This Week's Citation Classic

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Hughes J, Smith T W, Kosterlitz H W, Fothergill L A, Morgan B A & Morris H R.
Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* **258**:577-9, 1975. [Unit Res. Addictive Drugs and Dept. Biochem., Univ. Aberdeen, Scotland; Pharmaceutical Div., Reckitt and Colman Ltd., Hull; and Dept. Biochem., Imperial Coll., London, England]

This paper describes the structure, chemical synthesis, and actions of two endogenous opioid peptides, methionine-enkephalin and leucine-enkephalin, from pig brain. It also notes the sequence homology between methionine-enkephalin and the pituitary hormone β-lipotropin. [The *SCI*® indicates that this paper has been cited in over 1,460 publications since 1975.]

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"As a lecturer in the newly formed pharmacology department at the University of Aberdeen, my research centred on adrenergic release mechanisms. My chairman, Hans Kosterlitz, worked on opiate modulation of acetylcholine release and quantitative aspects of opiate receptor interactions. We shared a common interest in neuromodulatory mechanisms and in 1972 our research interests converged with our discovery of opiate receptor mediated inhibition of adrenergic transmission in the mouse vas deferens.[1] The vas was to become, along with Hans's guinea-pig ileum preparation, a standard assay for opiate action; it also provided the means of testing an idea developed over many discussions about the function of opiate receptors. We reasoned that these receptors might form part of a neurochemical system subject to activation by a specific chemical signal. The effects of morphine could then be viewed as mimicking the endogenous opiate ligand in the same way as nicotine mimics some actions of acetylcholine. The opportunity to test this hypothesis came on Hans's retirement in 1973 when he invited me to join him as deputy director in establishing a drug research unit. I had barely moved when Eric Simon,[2] Sol Snyder,[3] and Lars Terenius[4] demonstrated the existence of specific opiate binding sites. These findings provided additional support for our hypothesis.

"Serendipity plus acquired Scottish parsimony gave an early lead in October 1973. Before throwing out some 'unsuccessful' frozen extracts I retested them and this time obtained a small but positive response. The initial negative result was due to interfering nucleotides which had degraded on storage allowing the detection of the more stable enkephalin.

"By spring 1974 the peptide nature and properties of our material had been established and a paper was submitted[5] although editorial processes delayed this for a year. Meanwhile Lars, who had obtained similar positive results with his receptor binding technique, and I disclosed our findings at a Neurosciences Research Programme meeting in Boston. The cat was out of the bag and we knew that we could expect strong competition to identify the 'endogenous ligand.' Lars declined to participate in such a race and decided to concentrate on the clinical aspects of the discovery.

"By the following spring, Linda Fothergill had obtained sequence data that proved ambiguous. We surmised but could not prove that this was due to the presence of a second similar peptide. However, at a seminar I had given in Cambridge, I had met and discussed the problem with Howard Morris. I prepared a further 100 nmoles of material for Howard, who then used his elegant mass spectrometric technique to unequivocally identify both methionine- and leucine-enkephalin. The resulting paper marked the beginning of a vast research effort in neurobiology involving many scientific disciplines. This probably explains the paper's high citation rate.

"Hans and I have received a number of honours including the Lasker Prize, and Howard the BDH Gold Medal for this and other work on biological structures. We owed much to the excellence of our collaborators and to laboratory camaraderie which ensured that many a heated scientific argument was settled over a good malt, the endogenous Scottish ligand."

1. **Henderson G, Hughes J & Kosterlitz H W.** A new example of a morphine sensitive neuroeffector junction: adrenergic transmission in the mouse vas deferens. *Brit. J. Pharmacol.* 46:764-6, 1972.
2. **Simon E J, Hiller J M & Edelman I.** Stereospecific binding of the potent narcotic analgesic [^{3}H]etorphine to rat-brain homogenate. *Proc. Nat. Acad. Sci. US* 70:1947-9, 1973.
3. **Pert C B & Snyder S H.** Opiate receptor: demonstration in nervous tissue. *Science* 179:1011-14, 1973.
4. **Terenius L.** Stereospecific interaction between narcotic analgesics and a synaptic plasma membrane fraction of rat cerebral cortex. *Acta Pharmacol. Toxicol.* 32:317-20, 1973.
5. **Hughes J.** Isolation of an endogenous compound from the brain with pharmacological properties similar to morphine. *Brain Res.* 88:295-308, 1975.