Ghrelin

Overview: Ghrelin receptors (see Davenport *et al*., 2005) are activated by a 28 amino-acid peptide originally isolated from rat stomach, where it is cleaved from a 117 amino-acid precursor (ENSG00000157017). 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 (Matsumoto *et al*., 2001). Alternative splicing results in the formation of a second peptide, des-Gln^{14}-ghrelin with equipotent biological activity (Hosoda *et al*., 2000). A unique post-translational modification (octanoylation of Ser^{3}) occurs in both peptides, essential for full activity in binding to the ghrelin receptors in the hypothalamus and pituitary; and the release of growth hormone release from the pituitary (Kojima *et al*., 1999). Structure activity studies showed the first five N-terminal amino-acids to be the minimum required for binding (Bednarek *et al*., 2000), and receptor mutagenesis has indicated overlap of the ghrelin binding site with those for small molecule agonists and allosteric modulators of ghrelin function (Holst *et al*., 2009). In cell systems, the ghrelin receptor is constitutively active (Holst *et al*., 2004), 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 (Pantel *et al*., 2006).

Nomenclature	Ghrelin
Other names	GHS-R1a (Growth hormone secretagogue receptor type 1), growth hormone-releasing peptide receptor
Ensembl ID	ENSG00000121853
Principal transduction	$G_{q/11}$
Rank order of potency	Ghrelin = des-Gln-ghrelin (Matsumoto *et al*., 2001; Bedendi *et al*., 2003)
Selective antagonists	YIL781 (K_B 11 nM) (Esler *et al*., 2007)
Probes	[^{125}I-His^{9}]-ghrelin (0.4 nM, Katugampola *et al*., 2001), [^{125}I-Tyr^{4}]-ghrelin (0.5 nM, Bedendi *et al*., 2003), [^{125}I]-Tyr^{4}-des-octanoyl (0.7 nM, Bedendi *et al*., 2003)

Des-octanoyl ghrelin has been shown to bind (as [^{125}I]-Tyr^{4}-des-octanoyl ghrelin) and have effects in the cardiovascular system (Bedendi *et al*., 2003), which raises the possible existence of different receptor subtypes in peripheral tissues and the central nervous system. A potent inverse agonist has been identified ([D-Arg^{1}, D-Phe^{5}, D-Trp^{7,9},Leu^{11}]-substance P, pD_2 8.3; Holst *et al*. 2003). TZP101, described as a ghrelin receptor agonist (pK_i 7.8 and pD_2 7.5 at human recombinant ghrelin receptors), has been shown to stimulate ghrelin receptor-mediated food intake and gastric emptying but not elicit release of growth hormone, or modify ghrelin-stimulated growth hormone release, thus pharmacologically discriminating the orexigenic and gastrointestinal actions of ghrelin from the release of growth hormone (Fraser *et al*., 2008).

Abbreviations: **TZP101**, (4R,7S,10R,13R)-7-cyclopropyl-13-(4-fluorobenzyl)-3-oxa-6,9,12,15-tetraaza-4,9,10-trimethyl-4,5,6,7,10,12,13,15,16,17,18-undecahydro-1,2-benzocyclooctadecene-8,11,14-trione; **YIL781**, 6-(4-fluorophenoxy)-3-([(3*s*)-1-isopropylpiperidin-3-yl]methyl)-2-methylquinazolin-4(3*H*)-one

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