Multi-author Review
Galanin – 25 years with a multitalented neuropeptide

Coordinator: T. Hökfelt

Cell. Mol. Life Sci. 65 (2008) 1793 – 1795
1420-682X/08/121793-3
DOI 10.1007/s00018-008-8152-9

Cellular and Molecular Life Sciences

Galanin – 25 years with a multitalented neuropeptide

T. Hökfelt[a,*] and K. Tatemoto[b]

[a] Department of Neuroscience, Karolinska Institutet, Stockholm (Sweden), Fax: +468 331692, e-mail: Tomas.Hokfelt@ki.se
[b] Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo (Japan) and Department of Physiology, Medical School, University of Oulu, Oulu (Finland)

Online First 27 May 2008

Keywords. Coexistence, galanin receptor, G-protein coupled receptors, neurotransmitter, 7-transmembrane receptors.

Introduction (Part of a Multi-author Review)

In the last century, many neuropeptides and hormonal peptides were identified on the basis of bioassays. Thus, during the extraction/isolation procedure the purity of the compound was stepwise monitored by recording a specific biological response, e.g. for cholecystokinin the contraction of the gall bladder. In 1978 K.T., working with Prof. Viktor Mutt at the Department of Biochemistry, Karolinska Institutet in Stockholm, developed a novel method for the detection of biologically active peptides based on the C-terminal amide structure, which is a unique structure of many peptide hormones and neuropeptides [1]. Since peptides with this structure are likely to be biologically active, it was thought that the search for unknown peptide amides would result in the finding of novel peptides. In fact, this approach turned out to be very successful, and several previously unknown peptide amides could be isolated from tissue extracts using this chemical assay method. And this is how the 29 amino acid peptide galanin (named after the N-terminal glycine and C-terminal alanine) was identified in porcine intestinal extracts by its C-terminal alanine amide structure [2].

Several other peptides were identified by K.T. and Viktor Mutt based on this principle. Thus, they isolated two novel peptide amides, which were designated peptide HI (PHI) and peptide YY (PYY), from porcine intestinal extracts [3]. Subsequently, a peptide with a C-terminal tyrosine amide from porcine brain extracts was discovered, which was named neuropeptide Y [4], and finally pancreastatin [5].

The isolation work of galanin from porcine intestine was actually already completed in 1980 using the chemical assay method. But the structure of galanin was not determined until 1983, because no biological activity of this peptide was found in the bioassays performed in our laboratory. Therefore, a large quantity of natural galanin was prepared from porcine intestine and sent to a number of laboratories in Europe and North America to examine whether or not this novel peptide had any biological activity. The first positive report came from Dr. T. J. MacDonald, University of Western Ontario, London, Canada, who found an effect of galanin on plasma glucose levels in dog. Subsequently, Dr. Å. Rökaeus, Department of Pharmacology, Karolinska Institutet, found that galanin contracts rat smooth muscle preparations. At that point it was decided to determine the primary structure of galanin using a liquid-phase automatic sequencer in collaboration with Professor H. Jörnvall, Department of Medical Chemistry, Karolinska Institutet, and thus the first paper on galanin was published in 1983 [2]. Between 1983 and 1987, our natural galanin preparations were used for a number of biological, immunochemical and receptor binding studies until synthetic preparations became available [6].

Galanin was initially considered a peptide without a family, but it was observed that the galanin precursor molecule also contained a possibly bioactive peptide, galanin message-associated peptide (GMAP) [7]. However, up till fairly recently the significance of

* Corresponding author.

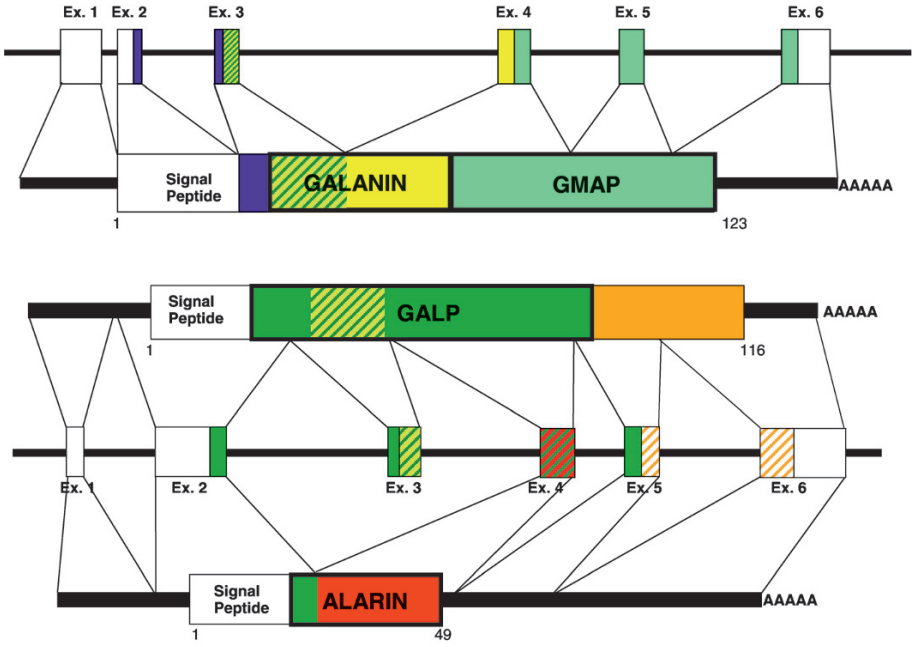

Figure 1. Organization of the preprogalanin and the preproGALP genes. The first exon encodes only the 5′-untranslated region of preprogalanin mRNA. Exon 2 starts with a translation initiation codon of the signal peptide and terminates before the proteolytic site preceding the mature galanin peptide. The first 13 amino acids of galanin are encoded by exon 3; the remaining 16 amino acids and most of GMAP by exons 4 and 5. The remaining portion of GMAP and the polyadenylation site are located in exon 6. Arrows indicate cleavage site of endopeptidases. With regard to preproGALP, the first exon is noncoding. PreproGALP is encoded by exons 2–6, and the segment with galanin homology [(GALP (9-21)] is contained in exon 3. The mature peptide GALP (1-60) is encoded by exons 2–5. Post-transcriptional splicing leads to exclusion of exon 3, resulting in a frame shift and a novel precursor protein. This protein harbours the signal sequence of preproGALP and the first 5 amino acids of the mature GALP peptide followed by another 20 amino acids, and further proteolytic cleavage leads to alarin (1–25). Arrows indicate cleavage sites of endopeptidases. Figure kindly provided by Prof. Barbara Kofler. From Ref. 13 with permission.

this peptide was uncertain, though more recent work suggests distinct biological actions (see Kofler et al., this issue). A novel member of the galanin family, galanin-like peptide (GALP), was discovered in 1999 [8] and recently a fourth member, alarin [9] (Fig. 1). One reason for the comparatively slow development in the field was that the first galanin receptor, GalR1, was not cloned until 1994 by Habert-Ortoli and collaborators [10], a major event in the history of galanin. Subsequently, two further receptors, GalR2 and -3, were discovered, an area that has been summarized in several reviews [11–13] (Fig. 2).

A further problem was the lack of pharmacological tools to dissect galaninergic mechanisms and functions. Here Bartfai, Langel and colleagues were active and presented the first ligands with antagonistic actions, chimeric peptides built up of galanin (1–12) combined with different peptide moieties [14]. These molecules have been important and very widely used tools in galanin research. However, for work on the central nervous system these compounds have to be administered intracerebrally, and not until 2005 was a non-peptide, blood-brain-barrier-penetrating, small-molecule galanin antagonist reported, surprisingly acting at GalR3 [15, 16].

The initial interest in galanin was modest, and has in a way remained so. A search in PubMed at the beginning of February 2008 resulted in 2914 hits under galanin versus 10175 for neuropeptide Y, in spite of the fact that these two peptides were discovered and published almost at the same time (see above). Nevertheless, a small but very active galanin community has developed, and the research has diverted into manifold directions.

The present volume of CMLS summarizes many of the important fields, where galanin and galanin receptors are involved. However, and unfortunately, it was not possible to include work from all areas. Our initial plans comprised more articles, but due to CMLS review rules we had to restrict the present volume to 10 papers. Some of the ones that we could not accommodate here, but give a recent reference for, deal with stem cells [17], food intake [18], cardiovascular control [19] and cancer [20]. The progress in the field has been recorded at three meetings which all have been published, the most recent one in a volume of *Neuropeptides* [21].

We would like to dedicate this volume of CMLS to the late Prof. Viktor Mutt (1923–1998), a pioneer and a great biochemist, and a great yet modest human being [see 22].

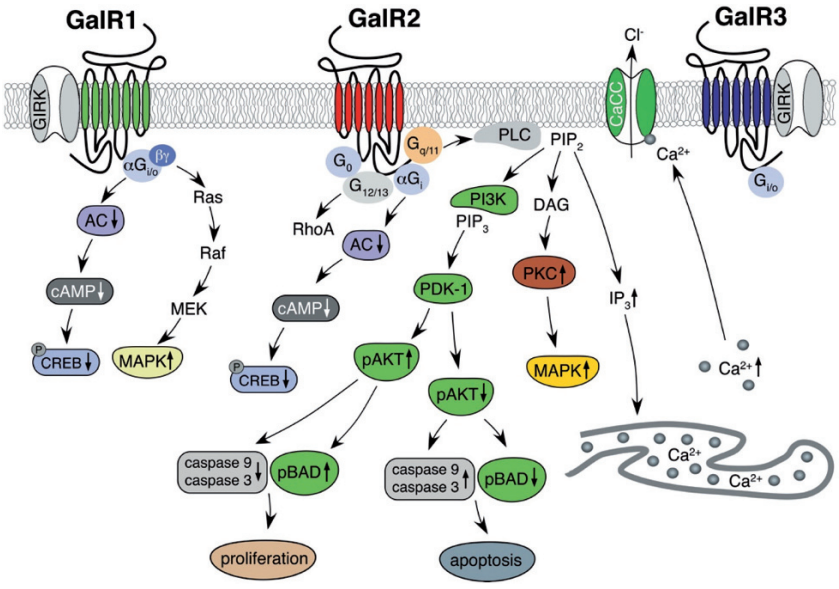

Figure 2. Signaling pathways of galanin receptor subtypes. AC, adenylate cyclase; CaCC, Ca^{2+}-dependent chloride channel; cAMP, 3′,5′-cyclic adenosine monophsophate; (p)CREB, (phosphorylated) cAMP response element binding protein; DAG, diacylglycerol; IP_3, inositol triphosphate; MEK, mitogen-induced extracellular kinase; PDK-1, phosphoinosotide-dependent protein-kinase I; PIP_2, phosphatidylinositol biphosphate; PIP_3, phosphatidylinositol triphosphate; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PLC, phospholipase C. Figure kindly provided by Prof. Barbara Kofler. From Ref. 13 with permission.

Acknowledgments. We thank Prof. Barbara Kofler for allowing us to reproduce Figures 1 and 2 and for suggesting the title. T.H.'s work on galanin over more than 3 decades has been supported by, in particular, the Wallenberg Foundations, the Swedish (Medical) Research Council and an Unrestricted Neuroscience Grant from Bristol-Myers Squibb.

1 Tatemoto, K. and Mutt, V. (1978) Chemical determination of polypeptide hormones. Proc. Natl. Acad. Sci. USA 75, 4115–4119.
2 Tatemoto, K., Rökaeus, Å., Jörnvall, H., McDonald, T. J. and Mutt, V. (1983) Galanin- a novel biologically active peptide from porcine intestine. FEBS 164, 124–128.
3 Tatemoto, K. and Mutt, V. (1980) Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. Nature 285, 417–418.
4 Tatemoto, K., Carlquist, M. and Mutt, V. (1982) Neuropeptide Y, a novel brain peptide with structural similarities to peptide YY and pancreatic polypeptide. Nature 296, 659–660.
5 Tatemoto, K., Efendic, S., Mutt, V., Makk, G., Feistner, G. J. and Barchas, J. D. (1986) Pancreastatin, a novel pancreatic peptide that inhibits insulin secretion. Nature 324, 476–478.
6 Yajima, H., Futaki, S., Fujii, N., Akaji, K., Funakoshi, S., Sakurai, M., Katakura, S., Inoue, K., Hosotani, R., Tobe, T. et al. (1885) Synthesis of galanin, a new gastrointestinal polypeptide. J. Chem. Soc. 13, 877–878.
7 Rökaeus, Å. and Brownstain, M. J. (1986) Construction of a porcine adrenal medullary cDNA library and nucleotide sequence analysis of two clones encoding a galanin precursor. Proc. Natl. Acad. Sci. USA 83, 6287–6291.
8 Ohtaki, T., Kumano, S., Ishibashi, Y., Ogi, K., Matsui, H., Harada, M., Kitada, C., Kurokawa, T., Onda, H. and Fujino, M. (1999) Isolation and cDNA cloning of a novel galanin-like peptide (GALP) from porcine hypothalamus. J. Biol. Chem. 274, 37041–37045.
9 Santic, R., Schmidhuber, S. M., Lang, R., Rauch, I., Voglas, E., Eberhard, N., Bauer, J. W., Brain, S. D. and Kofler, B. (2007) Alarin is a vasoactive peptide. Proc. Natl. Acad. Sci. USA 104, 10217–10222.
10 Habert-Ortoli, E., Amiranoff, B., Loquet, I., Laburthe, M. and Mayaux, J. F. (1994) Molecular cloning of a functional human galanin receptor. Proc. Natl. Acad. Sci. USA 91, 9780–9783.
11 Iismaa, T. P. and Shine, J. (1999) Galanin and galanin receptors. Results Probl. Cell Differ. 26, 257–291.
12 Branchek, T. A., Smith, K. E., Gerald, C. and Walker, M. W. (2000) Galanin receptor subtypes. Trends Pharm. Sci. 21, 109–116.
13 Lang, R., Gundlach, A. L. and Kofler, B. (2007) The galanin peptide family: receptor pharmacology, pleiotropic biological actions, and implications in health and disease. Pharmacol. Ther. 115, 177–207.
14 Bartfai, T., Fisone, G. and Langel, Ü. (1992) Galanin and galanin antagonists: molecular and biochemical perspectives. Trends Pharm. Sci. 13, 312–317.
15 Swanson, C. J., Blackburn, T. P., Zhang, X., Zheng, K., Xu, Z. Q., Hökfelt, T., Wolinsky, T. D., Konkel, M. J., Chen, H., Zhong, H. et al. (2005) Anxiolytic- and antidepressant-like profiles of the galanin-3 receptor (Gal3) antagonists SNAP 37889 and SNAP 398299. Proc. Natl. Acad. Sci. USA 102, 17489–17494.
16 Konkel, M. J., Lagu, B., Boteju, L. W., Jimenez, H., Noble, S., Walker, M. W., Chandrasena, G., Blackburn, T. P., Nikam, S. S., Wright, J. L. et al. (2006) 3-arylimino-2-indolones are potent and selective galanin GAL3 receptor antagonists. J. Med. Chem. 49, 3757–3758.
17 Shen, P. J., Yuan, C. G., Ma, J., Cheng, S., Yao, M., Turnley, A. M. and Gundlach, A. L. (2005) Galanin in neuro(glio)genesis: expression of galanin and receptors by progenitor cells in vivo and in vitro and effects of galanin on neurosphere proliferation. Neuropeptides 39, 201–205.
18 Leibowitz, S. F. (2007) Overconsumption of dietary fat and alcohol: mechanisms involving lipids and hypothalamic peptides. Physiol. Behav. 91, 513–521.
19 Diaz-Cabiale, Z., Parrado, C., Fuxe, K., Agnati, L. and Narvaez, J. A. (2007) Receptor-receptor interactions in central cardiovascular regulation. Focus on neuropeptide/alpha(2)-adrenoreceptor interactions in the nucleus tractus solitarius. J. Neural Transm. 114, 115–125.
20 Berger, A., Santic, R., Hauser-Kronberger, C., Schilling, F. H., Kogner, P., Ratschek, M., Gamper, A., Jones, N., Sperl, W. and Kofler, B. (2005) Galanin and galanin receptors in human cancers. Neuropeptides 39, 353–359.
21 Hökfelt, T. and Crawley, J. N. (eds.) (2005) Special issue on galanin. Neuropeptides, 39 (3).
22 Jörnvall, H., Agerberth, B. and Zasloff, M. (2008) Viktor Mutt - a giant in the field of bioactive peptides. Comprehensive Biochem. 46, in press.