that the impact of the paper was due to several factors. First, in the mid-1970s, VIP, substance P, somatostatin, and several other bioactive peptides could be added to a growing list of substances sharing a dual distribution to the nervous and endocrine systems. This suggested a biochemical basis for the "body-mind connection." Second, VIP was of general interest due to its biological properties. Subsequent work also demonstrated VIP nerves in many other locations, including cerebral blood vessels<sup>2</sup> and the genital tract.<sup>3</sup> Finally, data such as these documented the importance of immunocytochemistry, as only this method could exactly delineate the contacts the nerve terminals made with putative effector structures.

We have good recollections of the VIP work. A particularly good memory is that some discrepancies in VIP localization could be resolved, not by undignified quarrel at congresses and symposia, but by mutual exchange of antibodies.<sup>4</sup> This showed that different antibodies to the same antigen could provide quite different localizations, and it further underlined the importance of excessive cross-reactivity controls.

While this paper was on its way, Rehfeld was appointed professor of biochemistry in Aarhus, Denmark, and invited Larsson to join him there. After several profitable years in Aarhus, Larsson became research professor in Copenhagen and is now at the State Serum Institute, from where many of the valuable antibodies originated. Sundler remained at the Department of Histology (now named Department of Medical Cell Research) in Lund, where he is now chairman.

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2. Larsson L-I, Edvinsson L, Fahrenkrug J, Håkanson R, Öwman C, Schaffalitzky de Muckadell O & Sundler F. Immunohistochemical localization of vasodilatory polypeptide (VIP) in cerebrovascular nerves. *Brain Res.* 113:400-4, 1976 (Cited 285 times)
3. Larsson L-I, Fahrenkrug J & Schaffalitzky de Muckadell O. Vasoactive intestinal polypeptide occurs in nerves of the female genitourinary tract. *Science* 197:1374-5, 1977 (Cited 195 times)
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