Identification and functional characterization of novel neuropeptides: from frogs to humans

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The brain of amphibians possesses major advantages for the search of novel neuropeptides. Firstly, the concentration of most neuropeptides in the CNS of amphibians is several orders of magnitude higher than in the CNS of mammals. Secondly, the sequences of amphibian neuropeptides are usually very similar to those of mammals. Thirdly, amphibians possess the same repertory of neuropeptides as mammals. We have taken advantages of this situation to isolate neuropeptides from the brain of the European green frog *Rana esculenta* and to look for their orthologs in mammals. Using this comparative approach, we have notably characterized *(i)* secretoneurin, a peptide derived from the post-translational processing of secretogranin II; *(ii)* the somatostatin-14 (S14) paralog [Pro^2, Met^{13}]S14 together with S14, thereby providing the first evidence for the occurrence of two somatostatin variants in the brain of vertebrates; *(iii)* the first tetrapod urotensin II, thus demonstrating that this peptide was not the appanage of the fish caudal neurosecretory organ but was also present in the brain of vertebrates. Here, we will describe the discovery of a 26-amino acid RFamide peptide (26RFa), the latest member of the RFamide family that has been identified in vertebrates. 26RFa was initially isolated in the frog brain and the orthologs were subsequently characterized in fish, birds and mammals. The sequence of 26RFa has been strongly conserved in vertebrates, suggesting that the peptide plays important functions. Indeed, 26RFa has been found to exert a potent orexigenic effect in birds and mammals, to stimulate aldosterone secretion, to inhibit glucose-evoked insulin release, to activate the gonadotropic axis, and to induce analgesic effects in rodents. Finally, 26RFa receptor (GPR103) knock-out mice suffer from osteopenia and exhibit the characteristic kyphotic hump of osteoporotic patients indicating that 26RFa is required for bone morphogenesis. The discovery of the biologically active neuropeptide 26RFa in frog and subsequently in other vertebrates validates our comparative approach for the identification of novel neuropeptides in humans.