IUPHAR/BPS Guide to Pharmacology CITE
https://doi.org/10.2218/gtopdb/F28/2021.3

Ghrelin receptor in GtoPdb v.2021.3

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Abstract

The ghrelin receptor (**nomenclature as agreed by the NC-IUPHAR Subcommittee for the Ghrelin receptor [19]**) is activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (*GHRL*, Q9UBU3). The human gene encoding the precursor peptide has 83% sequence homology to rat prepro-ghrelin, although the mature peptides from rat and human differ by only two amino acids [74]. Alternative splicing results in the formation of a second peptide, [des-Gln^{14}]ghrelin with equipotent biological activity [49]. A unique post-translational modification (octanoylation of Ser^{3}, catalysed by ghrelin O-acyltransferase (*MBOAT4*, Q96T53) [133] occurs in both peptides, essential for full activity in binding to ghrelin receptors in the hypothalamus and pituitary, and for the release of growth hormone from the pituitary [58]. Structure activity studies showed the first five N-terminal amino acids to be the minimum required for binding [4], and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin function [44]. An endogenous antagonist and inverse agonist called Liver enriched antimicrobial peptide 2 (Leap2), expressed primarily in hepatocytes and in enterocytes of the proximal intestine [35, 68] inhibits ghrelin receptor-induced GH secretion and food intake [35]. The secretion of Leap2 and ghrelin is inversely regulated under various metabolic conditions [71]. In cell systems, the ghrelin receptor is constitutively active [45], but this is abolished by a naturally occurring mutation (A204E) that results in decreased cell surface receptor expression and is associated with familial short stature [93].

Contents

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