

# International Union of Pharmacology. LVI. Ghrelin Receptor Nomenclature, Distribution, and Function

ANTHONY P. DAVENPORT, TOM I. BONNER,<sup>1</sup> STEVEN M. FOORD, ANTHONY J. HARMAR, RICHARD R. NEUBIG,  
JEAN-PHILIPPE PIN, MICHAEL SPEDDING, MASAYASU KOJIMA, AND KENIJI KANGAWA

*Clinical Pharmacology Unit, University of Cambridge, Cambridge, United Kingdom (A.P.D.); Laboratory of Genetics, National Institute of Mental Health, Bethesda, Maryland (T.I.B.); GlaxoSmithKline Research and Development, Stevenage, Hertfordshire, United Kingdom (S.M.F.); Division of Neuroscience and Centre for Neuroscience Research, University of Edinburgh, Edinburgh, United Kingdom (A.J.H.); Department of Pharmacology, University of Michigan, Ann Arbor, Michigan (R.R.N.); Centre National de la Recherche Scientifique, Montpellier, France (J.-P.P.); Institut de Recherches Internationales Servier (I.R.I.S.), Neuilly-sur-Seine, France (M.S.); and National Cardiovascular Center Research Institute, Suita, Osaka, Japan (M.K., K.K.)*

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**Abstract**—Ghrelin is a 28-amino acid peptide originally isolated from rat stomach and is cleaved from a 117-amino acid precursor. The sequence of the mature peptide from rats and mice differs by two amino acids from that of human ghrelin. Alternative splicing of the ghrelin gene transcript can result in the translation of a second biologically active peptide, des-Gln<sup>14</sup>-ghrelin. Both peptides have a unique post-translational modification, octanoylation of Ser<sup>3</sup>, which is essential for the binding to receptors in hypothalamus and pituitary and stimulating the release of growth hormone from the pituitary. The growth hormone secretagogue receptor (GHS-R1a, Swiss-Prot code Q92847, LocusLink ID 2693), a rhodopsin-like seven transmembrane spanning G pro-

tein-coupled receptors belonging to Family A, was cloned in 1996 from the pituitary and hypothalamus and shown to be the target of growth hormone secretagogues (GHS), a class of synthetic peptide and non-peptide compounds causing growth hormone release from the anterior pituitary. In 1999, ghrelin was identified as the endogenous cognate ligand for this receptor. The purpose of this review is to propose an official International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR) nomenclature designating GHS-R1a as the ghrelin receptor to follow the convention of naming receptors after the endogenous agonist, abbreviated where necessary to GRLN.

Address correspondence to: Dr. Anthony Davenport, NC-IUPHAR Emerging Pharmacology Group, Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, U.K. E-mail: apd10@medschl.cam.ac.uk

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TABLE 2  
Classification of ghrelin receptor

Receptor	Ghrelin, GRLN
Receptor code	2.1:GHS:1:GHS1:HUMAN:00
Previous names	GHS-R, GHS-R1a (approved human gene symbol)
Structural information	7TM Human: 366aa (SwissProt Q92847), chr. 3q26.31 (LocusLink 2693) Rat: 364aa (SwissProt O08725), chr. 2Q24 (LocusLink 84022) Mouse: 364aa (SwissProt Q99P50), chr. 3A3 (LocusLink 208188)
Functional assays	In vitro pharmacology using human isolated vessels (Wiley and Davenport, 2002) In vitro pharmacology using isolated guinea pig papillary muscle (Bedendi et al., 2003)
Endogenous agonists	Ghrelin ( $IC_{50} = 8.1 \text{ nM}/EC_{50} = 1.5 \text{ nM}$ ) = des-Gln <sup>14</sup> -ghrelin ( $IC_{50} = 7.4 \text{ nM}/EC_{50} = 1.5 \text{ nM}$ ) (Matsumoto et al., 2001; Bedendi et al., 2003)
Selective agonists	GHRP-2 ( $IC_{50} = 0.4 \text{ nM}$ ) > MK-0677 ( $IC_{50} = 0.8 \text{ nM}$ ) > GHRP-6 ( $IC_{50} = 1.5 \text{ nM}$ ) (cloned rat receptor; McKee et al., 1997)
Antagonists	[D-Lys <sup>3</sup> ]-GHRP-6, EP-80317
Antagonist potencies	
Radioligand assays	Human hypothalamus, human cardiovascular tissue
Radioligands	[ <sup>125</sup> I-His <sup>9</sup> ]-ghrelin ( $K_d = 0.22\text{--}0.57 \text{ nM}$ ) (Katugampola et al., 2001) [ <sup>125</sup> I-Tyr <sup>4</sup> ]-ghrelin ( $K_d = 0.44 \text{ nM}$ ) (Muccioli et al., 2001) [ <sup>125</sup> I-Tyr <sup>4</sup> ]-ghrelin ( $K_d = 0.51 \text{ nM}$ ) (Bedendi et al., 2003)
Transduction	
Mechanism	Coupled to G- $\alpha$ -11 proteins
Receptor distribution	Humans, specific [ <sup>125</sup> I-His <sup>9</sup> ]-ghrelin binding was localized to the human vasculature including aorta, coronary arteries, pulmonary arteries, arcuate arteries (in the kidney), and saphenous veins; rats: binding sites were also localized to the vasculature in peripheral tissues as well as the granular layer of the cerebellum in the CNS (Katugampola et al., 2001)
Tissue function	Stimulates release of growth hormone from the anterior pituitary, gastric acid secretion, and motility; may alter appetite and energy balance; vasodilatation

aa, amino acid; chr., chromosome.

The GRLN receptor has 73% amino acid sequence identity with the orphan receptor GPR38. Of the receptors with identified ligands, it is most closely related to the neurotensin receptor-1 (35% overall protein identity). Bednarek et al. (2000) found that short peptides encompassing the first four or five residues of ghrelin functionally activate human GRLN receptor about as efficiently as the full-length ghrelin. The Gly-Ser-Ser(*n*-octanoyl)-Phe segment appears to constitute the “active core” required for agonist potency at the receptor.

### III. Distribution of Receptor and mRNA Encoding the Receptor

In the rat brain, mRNA encoding the receptor was detected in multiple hypothalamic nuclei (a major target for regulation of food intake and energy balance), pituitary gland, and dentate gyrus of the hippocampal formation. In other brain areas, discrete signals were detected in the CA2 and CA3 regions of the hippocampus, the substantia nigra, ventral tegmental area, and dorsal and median raphe nuclei. In human tissues, mRNA was detected in normal anterior pituitary, pituitary adenomas, hypothalamus (consistent with its role in regulating growth hormone release), and hippocampus. In human peripheral tissue, mRNA was detected in adrenal cortex, testes, pancreas, heart, and lung (McKee et al., 1997; Yokote et al., 1998).

In human tissue, specific [<sup>125</sup>I-His<sup>9</sup>]-ghrelin binding was localized to the vasculature including aorta, coro-

nary arteries, pulmonary arteries, arcuate arteries (in the kidney), and saphenous veins. [<sup>125</sup>I-His<sup>9</sup>]-ghrelin binding was significantly up-regulated (3- to 4-fold) in both atherosclerotic coronary arteries and saphenous vein grafts with advanced intimal thickening compared with normal vessels (Katugampola et al., 2001). In rats, binding sites were also localized to the vasculature in peripheral tissues as well as the granular layer of the cerebellum in the CNS (Katugampola et al., 2001). Antisera generated to the receptor have been used to map immunoreactivity in the hypothalamus, pituitary, and stomach of this species (Shuto et al., 2001).

### IV. Radiolabeled Ligands

Two radiolabeled analogs of ghrelin have been synthesized (Table 2). [<sup>125</sup>I-His<sup>9</sup>]-Ghrelin has been extensively characterized in human and rat tissues, where the ligand bound with a single affinity. In human heart, binding was saturable, specific, and reversible with an association rate constant ( $k_{obs}$ ) of  $0.16 \pm 0.004 \text{ min}^{-1}$ , a dissociation rate constant of  $0.068 \pm 0.0005 \text{ min}^{-1}$  (giving a kinetically derived  $K_D$  of 0.1 nM), and by saturation binding assay, a  $K_D$  of  $0.43 \pm 0.08 \text{ nM}$  and  $B_{max}$  of  $7.8 \pm 0.9 \text{ fmol mg}^{-1} \text{ protein}$ . Half-time for dissociation was 11 min. Optimum binding was over pH range 6.75 to 7.25 (Katugampola et al., 2001). [<sup>125</sup>I-His<sup>9</sup>]-Ghrelin binding was significantly up-regulated (3- to 4-fold) in both atherosclerotic coronary arteries and saphenous vein grafts with advanced intimal thickening compared

with normal vessels, suggesting a role in the development of atherosclerosis and may therefore represent a novel therapeutic target in the treatment of cardiovascular disease (Katugampola et al., 2001).

In human CNS tissue, [<sup>125</sup>I-Tyr<sup>4</sup>]-ghrelin bound with  $K_D$  values of 0.44 nM in hypothalamus and 0.41 nM in pituitary. Binding was inhibited by ghrelin, hexarelin, MK-0677, and the growth hormone secretagogue antagonist EP-80317 (Muccioli et al., 2001). Bedendi et al. (2003) characterized [<sup>125</sup>I-Tyr<sup>4</sup>]-ghrelin in guinea pig ventricle ( $K_d = 0.51 \pm 0.06$  nM,  $B_{max} = 10.9 \pm 1.8$  fmol  $mg^{-1}$  protein). In competition binding assays using this radioligand,  $IC_{50}$  values for unlabeled competing ligands, all expressed as nanomolar concentrations, were  $8.1 \pm 0.9$  for ghrelin,  $7.4 \pm 0.4$  for des-Gln<sup>14</sup>-ghrelin,  $12.5 \pm 1.7$  for des-octanoyl ghrelin, and  $20.8 \pm 2.3$  for hexarelin.

### V. Agonists

The rank order of potency for endogenous agonists is as follows: ghrelin ( $IC_{50} = 8.1$  nM,  $EC_{50} = 1.5$  nM) = des-Gln<sup>14</sup>-ghrelin ( $IC_{50} = 7.4$  nM,  $EC_{50} = 1.5$  nM) (Matsumoto et al., 2001; Bedendi et al., 2003). Other growth hormone-releasing peptides (GHRP) such as GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH<sub>2</sub>) as well as synthetic low molecular weight peptides such as hexarelin ( $IC_{50} = 24$  nM) also compete for the binding of [<sup>125</sup>I-Tyr<sup>4</sup>]-ghrelin in human hypothalamus with a comparable affinity to the unlabeled peptide, although nonpeptide (MK-0677) secretagogues developed using GHRP-6 as a template were less potent in this assay ( $IC_{50} = 330$  nM; Muccioli et al., 2001).

For artificially expressed receptors, McKee et al. (1997) reported [<sup>35</sup>S]MK-0677 bound to the rat receptor sequence transfected into COS-7 cells with a  $K_D = 0.7$  nM. The rank order of competition for peptide and nonpeptide secretagogues was GHRP-2 ( $IC_{50} = 0.4$  nM) > MK-0677 ( $IC_{50} = 0.8$  nM) > GHRP-6 ( $IC_{50} = 1.3$  nM). Synthesis of these peptide and nonpeptide growth hormone secretagogues led to the cloning of the growth hormone secretagogue receptor in 1996 (Howard et al., 1996), prior to the discovery of ghrelin as the endogenous ligand in 1999 (Kojima et al., 1999).

### VI. Antagonists

Selective ghrelin antagonists that have been characterized in detail are not yet available. Some growth hormone secretagogue receptor antagonists such as EP-80317 are reported to compete for the binding of [<sup>125</sup>I-Tyr<sup>4</sup>]-ghrelin in human hypothalamus with  $IC_{50} = 14$  nM comparable with unlabeled ghrelin in this preparation (Muccioli et al., 2001).

### VII. Physiological Role

Early studies in humans and rats showed that ghrelin potently stimulates release of growth hormone from the

anterior pituitary. Ghrelin is thought to act on GRLN receptors present on pituitary somatotrophs, and ghrelin binds to GRLN receptors on growth hormone-releasing hormone (GHRH) positive cells in the hypothalamus triggering GHRH liberation. Ghrelin therefore is believed to be involved in the regulation of GH secretion together with the GH liberator GHRH and the GH inhibitor somatostatin.

Ghrelin stimulates gastric acid secretion and motility. Central and peripheral administration of ghrelin to animals increases food intake leading to weight gain and reduced fat utilization suggesting that the peptide (with several other peptides) may have significant effects on appetite and energy balance (Asakawa et al., 2003; Bagnasco et al., 2003; Cowley et al., 2003). In a number of species including humans, circulating ghrelin levels significantly increase during fasting and decrease as a response to food intake (Sugino et al., 2002). This regulatory mechanism of ghrelin secretion is believed to be mediated via cholinergic afferences from the gastrointestinal tract (Date et al., 2000; Sugino et al., 2003). At the same time, ghrelin levels are low in obese and high in lean individuals, suggesting that ghrelin is not only important for the acute regulation of food intake but also plays an important role in the regulation of long-term energy homeostasis. These functions are consistent with the major source of ghrelin in endocrine cells in the upper gastrointestinal tract (Hosoda et al., 2000; Inui, 2001).

Ghrelin has a number of actions in the cardiovascular system, consistent with the localization of receptors to cardiovascular tissue. In humans, the peptide is a potent vasodilator in vivo (Okumura et al., 2002) and in vitro (Wiley and Davenport, 2002). Ghrelin elicits these actions independent of the endothelium, indicating a direct effect on the vascular smooth muscle (Wiley and Davenport, 2002). In agreement, the ghrelin-induced vasodilatation in vivo is not altered by coadministration of the nitric-oxide synthase inhibitor *N*<sup>G</sup>-monomethyl-L-arginine. Immunoreactive ghrelin has been detected in endothelial cells throughout the human vasculature, suggesting that the peptide may function as a ubiquitous endothelium-derived vasoactive peptide (Kleinz and Davenport, 2003; <http://www.wpa2online.org/20031022P>).

### VIII. Pathophysiological Role

Ghrelin functions as a vasodilator in humans. Receptors are significantly up-regulated in human atherosclerosis suggesting a role in compensating for the increased vasoconstriction in this condition (Katugampola et al., 2001; Wiley and Davenport, 2002). The precise pathophysiological role of ghrelin has not been established. In a rat model of chronic heart failure and in human chronic heart failure patients, ghrelin caused a fall in mean arterial blood pressure and had beneficial effects

on stroke volume and cardiac output (Nagaya et al., 2001a,b,c); however, whether the observed effects of ghrelin are completely or partially mediated via central GH release remains unclear.

Ghrelin circulates at high levels in the plasma in humans. Levels are reduced in obese humans compared with lean control subjects, but whether this is cause or effect is not clear. Patients with anorexia nervosa have higher than normal plasma ghrelin levels that decrease if weight gain occurs (Tanaka et al., 2003).

Prader-Willi syndrome is a genetic disorder characterized by mild mental retardation, short stature, abnormal body composition, muscular hypotonia, and distinctive behavioral features. Excessive eating causes progressive obesity with increased cardiovascular morbidity and mortality. It is a complex disease and is likely to have many defects, one of which may be ghrelin. In patients, circulating oxytocin levels were abnormally low and ghrelin levels abnormally high. Thus, oxytocin and ghrelin might be involved in the hyperphagia (Haqq et al., 2003).

Low ghrelin concentration may be a risk factor for type 2 diabetes and hypertension. Poykko et al. (2003) characterized the effect of the ghrelin Arg51Gln (which changes the carboxy terminus of the mature peptide) and Leu72Met mutations on ghrelin concentrations in the population-based hypertensive and control cohorts. Ghrelin concentrations were negatively associated with fasting insulin, systolic and diastolic blood pressure, and the prevalence of type 2 diabetes and insulin resistance. In the control cohort, low ghrelin was associated with hypertension (blood pressure >140/90 mm Hg). Subjects with the ghrelin 51Gln allele had lower ghrelin concentrations than the Arg51Arg homozygotes and may have a role in the etiology of type 2 diabetes and the regulation of blood pressure.

## IX. Genetically Modified Animals

### A. Ghrelin Receptor

Deletion of the gene-encoding GRLN receptor in mice produced the expected phenotype. Homozygous mice did not show growth hormone release or increased food intake as a result of ghrelin treatment (Sun et al., 2004).

### B. Peptide

Mice with deletion of the gene-encoding ghrelin did not display any phenotypic changes compared with controls; neither growth nor appetite was changed (Sun et al., 2003).

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