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The galanin peptide family: Receptor pharmacology, pleiotropic biological actions, and implications in health and disease

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Abstract

The galanin peptide family consists of the "parental" galanin, galanin-message-associated peptide (GMAP) which derives from the same peptide precursor gene product as galanin, galanin-like peptide (GALP) encoded by a different gene, and the recently discovered peptide alarin which is encoded by a splice variant of the GALP gene. The galanin receptor family currently comprises 3 members, GalR1, GalR2, and GalR3, which are all G-protein-coupled receptors. This review will provide an overview of the comprehensive, pharmacological characterization of endogenous and synthetic galanin receptor ligands and their interactions with the galanin receptors, a summary of the various (pleiotropic) biological actions of galanin and GALP (and alarin), and briefly discuss the implications of pathological changes for health and disease and potential clinical therapeutics. Since its discovery more than 20 years ago, a large number of putative physiological functions have been ascribed to galanin, and active research still continues to validate these functions and determine their importance for physiology and pathology. Since the more recent identification of GALP, considerable research has identified functions for this peptide in the central nervous system (CNS), but the identity of its preferred, native receptor is still unknown. Little is known of the role of alarin apart from evidence of its expression and a vasoactive action in the skin. The wide range of functions of the galanin peptide family indicates an essential role for galanin signaling in "mind and body homeostasis" and a potential therapeutic efficacy in a variety of human diseases, particularly epilepsy, Alzheimer's disease, and diabetes.

Keywords: Galanin; Galanin-like peptide; Alarin; GalR1-3; G-protein coupled receptors

Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotrophic hormone; BNST, bed nucleus of the stria terminalis; cAMP, cyclic adenosine monophosphate; CHO, Chinese hamster ovary cells; CNS, central nervous system; D-β-H, dopamine-β-hydroxylase; DRG, dorsal root ganglia; EPM, elevated plus-maze; Galanin-KO, galanin knockout; Galanin-LI, galanin-like immunoreactivity; Galanin-OE, galanin overexpressing; GALP, galanin-like peptide; GalR1/2/3, galanin receptor 1/2/3; GalR1-KO, galanin receptor 1 knockout; GI, gastrointestinal; GIRK, G-protein-regulated inwardly rectifying K^+channel; GMAP, galanin message-associated peptide; GnRH, gonadotropin-releasing hormone; GPCR, G-protein-coupled receptor; HEK, human embryonic kidney 293 cells; LH, luteinizing hormone; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NPY, neuropeptide Y; pCREB, phosphorylated cAMP response element binding protein; PKC, protein kinase C; PLC, phospholipase C; POMC, pro-opiomelanocortin; PTX, pertussis toxin; PVN, paraventricular nucleus; SSSE, self-sustaining status epilepticus.

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1. Galanin family peptides

The neuropeptide galanin is a 29 amino acid, C-terminally amidated peptide initially isolated from porcine intestine (Tatemoto et al., 1983) but later found in many other species. The N-terminal 1–15 amino acids are highly conserved, although human galanin is unique in having 30 amino acids with no amidation of the N-terminus (Evans & Shine, 1991). Galanin is proteolytically processed from a 123-(porcine, human) or 124-(murine) amino acid precursor pro-peptide along with a 59 or 60 amino acid peptide known as galanin message-associated peptide (GMAP) (Rokaeus & Brownstein, 1986; Vrontakis et al., 1987; Kaplan et al., 1988b; Evans & Shine, 1991). The peptide precursor of galanin, "preprogalanin" is encoded by a single-copy gene organized into 6 small exons spanning about 6 kb of genomic DNA, depending on the species (Kofler et al., 1996; Fig. 1).

Galanin has been shown to have a widespread distribution in the central and peripheral nervous systems of many mammalian species and diversity of biological effects, which will be

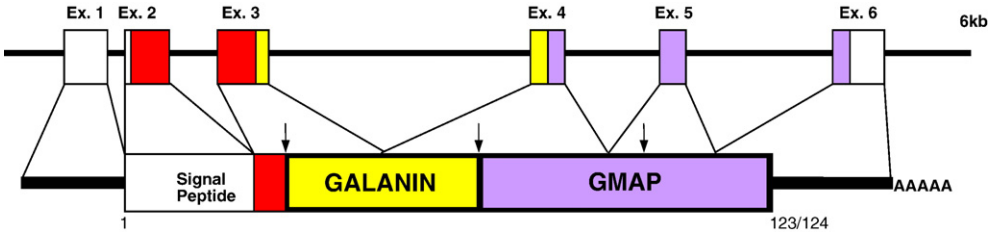

Fig. 1. Organization of the preprogalanin gene (modified from Kofler et al., 1996). The first exon encodes only the 5′-untranslated region of preprogalanin mRNA. Exon 2 starts with the translation initiation codon of the signal peptide and terminates before the proteolytic site preceding the mature galanin 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 sites of endopeptidases.