Gonadotropin-releasing hormone (GnRH)

Overview: Gonadotropin-releasing hormone (GnRH) is a hypothalamic decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pr-Gly-NH_2, also known as luteinizing hormone-releasing hormone, gonadoliberin, luliberin, gonadorelin, ENSG00000147437) designated GnRH I, to distinguish it from related peptides such as GnRH II (pGlu-His-Trp-Ser-His-Gly-Trp-Tyr-Plo-Gly-NH_2, also known as chicken GnRH-II, ENSG00000180290) and GnRH III (pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH_2 also known as lamprey GnRH III). Receptors for all three ligands exist in amphibians but only GnRH I and GnRH II (and their cognate receptors) have been found in mammals (Sealfon *et al.*, 1997; Millar, 2005). $GnRH_1$ and $GnRH_2$ receptors (provisonal nomenclature, also called Type I and Type II respectively) have been cloned from numerous species (most of which express two or three types of GnRH receptor) and grouped phylogenetically (Silver *et al.*, 2005). $GnRH_1$ receptors are expressed primarily by pituitary gonadotrophs in mammals and mediate central control of reproduction. They are selectively activated by GnRH I and all lack the C-terminal tails found in other 7TM receptors. $GnRH_2$ receptors all possess C-terminal tails and (where tested) are selective for GnRH II (over GnRH I). An alternative phylogenetic classification (see Millar *et al.*, 2004) divided these receptors into three classes and includes both GnRH I-selective mammalian and GnRH II-selective non-mammalian receptors as $GnRH_1$ receptors. Although thousands of peptide analogues of GnRH I have been synthesized, and several (agonists and antagonists) are used therapeutically (Kiesel *et al.*, 2002), the potency of most of these peptides at $GnRH_2$ receptors is unknown.

Nomenclature	$GnRH_1$	$GnRH_2$
Other names	Type I GnRHR, LHRH receptor, GnRH I receptor	Type II GnRHR
Ensembl ID	ENSG00000109163	ENSG00000180290
Principal transduction	$G_{q/11}$	$G_{q/11}$
Rank order of potency	GnRH I > GnRH II	GnRH II > GnRH I
Selective agonists	Triptorelin, buserelin, leuprorelin, nafarelin, histrelin, goserelin	–
Selective antagonists	Antide (9.0, Neill, 2002), cetrorelix (8.8, Neill, 2002), ganirelix, abarelix	Trptorelix-1 (Maiti *et al.*, 2003)
Probes	[^{125}I]-GnRH I, [^{125}I]-buserelin	[^{125}I]-GnRH II

$GnRH_1$ and $GnRH_2$ receptors couple primarily to $G_{q/11}$ (Grosse *et al.*, 2000) but coupling to G_s and G_i is evident in some systems (Krsmanovic *et al.*, 2003). $GnRH_2$ receptors may also mediate (heterotrimeric) G protein-independent signalling to protein kinases (see Caunt *et al.*, 2006). There is increasing evidence for expression of GnRH receptors on hormone-dependent cancer cells where they can exert antiproliferative and/or proapoptotic effects and mediate effects of cytotoxins conjugated to GnRH analogues (Limonta *et al.*, 2003; Harrison *et al.*, 2004); (Schally and Nagy, 2004; Cheng and Leung, 2005). In some human cancer cell models GnRH II is more potent than GnRH I, implying mediation by $GnRH_2$ receptors (Grundker *et al.*, 2002). However, $GnRH_2$ receptors that are expressed by some primates are probably not expressed in humans because the human *GNRHR2* gene contains a frame shift and internal stop codon (Morgan *et al.*, 2003). The possibility remains that this gene generates $GnRH_2$ receptor-related proteins (other than the full-length receptor) that mediate responses to GnRH II (see Neill *et al.*, 2004). Alternatively, there is evidence for multiple active GnRH receptor conformations (Caunt *et al.*, 2004; Maudsley *et al.*, 2004; Millar *et al.*, 2004) raising the possibility that $GnRH_1$ receptor-mediated proliferation inhibition in hormone-dependent cancer cells is dependent upon different conformations (with different ligand specificity) than effects on $G_{q/11}$ in pituitary cells (Maudsley *et al.*, 2004). Loss-of-function mutations in the $GnRH_1$ receptor and deficiency of GnRH I are associated with hypogonadotropic hypogonadism although some 'loss of function' mutations may actually prevent trafficking of 'functional' $GnRH_1$ receptors to the cell surface, as evidenced by recovery of function by non-peptide antagonists (Leanos-Miranda *et al.*, 2003). GnRH receptor signalling may be dependent upon receptor oligomerization (Conn *et al.*, 1982; Kroeger *et al.*, 2001).

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