Peptides Involved in Appetite Modulation

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Sonia A Tucci , Lynsay Kobelis and Tim C Kirkham

University of Liverpool, Eleanor Rathbone Building, Bedford Street South, Liverpool, L69 7ZA, UK

Sonia Tucci is a Lecturer in Behavioral Neuroscience and Tim Kirkham is a Professor of Biopsychology, both at the University of Liverpool. Their research interests currently center on the pharmacological analysis of the controls of appetite and ingestive behavior, and particularly the role of central endocannabinoids in the regulation of appetite. Lynsay Kobelis is conducting doctoral research into opioid-cannabinoid interactions in feeding.

Introduction

Table 1a | Central appetite regulatory peptides: receptor classification, peptide and receptor localization.

Peptide	Receptors	Peptide mRNA localization (appetite related)	CNS receptor localization	References
Orexigenic				
NPY	NPY Y_{1-6}: Y_1 and Y_5, involved in feeding	ARC	Hypothalamus, hippocampus, AMY, piriform and cingulate cortices	239-240
AgRP	MC_{1-5}: MC_3 and MC_4 involved in feeding	ARC	ARC, PVN, AMY, spinal cord	163, 170, 241
MCH	MCH_1 MCH_2	LH, perifornical area, zona incerta	Cerebral cortex, caudate-putamen, hippocampal formation, AMY, hypothalamus, THAL	242-243
Orexin	OX_1 OX_2	Posterolateral hypothalamus, perifornical area, LH, zona incerta	VMH, PVN, LPO, LC, hippocampus, tenia tecta and raphé nucleus	180-181
Galanin	GAL_{1-3}	PVN, PFH, LH, and ARC	VMN, PVN, stria terminalis, piriform cortex, AMY	244-245
Opioids: β-endorphin, [Met]enkephalin, **[Leu]enkephalin**, **dynorphin A**, **dynorphin B**, α-neoendorphin	μ: (β-endorphin) δ: (β-endorphin, [Met]enkephalin), **[Leu]enkephalin** κ: (**dynorphin A**)	Pro-enkephalin and pro-dynorphin mRNA are widely distributed throughout the brain. POMC mRNA is restricted to ARC	Widely distributed, with differential distribution for each subtype, with all present within hypothalamic nuclei	203, 246-251
Anorexigenic				
α-MSH	MC_{1-5}: MC_3 and MC_4 involved in feeding	ARC	ARC, PVN, AMY, spinal cord	163, 170, 241
CART	Not identified	PVN, ARC, PBN, perifornical cells in the hypothalamus	Not identified	219, 252
NT	NT_{1-3}	Median eminence, preoptic area PVN, supraoptic, VMN	Cerebral cortex, DH, VTA	253-254

(Bold text denotes compounds available from Tocris)

It is generally considered that the expression of appetite is chemically coded in the hypothalamus through the interplay of hormonal and neural mechanisms.[1] In brief, it is proposed that the hypothalamus houses opposing sets of neuronal circuitry: an appetite-stimulatory circuit and an appetite-inhibitory circuit.[2] These circuits are influenced by peripheral hormonal and afferent neural signals that provide feedback and integrative processing of nutritional status, energy intake and expenditure. The appetite-stimulatory circuit expresses orexigenic neurotransmitters which promote appetite, while anorexigenic neurotransmitters released by the inhibitory circuit decrease appetite. In addition to modulation by signals originating in the periphery, these integrative functions are affected by a wide range of neural influences within the brain, reflecting sensory, cognitive, memory and affective processes.

This review provides a sketch of the increasing number of peptides that have been implicated in appetite regulation and energy homeostasis, and outlines the putative roles of most of the currently known players. The extensive literature on the physiological control of food intake, metabolism and body weight regulation is discussed in greater depth in several recent publications.[3-11] It should be

Table 1b | Peripheral appetite regulatory peptides: receptor classification, peptide and receptor localization.

Peptide	Receptors	Peptide mRNA localization (appetite related)	CNS receptor localization	References
Orexigenic				
Ghrelin	GHS-R1a	Neuronal group adjacent 3rd ventricle between DMN, VMN, PVN and ARC	Hypothalamus, hippocampus, VTA, pituitary gland, SN, DRN, VRN	226
Anorexigenic				
Adiponectin	AdipoR1 and AdipoR2	Adipose tissue	ARC, area postrema	58-60
Leptin	OB-R (at least 5 isoforms; OB-Ra-e) OB-Rb important in regulation of food intake	Adipose tissue	ARC, VMN, DMN, LH, PVN	227-230
Insulin	IR-A IR-B IGF	β cells in pancreas Brain?	Olfactory bulb, hypothalamus, hippocampus, choroid plexus, cerebellum	44, 231
PYY_{3-36}	NPY Y_2	Endocrine L cells in GI tract	DH, medial preoptic, lateral anterior, PVN, DMN tuberal, perifornical, ARC nuclei	97, 232
PP	NPY Y_4/Y_5	PP cells in pancreas, PVN, ARC and SON	ARC, PVN, rostral forebrain, AMY, THAL, SN, LC, BS	96, 98, 111
GLP-1	GLP-1R	NTS, ARC, PVN	ARC, PVN, VMN, SON	233
OXM	GLP-1R?	NTS, BS	ARC, PVN, VMN, SON	130
Amylin	Modified calcitonin receptors, AMY_{1-3}	β cells in pancreas	Area postrema, NTS, hypothalamus	135, 234
CCK	CCK_1 (CCK-A) CCK_2 (CCK-B)	ARC, VMN, medial and lateral preoptic area, VTA	CCK_1: PVN, DMN, SON, NAcc, BS CCK_2: widely distributed	135-237
Bombesin and related peptides	BB_1 BB_2 bb_3	Stomach, spinal cord, anterior hypothalamus, ARC, PVN, AMY, NAcc, BS	Basal forebrain magnocellular complex, AMY	152, 236, 238

(Bold text denotes compounds available from Tocris)

noted that for the purposes of this review, appetite-modulating peptides are considered in terms of their peripheral or central origins and actions; however, most peptides that were originally thought to be exclusively synthesized in the periphery are now also known to be produced in the central nervous system (CNS). A summary of the featured peptides, along with their receptors and anatomical distributions, can be found in Table 1. Tables 2, 3 and 4 show the commonly used doses, agonists and antagonists of the peptides discussed.

Peripheral Peptides Regulating Appetite

Leptin

Leptin is a 146 amino acid, glycosylated protein. This adipokine is produced predominantly by white adipose tissue, although low levels of expression are also detected in the hypothalamus.[12,13] Leptin has been central to the investigation of appetite and body weight regulation since it was identified as the product of the *ob* gene. Genetic mutation of this gene is found in leptin-deficient, phenotypically hyperphagic and obese *ob/ob* mice. Furthermore, mutations in the leptin receptor gene are associated with obesity in *fa/fa* rats and *db/db* mice. In humans and animals, circulating leptin levels are directly related to the number and size of adipocytes, and so correlate better with total fat mass than with body weight.[14]

Leptin has been proposed to convey information to the hypothalamus regarding the amount of energy stored in adipose tissue. Increasing levels are suggested to suppress appetite and affect energy expenditure in order to regulate body weight. Administration of leptin has been found to reduce food intake in all species studied to date,[15] including humans,[16] non-human primates,[17] rodents[18,19] and sheep.[20]

Table 2 | Peripheral anorexigenic peptides. Commonly used doses, agonists and antagonists.

Peptide	Dose	Agonists	Antagonists	References
Leptin	0.1-2.5 mg/kg (systemic) 0.5-10 µg (i.c.v.) 10 mg (humans)	**LEP (116-130)**	Leptin tA recombinant. Soluble form of the OB-R Leptin antibody	228, 229, 241, 255-259
Insulin	0.5-8 mU (i.c.v.)	Peptides S519 and S371	Peptide RB537	229, 260
Adiponectin	50 mg/kg	Recombinant adiponectin		261-262
PYY_{3-36}	100 µg/kg (systemic) 0.1-10 µg (central)	WO 0247712	JNJ-5207787 **BIIE 0246**	263-265
PP	0.1-10 µg (central)	**GR 231118 (1229U91), hPancreatic Polypeptide, [cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31},Aib^{32}, Gln^{34}]-hPancreatic Polypeptide**		266-268
GLP-1	10 µg (i.c.v.) 0.9 pmol/kg/min (humans)	**Exendin-4**	**Exendin-3 (9-39)**	129-130
Amylin	1-3 pmol/kg (systemic)	Pramlintide	**AC 187**	136, 138, 271
OXM	1-3 nmol (i.c.v.) 3-100 nmol/kg (systemic)	**Exendin-4**	**Exendin-3 (9-39)**	129-130
CCK	1 µg (i.c.v.) 10 nmol/kg	CCK_1: **A-71623** AR-R 15849 GW5823 CCK_2: **Gastrin** A-63387	CCK_1: **Devazepide,** SR29897 CCK_2: **LY 225910, YM 022, CI 988, LY 288513, PD 135158**	144, 145, 272-280
Bombesin, and related peptides	GRP: 32 nmol/kg Bombesin (4 mg/kg) 4 mg/kg/min (humans)	**BIM 187, GRP (1-27)** **Neuromedin B** **Neuromedin C** **Alytesin** **Litorin (Amphibian)**	**PD 176252, PD 168368, BIM 23042, BIM 23127** **ICI 216,140** **[D-Phe^{12}, Leu^{14}]Bombesin** **[D-Phe^{12}]Bombesin**	151, 152, 281-284

(Bold text denotes compounds available from Tocris)

LEP (116-130) (mouse), Synthetic Leptin Peptide Fragment

LEP (116-130) (mouse)
Cat. No. 2985

Ser-Cys-Ser-Leu-Pro-Gln-Thr-Ser-Gly-Leu-Gln-Lys-Pro-Glu-Ser-NH_2

LEP (116-130) is a synthetic leptin peptide fragment that restricts weight gain, reduces food intake and blood glucose levels in *ob/ob* and *db/db* mice. The peptide does not act through interaction with the long form of the leptin receptor.

Grasso *et al* (1997) In vivo effects of leptin-related synthetic peptides on body weight and food intake in female ob/ob mice: localization of leptin activity to domains between amino acid residues 106-140. Endocrinology ***138*** 1413. **Grasso** *et al* (1999) Inhibitory effects of leptin-related synthetic peptide 116-130 on food intake and body weight gain in female C57BL/6J *ob/ob* mice may not be mediated by peptide activation of the long isoform of the leptin receptor. Diabetes ***48*** 2204. **Rozhavskaya** *et al* (2000) Design of a synthetic leptin agonist: effects on energy balance, glucose homeostasis and thermoregulation. Endocrinology ***141*** 2501.

Moreover, in rodents, microinjections of leptin into the ventromedial hypothalamus (VMH)[21] and the arcuate nucleus (ARC)[22] can potently decrease food intake, suggesting that leptin's actions are mediated chiefly by the hypothalamus. Activation of these brain regions by leptin is partly attributable to its actions on ARC neurons that lie outside the blood–brain barrier.[23] However active transport of leptin across the blood–brain barrier has been demonstrated.[24,25]

Leptin responsive neurons in the ARC include those containing the orexigenic peptides neuropeptide Y (NPY) and agouti related peptide (AgRP), and those containing the anorexigenic peptides α-melanocyte-stimulating hormone (α-MSH) and cocaine and amphetamine regulated transcript (CART). The NPY/AgRP neurons are inhibited by leptin, while α-MSH/CART neurons are activated.[26] There are also potentially synergistic interactions between leptin and the short-term satiety signal cholecystokinin (CCK), which may involve integration at the level of primary sensory afferents.[27]

Circulating leptin levels also vary in an adiposity-independent manner; decreasing during fasting and increasing with re-feeding. These changes have been linked to insulin and glucose regulation. For example, insulin increases leptin production and plasma levels of leptin are correlated with plasma glucose levels.[28-30]

It has been suggested that the influence of leptin on energy expenditure may be most prominent in terms of body weight regulation, as its effects on food intake are transient.[31] One means by which leptin increases energy expenditure is via sympathetic activation of brown adipocytes, leading to thermogenesis in brown adipose tissue (BAT).[32] The effects of leptin on thermogenesis are also seen in non-rodent species with comparatively low levels of BAT. In sheep, central administration of leptin markedly enhances postprandial thermogenesis in both diffuse adipose depots (retroperitoneal and gluteal fat) and muscle.[33]

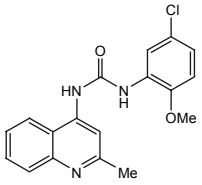
As noted above, genetic mutations resulting in leptin insufficiency or leptin receptor deficiencies support the notion that this peptide plays an important role in long-term energy homeostasis. Although several studies have reported that leptin can be an effective pharmaceutical tool for treating obesity in leptin-deficient states, the administration of exogenous leptin fails to significantly reduce adiposity in most cases of human obesity. Furthermore, deficiencies in leptin production or leptin receptor expression have been linked to only a very few cases of human obesity.[34] Indeed, increased adipocyte leptin content and high circulating leptin levels are common in the obese, which has lead to the idea of leptin resistance. This hypothesis explains the failure of an upregulated leptin signal to modify appetite and prevent weight gain. Leptin resistance seems to be caused in part by a reduction in its transport across the blood–brain barrier, as well as its decreased ability to initiate cellular activation within the brain.[15] Leptin enters the brain through active transport, which involves a short form of the leptin receptor (ObRa) at the choroid plexus. Studies in rodents have shown that feeding animals a high-fat diet decreases ObRa levels within the hypothalamus[24,35] and, consistent with this leptin transport is reduced in obese humans.[36] An additional cause may be a defect in leptin signaling related to the suppressor of cytokine signaling 3 (SOCS3) and insulin receptor substrate/phosphatidylinositol 3-kinase (IRS/PI 3-K) signaling pathways.[37,38] Various studies have demonstrated the importance of SOCS3 in determining the degree of leptin sensitivity.[39-41] For example, a specific increase in SOCS3 expression is seen in ARC neurons of mice with diet-induced obesity and this may be a primary cause of leptin resistance.[42]

Insulin

Insulin is a 51 amino acid protein produced mainly by the pancreatic β cells in response to elevated blood glucose concentrations. There is also evidence of some neuronal synthesis, however the majority of insulin in the brain is of peripheral origin.[43,44] As with leptin, circulating levels of insulin are proportional to adiposity.[45] Insulin interacts with specific receptors in the hypothalamus[46] and, along with leptin, regulates the synthesis and release of NPY.[47] The expression of NPY in ARC neurons is decreased after systemic or central administration of insulin and leptin, whereas these NPY neurons are activated when the levels of these hormones fall during undernutrition.[48] Intraventricular or intrahypothalamic administration of insulin inhibits food intake and produces a sustained loss of body weight in both rodents[49] and

PQ 401, IGF-IR Inhibitor

PQ 401
Cat. No. 2768



PQ 401 is an insulin-like growth factor receptor (IGF-IR) inhibitor. The compound suppresses IGF-stimulated IGF-IR autophosphorylation with an IC_{50} value of 12 μM and it inhibits growth of MCF-7 breast cancer cells *in vitro* and *in vivo*.

Anderson *et al* (2006) Parallel synthesis of diarylureas and their evaluation as inhibitors of insulin-like growth factor receptor. J.Comb.Chem. ***8*** 784. **Gable** *et al* (2006) Diarylureas are small-molecule inhibitors of insulin-like growth factor I receptor signaling and breast cancer cell growth. Mol.Cancer ***5*** 1079. **Sivakumar** *et al* (2009) Autocrine loop for IGF-I receptor signaling in SLUG-mediated epithelial-mesenchymal transition. ***34*** 329.

primates.[50] In contrast, injection of insulin antibodies into the hypothalamus of rats increases food intake and results in body weight gain.[51] Additionally, mice with a genetic deletion of neuronal insulin receptors are hyperphagic and obese.[52] Insulin secretion is stimulated acutely in response to meals. Obesity, in the vast majority of obese humans, is associated with both hyperinsulinemia and hyperleptinemia, indicative of insulin, as well as leptin resistance.

Adiponectin

Adiponectin (also known as Acrp30 and apM1) is a 244 amino acid polypeptide that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. It is exclusively produced by mature adipocytes[53] and levels are reduced in obesity, particularly visceral obesity.[54] This is thought to contribute, via a peripheral mechanism, to diminished insulin sensitivity and the development of insulin resistance.[55] Although adiponectin does not appear to cross the blood–brain barrier,[56,57] the ARC[58] and the area postrema[59] respond to adiponectin, indicating that these cells may be involved in relaying the signal to other brain regions. In the hypothalamus, actions of adiponectin are mediated via two adiponectin receptors (AdipoR1 and AdipoR2), which have opposing effects.[60] Deletion of the AdipoR1 gene results in obesity caused by reduced energy expenditure, whereas deletion of the AdipoR2 gene results in increased energy expenditure and a lean phenotype.[61] Central administration of adiponectin reduces body weight,[62] primarily a result of an increase in energy expenditure. In wild-type and *ob/ob* mice, adiponectin increases uncoupling protein 1 (UCP1, thermogenin) mRNA levels in BAT and promotes thermogenesis, without altering food intake.[62] To date the effects of adiponectin on food intake have been inconclusive, with studies showing either a lack of effect,[62] a reduction,[63] or an increase.[58] Clearly, adiponectin is an important peripheral hormone pertinent to determining levels of insulin sensitivity, but further work is required to resolve actions of this hormone within the brain.

Ghrelin

Ghrelin, a 28 amino acid acylated peptide, is the endogenous ligand for the growth hormone secretagog receptor (GHS-R) and was the first circulating hormone shown to stimulate eating and weight gain. It is primarily secreted by specialized enterochromaffin cells located in the mucosa of the gastric fundus,[64] although several studies have demonstrated that it is also synthesized in the CNS, notably within hypothalamic regions.[65,66] In lean humans, ghrelin levels rise during the intervals between meals (or during fasting) and peak before meal onset, leading to the notion that ghrelin might act as a meal initiation signal. Ghrelin levels fall in the hour after a meal or glucose load, with the extent of postprandial suppression being proportional to caloric intake. Significantly, ghrelin infusion has been reported to increase food intake in healthy volunteers[67] and in patients with anorexia due to cancer[68] and chronic renal failure.[69] Importantly, these effects occur at doses that are within the normal physiological range for circulating endogenous ghrelin. In humans, circulating ghrelin levels are decreased in acute states of positive energy balance and in obesity, and are elevated during sustained fasting with weight loss and in anorexia nervosa.[70,71] In addition to having reduced ghrelin levels, obese individuals do not exhibit the postprandial decline in plasma concentrations observed in the lean.[72] It has been suggested that this lack of ghrelin suppression may lead to increased food consumption and contribute to the pathophysiology of obesity. Of course, ghrelin levels in obesity might already be reduced to a level where no further fall is detectable. It could be that the reduced ghrelin levels in the obese may reflect a consequence of overconsumption, rather than a cause.

Ghrelin (human), Endogenous Ghrelin Receptor Agonist

Ghrelin (human)
Cat. No. 1463

^{n}Octanoyl
|
Gly-Ser-Ser-Phe-Leu-Ser-Pro-Glu-His-Gln-Arg-Val-Gln-Gln-Arg-Lys-Glu-Ser-Lys-Lys-Pro-Pro-Ala-Lys-Leu-Gln-Pro-Arg

Ghrelin is the endogenous agonist peptide for the ghrelin (GHS) receptor and is produced mainly by the stomach. The compound stimulates release of growth hormone from the pituitary gland *in vitro* and *in vivo*, and regulates feeding, growth and energy production.

Kojima *et al* (1999) Ghrelin is growth-hormone-releasing acylated peptide from stomach. Nature ***402*** 656. **Tolle** *et al* (2001) In vivo and in vitro effects of ghrelin/motilin-related peptide on growth hormone secretion in the rat. Neuroendocrinology ***73*** 54. **Inui** (2001) Ghrelin: an orexigenic and somatotrophic signal from the stomach. Nature Rev.Neurosci. ***2*** 551.

The metabolic effects of ghrelin are opposite to those of leptin and it has been proposed that these two peptides exert a counter-regulatory action on each other.[73] In addition to possibly playing a role in the initiation of eating, peripheral and central administration of ghrelin[74,75] enhances carbohydrate metabolism and reduces fat utilization and energy expenditure.[74] Central ghrelin appears to partition nutrients toward fat storage by favoring an increase in glucose and triglyceride uptake, increasing lipogenesis and inhibiting lipid oxidation in white adipocytes. This may also suggest an alternative role for the pre-meal surge in ghrelin. Rather than being a signal of meal initiation, this increase may trigger processes in the CNS that prepare the body to receive and appropriately process incoming nutrients. One mediator of the orexigenic effect of ghrelin is AMP-activated protein kinase (AMPK),[76,77] a key enzyme regulator of energy homeostasis both centrally and peripherally.[78,79] In addition, ghrelin seems to achieve its orexigenic action through stimulation of hypothalamic circuits, in part by activating the arcuate NPY/AgRP pathways and opposing anorexigenic signals.[80-82] Ghrelin-induced eating may also be mediated via the endogenous cannabinoid system, since feeding induced by intraparaventricular nuclear ghrelin is reversed by the CB_1 receptor antagonist rimonabant.[83]

Despite the great interest in ghrelin and its putative role in stimulating eating, there are some inconsistencies in the data indicating that caution should be exercised. For example, it should be noted that ghrelin has only modest affects on food intake in animal models compared to other endogenous orexigens. Furthermore, ghrelin-deficient mice (*ghrl*–/–) exhibit normal spontaneous food intake patterns and growth rates, normal levels of hypothalamic orexigenic and anorexigenic neuropeptides and a normal hyperphagic response to fasting. Such findings suggest that ghrelin is not imperative in the regulation of appetite.[84] Additionally, differences apparently exist between people in the change of subjective desire to eat resulting from food restriction and ghrelin levels. Caloric restriction over 4 days in healthy men, sufficient to significantly reduce lean body mass and increase appetite, was not accompanied by changes to serum ghrelin levels.[85] Stronger evidence may be required to fully support the proposed role of ghrelin as a 'hunger signal' in normal feeding.

Various approaches have been used to block ghrelin activity. GHS-R1a antagonists reduce food intake acutely in lean, diet-induced obese and *ob/ob* mice and repeated administration to *ob/ob* mice results in reduced weight gain.[86] A similar acute effect has been demonstrated in rats.[87] However, it seems that not all GHS-R1a antagonists have similar effects on appetite. For instance, BIM-28163, a ghrelin analog with full competitive GHS-R1a antagonist properties, prevents ghrelin-stimulated growth hormone release in rats but stimulates food intake and weight gain.[88,89] This suggests the existence of a novel receptor regulating the orexigenic actions of ghrelin.

Another approach to blocking the orexigenic effects of ghrelin is the use of RNA-Spiegelmers (stable oligonucleotides with specific target binding properties). NOX-B11, a high affinity Spiegelmer specific for octanoylated ghrelin, reduces ghrelin-induced food intake[90] and produces weight loss in mice with diet-induced obesity.[91]

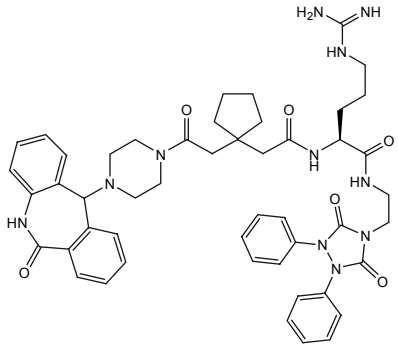
Another approach under investigation is the use of anti-ghrelin 'vaccines', which cause weight loss in rats[92] and pigs[93]. A recent phase I/II clinical trial showed no evidence of an effect on weight in obese humans, despite producing a robust antibody response.[94]

Peptide YY_{3-36}

Peptide YY_{3-36} (PYY_{3-36}) is produced by the endocrine L cells of the small and large bowel in response to the presence of food. Levels of the peptide are reported to increase postprandially and to decrease food intake.[95] Recently it has been shown that PYY_{3-36} is also produced by neurons of the paraventricular nucleus (PVN), ARC and supraoptic nuclei of the human hypothalamus.[96] Based on structural and evolutionary criteria, PYY_{3-36} is closely related to NPY and pancreatic polypeptide (PP),[97] which all act on the NPY receptor family.[98] In common with leptin, PYY_{3-36} has been shown to cross the blood brain barrier and act on the Y_2

BIIE 0246, Potent, Selective Non-Peptide NPY Y_2 Antagonist

BIIE 0246 formate
Cat. No. 1700



BIIE 0246 is a potent, selective and competitive non-peptide neuropeptide Y Y_2 antagonist (IC_{50} = 15 nM). The compound displays > 650-fold selectivity over Y_1, Y_4 and Y_5 receptors and is active *in vivo*.

Doods *et al* (1999) BIIE0246: a selective and high affinity neuropeptide Y Y_2 receptor antagonist. Eur.J.Pharmacol. ***384*** R3. **Dumont** *et al* (2000) BIIE0246, a potent and highly selective non-peptide neuropeptide Y Y_2 receptor antagonist. Br.J.Pharmacol. ***129*** 1075. **Malmstrom** (2001) Vascular pharmacology of BIIE0246, the first selective non-peptide neuropeptide Y Y_2 receptor antagonist, *in vivo*. Br.J.Pharmacol. ***133*** 1073.

receptor, a presynaptic inhibitory autoreceptor on NPY neurons.[95,99] Activation of Y_2 causes a decrease in NPY release and an increase in α-MSH release.[95] In addition, PYY_{3-36}-deficient mice show alterations in their energy metabolism, supporting a role for PYY_{3-36} in the regulation of energy homeostasis.[100,101] Obese humans have low levels of PYY_{3-36}, suggesting that a deficiency may contribute to the pathogenesis of obesity. Infusion of PYY_{3-36} significantly decreases cumulative 24-hour energy intake in both obese and lean subjects. In contrast to the negligible effect on appetite caused by the daily fluctuations in circulating leptin, PYY_{3-36} has been shown to inhibit food intake in rodents and humans at physiological concentrations. Unlike leptin, there is no evidence of resistance to PYY_{3-36} in obese subjects.[102] Although these results are potentially of great importance, it should be noted that central administration of PYY_{3-36} can stimulate eating.[103] The absence of obesity-associated resistance to the anorectic properties of PYY_{3-36} makes it an attractive target for treatment. At the moment, intranasal PYY_{3-36} is undergoing long term phase II studies. However, its use seems to be hindered by adverse side effects such as nausea and vomiting.[104]

Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a 36 amino acid peptide derived from pre-proglucagon. It is released by the pancreatic islet cells in response to food intake and in proportion to the calories ingested. Low levels of PP have been found in obese humans and genetically obese mice[105] and high levels occur in patients with anorexia nervosa.[106] Furthermore, peripheral administration of PP has been shown to reduce food intake in lean and obese rodents and *ob/ob* mice are less sensitive to the peptide's actions.[107] In humans, PP infusion can produce marked, apparently long-lasting intake suppression,[108] leading to the proposal that PP may act as a circulating satiety signal. The mechanism by which PP reduces food intake has not yet been established, although actions on gastric emptying, or regulation of NPY, orexin and ghrelin have been proposed.[109,110] It has been shown that PP signals via the NPY Y_4 and Y_5 receptors and therefore could directly activate neurons in the hypothalamus.[111] The suppressive effects of PP are relatively modest, and have not been consistently replicated, even at high doses. The potential role of PP is further complicated by the finding that central administration of the peptide can induce moderate hyperphagia, potentially via actions on Y_5 receptors. Although there is some evidence for PP production within the CNS, circulating PP can enter the brain, so there is clearly a need for the opposing actions of centrally and peripherally administered exogenous PP to be investigated further. Knowledge of the actions of PP has resulted in the development of two synthetic peptide hormones; TM30339, a selective Y_4 receptor agonist, which is likely to be the subject of phase I/II studies in the near future, and TM30338, a dual Y_2-Y_4 receptor agonist that causes an acute reduction in food intake.[104]

[cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31},Aib^{32},Gln^{34}]-hPancreatic Polypeptide, Potent, Selective NPY Y_5 Agonist

[cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31},Aib^{32},Gln^{34}]-hPancreatic Polypeptide
Cat. No. 1365

Gly-Pro-Ser-Gln-Pro-Thr-Tyr-Pro-Gly-Asp-Asn-Ala-Thr-Pro-Glu-Gln-Met-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-Arg-Tyr-Ile-Asn-Met-Ala-Aib-Arg-Gln-Arg-Tyr-NH_2

[cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31},Aib^{32},Gln^{34}]-hPancreatic Polypeptide is a potent, selective peptide agonist for the NPY Y_5 receptor (IC_{50} values for inhibition of NPY binding to human Y_5, Y_4, Y_2, and Y_1 receptors are 0.24, 51, > 500 and 530 nM respectively, K_i at Y_5 = 0.1-0.15 nM). The compound stimulates food intake *in vivo*.

Cabrele *et al* (2000) The first selective agonist for the neuropeptide YY_5 receptor increases food intake in rats. J.Biol.Chem. ***275*** 36043. **Dumont** *et al* (2005) BODIPY®-conjugated neuropeptide Y ligands: new fluorescent tools to tag Y1, Y2, Y4 and Y5 receptor subtypes. Br.J.Pharmacol. ***146*** 1069.

Glucagon-like Peptide 1

Like PP, glucagon-like peptide 1 (GLP-1) is a derivative of pre-proglucagon, and there are two circulating forms identified in mammals: the predominant GLP-1 (7-36) amide, and GLP-1 (7-37). GLP-1 is co-secreted with PYY_{3-36} in response to nutrients in the gut, especially carbohydrates.[112] Like other gastrointestinal peptides GLP-1 is also produced in the CNS,[113] particularly the nucleus of the solitary tract (NTS) and hypothalamus, with high levels of GLP-1 receptor mRNA present in ARC and PVN. A physiological role of GLP-1 as an anorectic or satiety factor is suggested due to the observations that intracerebroventricular (i.c.v.) injection suppresses food intake and body weight gain in normal and obese rats. Additionally, daily administration of exendin-(9-39), a GLP-1 receptor antagonist, augments food intake and body weight.[114] The anorectic effects of GLP-1 may be mediated through NPY signaling since GLP-1 inhibits, and exendin-3 (9-39) promotes, NPY-induced feeding.[115] Exendin-3 (9-39) also blocks leptin-induced inhibition of food intake, and GLP-1 neurons in the NTS co-express leptin receptors, thereby suggesting that the GLP-1 pathway may be one of the mediators of the anorectic effects of leptin[1]. Intraventricular GLP-1 powerfully inhibits feeding in rodents, and this response is blocked by the concurrent administration of exendin-3 (9 39). In addition, GLP-1 functions as an incretin, enhancing insulin secretion and suppressing glucagon secretion after a meal.[116,117] In humans, infusion of GLP-1 at the start of a meal suppresses feelings of hunger and increases satiety scores, without affecting

Exendin-4, Potent GLP-1 Receptor Agonist

Exendin-4
Cat. No. 1933

His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

Exendin-4 is a high affinity glucagon-like peptide 1 (GLP-1) receptor agonist (K_d = 136 pM) that was originally isolated from *Heloderma suspectum* venom. The compound potently induces cAMP formation without stimulating amylase release in pancreatic acini. It potentiates glucose-induced insulin secretion in isolated rat islets and protects against glutamate-induced neurotoxicity.

Eng *et al* (1992) Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. J.Biol.Chem. ***267*** 7402. **Goke** *et al* (1993) Exendin-4 is a high potency agonist and truncated exendin-(9-39)-amide an antagonist at the glucagon-like peptide 1-(7-36)-amide receptor of insulin-secreting β-cells. J.Biol.Chem. ***268*** 19650. **Thorens** *et al* (1993) Cloning and functional expression of the human islet GLP-1 receptor. Demonstration that exendin-4 is an agonist and exendin-(9-39) an antagonist of the receptor. Diabetes ***42*** 1678. **Perry** *et al* (2002) Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J.Pharmacol.Exp. Ther. ***302*** 881.

palatability.[118] It also causes a small dose-dependent inhibition in food intake in both lean and overweight subjects.[119] Prandial injections of GLP-1 given to obese but otherwise healthy volunteers for five days resulted in a mean body weight loss of 0.55 kg.[120] The combination of enhanced insulin release with reduction in food intake makes GLP-1 an attractive potential treatment for patients with type II diabetes.

It is important to note some discrepancies that could affect interpretations of the role of GLP-1. For instance, GLP-1 receptor knockout mice do not exhibit any abnormalities in feeding behavior and have no tendency to become obese.[121] Additionally, GLP-1 induces conditioned taste aversion suggesting that the peptide may suppress feeding by inducing a sensation of sickness.[122] Human studies with exendin-4 (exenatide), a naturally-occurring peptide with sequence homology to GLP-1, have shown it produces significant reductions in body weight.[123] The therapeutic potential of extendin-4 is limited by its side effects, which include nausea and vomiting.[124] Liraglutide, another analog of GLP-1, improves glycemic control in association with weight loss. However, similarly to exendin-4, it induces nausea.[125] CJC-1134, a newly developed GLP-1 analog, seems to have better tolerability.[104]

Oxyntomodulin

Oxyntomodulin (OXM) is a 37 amino acid peptide which is derived from pre-proglucagon processing in the L cells of the small intestine and in the CNS.[126] OXM is released in response to food ingestion and in proportion to meal caloric content.[127] Levels are markedly elevated in tropical malabsorption and after jejuno-ileal bypass surgery for morbid obesity; conditions that are both associated with anorexia and weight loss.[128] Despite the high OXM-like immunoreactivity in the CNS, notably in the hypothalamus, little is known about its physiological role. OXM has been shown to cause a robust and sustained inhibition of food intake following systemic and central administration in rats and humans.[128-132] Furthermore, chronic i.c.v. administration causes a marked reduction in body weight gain and adiposity,[133] suggesting OXM as a potential regulator of appetite and body weight. The anorectic effects of OXM are abolished in GLP-1R(-/-) mice and can be blocked by exendin-(9-39). This indicates that OXM actions are dependent, at least in part, on GLP-1R, suggesting complex interactions of different pre-proglucagon-derived peptides acting at a common target.[131] In healthy humans, systemic administration of OXM significantly reduces hunger and food intake.[128] The mechanism of action of OXM remains unclear. It has been suggested that the circulating peptide may access the brain via the ARC and exert its anorectic actions through indirect activation of pro-opiomelanocortin (POMC) neurons in the hypothalamus and through inhibition of fasting ghrelin levels.[128] Therefore, OXM could offer a novel route for the development of therapeutic agents in the treatment of obesity.

Amylin

An additional pancreatic peptide that reduces food intake is amylin. Amylin is a 37 amino acid peptide belonging to the family of calcitonin gene-related peptides (CGRP) and is a physiological product of pancreatic β cells. It is co-secreted with insulin in a molar ratio that usually remains constant but which may be altered by disease states, including obesity and diabetes.[104] Amylin crosses the blood-brain barrier via specific transport systems[134] and suppresses feeding in food-deprived and free-feeding rodents. It is proposed to act on receptors in the area postrema (AP),[135] although the highest

AC 187, Potent and Selective Amylin Receptor Antagonist

AC 187
Cat. No. 3419

Ac-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr-NH_2

AC 187 is an orally active, potent amylin receptor antagonist (IC_{50} = 0.48 nM) that displays 38-fold and 400-fold selectivity over calcitonin and CGRP receptors respectively. The compound increases glucagon secretion, accelerates gastric emptying, alters plasma glucose levels and increases food intake *in vivo*.

Reidelberger *et al* (2004) Amylin receptor blockade stimulates food intake in rats. Am.J.Physiol.Inter.Comp.Physiol. ***287*** R568. **Jhamandas and MacTavish** (2004) Antagonist of the amylin receptor blocks β-amyloid toxicity in rat cholinergic basal forebrain neurons. J.Neurosci. ***24*** 5579. **Gedulin** *et al* (2006) Role of endogenous amylin in glucagon secretion and gastric emptying in rats demonstrated with the selective antagonist, AC187. Regul.Pept. ***137*** 121.

Table 3 | Orexigenic peptides. Commonly used doses, agonists and antagonists.

Peptide	Dose and site of administration	Agonists	Antagonists	References
Ghrelin	30-300 pmol (intrahypothalamic) 1-10 nmol (systemic)	RC-1291 MK-0677 **Tabimorelin** **L-692,585**	**[D-Arg^1,D-Phe^5,D-Trp^{7,9},Leu^{11}], Substance P*** **[D-Lys^3]-GHRP-6**	254, 285-288
NPY	0.5-5 μg (central) 100 μg (humans)	Y_1: **[Leu^{31},Pro^{34}]-NPY** [Arg^6,Pro^{34}]-pNPY **[D-Trp^{34}]-NPY** [Phe^7,Pro^{34}]-pNPY Y_2: **PYY$_{3-36}$** Y_5: **[cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31} Aib^{32},Gln^{34}]-hPP** [Leu^{31},Pro^{34}]-PYY [hPP$^{1-17}$, Ala^{31}, Aib^{32}]-NPY **BWX 46**	D-NPY (27-36) Y_1: **BIBO 3304**, **GR 231118 (1229U91)** **BVD 10** **PD 160170** **BIBO 3304** **BIBP 3226** Y_2: **BIIE 0246** Y_5: **L-152,804, CGP 71683** **NTNCB**	265, 289-306
AgRP	1 nmol (i.c.v.)	**α-MSH** **NDP-MSH (Nle^4,D-Phe^7-α-MSH)** MC_3: **γ_1-MSH** MC_4: **MT-II, THIQ**	**HS 014**, **HS 024**	213, 307, 308
MCH	0.5 μg (PVN)	**[Ala^{17}]-MCH** S36057 R2P	T-226296 , SNAP7941, ATC 0065, ATC 0175, GW3430	177, 308-311
Orexin	3-30 nmol	**Orexin A, Orexin B** OX_2: **[Ala^{11}, D-Leu^{15}]-Orexin B**	OX_1: **SB 408124** **SB 334867** SB 284422	312-313
Galanin	0.5 -2.5 nmol	**Galanin (1-15)** **Galanin (1-30)** **Galanin (2-29)** **M617**	**M40**, **M871**	314
Opioid β-endorphin **[Leu]-/[Met]-enkephalin** and analogues (DADL, **DSLET**, DALA, DTLET) Dynorphin A	1-2 nmol (VMH, PVN, NAC, VTA) 0.7 - 7.0 nmol (VMH, PVN, NAC) 0.3 pmol – 10 nmol (VMH, PVN, NAC)	**Salvinorin A** μ: **Loperamide**, **Fentanyl**, **DAMGO**, **Endomorphin-1**, **Endomorphin-2** Sufentanil PL 017 δ: **SNC 80**, **SNC 121**, SNC 162, **BW 373U86**, **FIT**, **[D-Ala^2]-Deltorphin II**, **DPDPE**, **DSLET** δ_1: **SB 205607** δ_2: DELT DSBULET**, Naltriben** κ: **BAM 22P, ICI 199,441, ICI 204,448,** U 69593**, U-54494A ,** κ_1: **U-50488** κ_2: **GR 89696** κ_3: NalBzOH	**Diprenorphine**, **Buprenorphine** μ: **β−FNA** **Cyprodime**, **CTOP**, **CTAP** **Naloxonazine** (μ_1) **Naloxone** and **Naltrexone** (μ-preferring, general antagonists) δ: **Naltrindole** **Naltriben**, **SDM25N**, **ICI 154**, **129**, **ICI 174,864** δ_1: DALCE, **BNTX** δ_2: ***N*-Benzylnaltrindole** κ: ***nor*-BNI**	204, 315

(Bold text denotes compounds available from Tocris)

*inverse agonist

density of amylin binding sites (modified calcitonin receptors, AMY1-3) occur in the hypothalamus. In concordance, amylin-deficient mice exhibit higher than normal weight gain. Intra-AP treatment with the amylin antagonist AC 187 blocks the anorectic actions of peripherally administered amylin.[136] Importantly, AC 187 increases food intake when administered alone, either centrally or peripherally, by increasing meal size and meal frequency.[137] Several clinical trials have demonstrated that in diabetic patients, the amylin analog pramlintide causes a modest reduction in body weight.[138] Pramlintide has recently been granted Food and Drug Administration approval.[139]

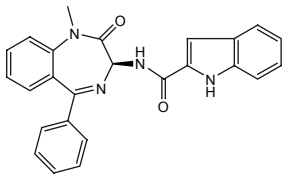
Cholecystokinin

Cholecystokinin (CCK) is a linear peptide that is synthesized as a pre-prohormone and then cleaved to generate a family of peptides. The predominant forms in plasma are CCK-8, CCK-33 and CCK-39. CCK is produced by endocrine I cells in the duodenum and jejunum and was the first gut hormone shown to dose-dependently decrease food intake in several species, including humans.[140-142] It has been proposed to act as a satiety signal via CCK_1 receptor activation on vagal afferents.[140] Otsuka Long Evans Tokushima Fatty (OLEFT) rats lack CCK_1 receptors and are insensitive to the anorexigenic action of CCK. These animals are hyperphagic and obese, and exhibit deficits in hypothalamic NPY gene expression.[143] CCK_1 receptor antagonists increase food intake in several species,[144] whereas CCK_1 agonists have the opposite effect.[145] Peripheral CCK has a rapid but relatively short-lived effect on feeding, which is consistent with a role in mediating meal termination and satiety.[146] In rats, CCK administration fails to result in weight reduction since reduced meal size is largely compensated for by an increase in meal frequency.[147] In humans, CCK-33 infusion reduces hunger ratings and increases feelings of fullness, while opposite effects have been observed following infusion of the CCK_1 antagonist, loxiglumide.[148,149] Conversely, there is evidence that CCK may play a role in longer-term energy regulation by synergizing with the actions of leptin. Central leptin administration potentiates the feeding inhibition of peripheral CCK, and CCK/leptin in combination results in greater weight loss over 24 hours than leptin alone. This synergy may occur by CCK activating brainstem neurons that project to the hypothalamus combined with the direct hypothalamic actions of leptin.[27]

Devazepide, Selective, Orally Active CCK_1 Receptor Antagonist

Devazepide

Cat. No. 2304



Devazepide is a potent, orally active CCK_1 receptor antagonist that displays appetite-stimulant effects. The compound blocks the anorectic response to CCK-8 and increases food intake in rats following systemic and i.c.v administration.

Ebenezer (2002) Effects of intracerebroventricular administration of the CCK1 receptor antagonist devazepide on food intake in rats. Eur.J.Pharmacol. ***441*** 79. **Reidelberger** *et al* (2003) Effects of peripheral CCK receptor blockade on food intake in rats. Am.J.Physiol.Reg.Integr.Comp.Physiol. ***285*** R429. **Ritter** (2004) Increased food intake and CCK receptor antagonists: beyond abdominal vagal afferents. Am.J.Physiol.Reg.Integr.Comp.Physiol. ***286*** R991.

Bombesin and Bombesin Related Peptides

Bombesin is a 14 amino acid amphibian peptide, with three mammalian analogs: gastrin-releasing peptide (GRP), neuromedin B (NMB) and neuromedin C (NMC). These peptides exert their effects through the GRP-preferring bombesin receptor (BB_2, GRP-R), NMB-preferring bombesin receptor (BB_1, NMB-R), or the bombesin receptor subtype-3 (bb_3, BRS 3). Feeding suppression by bombesin/bombesin-like peptides has been reported in a variety of species including humans.[150,151] Peripheral and/or central administration of bombesin/bombesin-like peptides reduces meal size in a dose-dependent manner in rats[150] and other species.[152] In humans, infusions of GRP and bombesin reduce food intake by enhancing satiety, although effective doses of bombesin may reduce food palatability and induce nausea.[151,153] Specific receptor antagonists can attenuate the anorectic actions of exogenously administered bombesin-like peptides, and the blockade of bombesin receptors within the CNS can induce a significant elevation in food intake. Although in some cases antagonists for bombesin-like peptide receptors promote food ingestion, the contribution of endogenous bombesin-like peptides on the normal regulation of food intake is still unknown.[152] Studies using knockout mice may provide new avenues for such research. Deficiencies in BB_2 and/or bb_3 do not affect feeding, although the hypophagic response to low-dose bombesin is suppressed in BB_2-deficient mice.[154] Although bombesin-like peptides have very low affinity for the bb_3 receptor, bb_3-deficient mice exhibit increased food consumption and age-related, mild obesity.[155] These developments are associated with an enhanced hyperphagic response to the orexigen melanin-concentrating hormone (MCH) and levels of hypothalamic MCH receptor and prepro-MCH mRNA are elevated.[156] Further studies with bombesin/bombesin-like peptides using both traditional pharmacological, as well as gene-targeting strategies, may well contribute to the development of new therapeutics for the treatment of obesity.

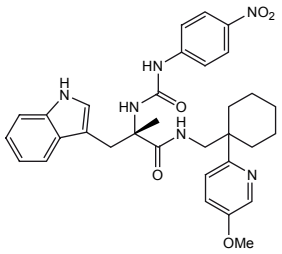
Orexigenic Hypothalamic Neuropeptides

Neuropeptide Y

Neuropeptide Y (NPY), a 36 amino acid peptide, is one of the most abundant neuropeptides in the periphery and the CNS.[157] Research has centred on the ARC-PVN axis, revealing that NPY levels in the PVN of the hypothalamus increase rapidly before meal times and remain elevated as long as food is withheld. Levels are also entrained by circadian pacemakers in the suprachiasmatic nucleus, suggesting that NPY plays a role in the central, episodic control of meal initiation. NPY is a particularly potent stimulator of feeding behavior in animal models and acts through activation of Y_1 and Y_5 receptors.[99] A robust and rapid feeding response is induced by i.c.v. and intrahypothalamic NPY injections,[158] while NPY antagonists or anti-serum decrease food intake.[1] As well as during fasting, NPY processing is upregulated in genetic models of obesity in which leptin signaling is dysfunctional (including *ob/ob* and *fa/fa*). NPY is downregulated by leptin in normal animals.[159] NPY neurons originating in the ARC co-express orexigens. These are released within the PVN and act synergistically with NPY to stimulate feeding.[160] NPY also acts to restrain the activity of anorexigenic melanocortin neurons, while itself being regulated by leptin. Although the actions of NPY, and the number of its interactions with other feeding-related systems, have generated great interest, there are some remaining questions. Contrary to expectations, NPY knockout mice do not show a lean phenotype. Furthermore, selective knockout of NPY Y_1 or Y_5 receptors leads to a fat phenotype.[161] Additionally, NPY exerts significant effects on other physiological systems, unrelated to feeding and body weight, which may limit its use as a drug target for obesity.[99] However, the substantial NPY-induced feeding response has stimulated pharmaceutical companies to support programs focused on the NPY receptor as a potential target for antiobesity drugs.

PD 176252, NMB (BB_1) and GRP (BB_2) Receptor Antagonist

PD 176252
Cat. No. 2602



PD 176252 is a non-peptide neuromedin B receptor (BB_1) and gastrin-releasing peptide receptor (BB_2) antagonist (K_i values are 0.17 and 1.0 nM for BB_1 and BB_2 respectively). The compound inhibits proliferation of rat C6 glioma cells (IC_{50} = 2 μM) and inhibits NCI-H1299 xenograft proliferation in nude mice (IC_{50} = 5 μM).

Ashwood *et al* (1998) PD 176252 - the first high affinity non-peptide gastrin-releasing peptide (BB_2) receptor antagonist. Bioorg.Med.Chem.Lett. ***8*** 2589. **Moody** *et al* (2000) Nonpeptide neuromedin B receptor antagonists inhibit the proliferation of C6 cells. Eur.J.Pharmacol. ***409*** 133. **Moody** *et al* (2003) Nonpeptide gastrin releasing peptide receptor antagonists inhibit the proliferation of lung cancer cells. Eur.J.Pharmacol. ***474*** 21.

BVD 10, Highly Selective Y_1 Antagonist

BVD 10
Cat. No. 2177

Ile-Asn-Pro-Ile-Tyr-Arg-Leu-Arg-Tyr-OMe

BVD 10 is a highly selective NPY Y_1 receptor antagonist (K_i values are 25.7, 1420, 2403 and 7100 nM at Y_1, Y_2, Y_4 and Y_5 receptors respectively). The compound is devoid of agonist activity at Y_4 receptors.

Balasubramaniam *et al* (2001) Highly selective and potent neuropeptide Y (NPY) Y1 receptor antagonists based on [Pro[30], Tyr[32], Leu[34]]NPY(28-36)-NH_2 (BW1911U90). J.Med.Chem. ***44*** 1479. **Jois and Balasubramaniam** (2003) Conformation of neuropeptide Y receptor antagonists: structural implications in receptor selectivity. Peptides ***24*** 1035. **Jois** *et al* (2006) Modeling of neuropeptide receptors Y1, Y4, Y5, and docking studies with neuropeptide antagonist. J.Biomol.Struct.Dyn. ***23*** 497.

Agouti-related Peptide

Agouti-related peptide (AgRP) is an orexigenic neuropeptide that has little intrinsic signaling activity. Instead it functions primarily by inhibiting binding of α-MSH (see below), acting as an antagonist at melanocortin (MC) receptors. AgRP is synthesized by neurons with cell bodies in the ARC and is co-secreted with NPY.[162] The peptide increases food intake through antagonism of MC_3 and MC_4 receptors via blockade of the anorexigenic agonist α-MSH.[163] Alternative mechanisms of action might be mediated by orexin or opioid receptors.[164] Acute central administration of AgRP in rodents can increase food intake for several days. This long lasting effect of AgRP is unique when compared with the actions of all other orexigenic peptides, including NPY, MCH and orexins.[165,166] Chronic administration of AgRP to rodents promotes sustained hyperphagia and obesity[167] and AgRP expression is upregulated in *ob/ob* leptin-deficient mice.[168] Hypothalamic AgRP immunoreactivity is elevated in dietary obese rats and genetically obese *ob/ob* and *db/db* mice, and is reduced in fasting animals.[169,170] The NPY/AgRP system is inhibited by leptin and insulin and activated by ghrelin.[1,80] In addition, AgRP secretion appears to be chiefly triggered by any impairment of energy balance.[169] High circulating levels of AgRP have been documented in human obesity[171] and a polymorphism in the human AgRP gene (c. 199G→A), which seems to be correlated with late-onset obesity, has been described.[172]

Melanin-Concentrating Hormone

Melanin-concentrating hormone (MCH) is a 19 amino acid cyclic neuropeptide present in neurons of both the central and peripheral nervous systems, notably those originating in the lateral hypothalamus (LH) and zona incerta. MCH has been described over the past few years as a candidate orexigenic factor in the mammalian brain. Intraventricular MCH administration produces a dose-dependent increase of food intake with the ability to augment ongoing feeding.[165] MCH mRNA levels are increased by food deprivation in leptin deficient *ob/ob* mice and in dietary obese rats.[173,174] Leptin treatment restores fasting-induced MCH upregulation and prevents MCH-induced hyperphagia. Compared to NPY, the acute feeding effects of MCH are small and short-lasting. Twice-daily administration of MCH reliably increases food intake, although this effect is lost after 5 consecutive days without significant increases in body weight. The effects of MCH on feeding may be short-term due to possible down regulation of the target receptor. MCH over-expressing transgenic mice are obese and develop marked hyperphagia when maintained on a high-fat diet,[175] whereas MCH receptor (MCH_1) knockouts are lean, hypophagic, resistant to diet-induced obesity and have increased metabolic activity.[176] Additional evidence for a role in feeding comes from the ability of MCH_1 antagonists (e.g. T226296 and SNAP-7941) to block MCH-induced feeding, to reduce food intake alone and to reduce body weight with chronic administration to dietary obese rats.[177] Induction of apoptosis of MCH-expressing neurons *in vivo* produces a phenotype (MCH/ataxin-3 mice) that develops a late onset syndrome characterized by leanness, hypophagia and, in males, increased energy expenditure.[178] These phenotypes are remarkably similar to those of mice with induced mutations of the MCH gene, suggesting that MCH itself is a key molecule that regulates energy balance.[179]

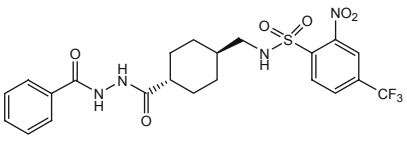
Orexin

Orexin A and B (hypocretin-1 and -2) are the endogenous ligands for the OX_1 and OX_2 G-protein-coupled receptors.[180,181] The orexin peptides (OXA and OXB) are processed from a common 130 amino acid precursor. The C-terminal residues of both peptides share 13 amino acid identities, suggesting that they have related structures and functions.[182] The cell bodies of orexin-containing neurons were originally reported to be largely confined to the LH; an area classically linked to feeding stimulation, leading to the examination of the potential for these peptides to affect food intake or body weight regulation. It is now known that orexin-producing neurons are more widely distributed, with clusters of neurons in various hypothalamic nuclei innervating the forebrain and hindbrain. Several studies have hypothesized a fundamental role of orexins in endocrine and autonomic responses to falling glucose levels. For example, hypoglycemia induces c-Fos expression in orexin neurons and increases orexin mRNA expression.[183,184] Hence, orexin neurons may represent one of the populations of 'glucose inhibited' neurons in the LH that respond to falling glucose levels with an increase in activity.[185] Also of note, orexin neurons co-express the orexigens dynorphin and galanin, and synapse on MCH neurons within the LH and NPY neurons in the ARC.[186]

The role of orexins in appetite regulation is not well defined. However, i.c.v. injections of OXA and OXB stimulate feeding in a dose-related fashion. OXA is significantly more effective than OXB, possibly due to its activation of both OX_1 and OX_2 receptor subtypes.[187]

S 25585, Potent, Selective NPY Y_5 Antagonist

S 25585
Cat. No. 3432

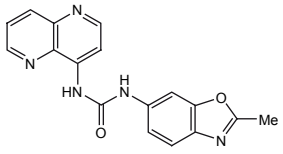


S 25585 is a potent neuropeptide Y Y_5 receptor antagonist (IC_{50} values are 5.4, > 1000, > 10 000 and > 10 000 nM at Y_5, Y_1, Y_2 and Y_4 receptors respectively) that displays no affinity for a wide range of other receptors. The compound does not produce a conditioned taste aversion, suppress sodium appetite or cause pica in rats. It significantly inhibits NPY-induced feeding but not through blockade of Y_5 receptors.

Della-Zuana *et al* (2004) A potent and selective NPY Y_5 antagonist reduces food intake but not through blockade of the NPY Y_5 receptor. Int.J.Obes. ***28*** 628. **Beauverger** *et al* (2005) Functional characterization of human neuropeptide Y receptor subtype 5 specific antagonists using a luciferase reporter gene assay. Cell.Signal. ***17*** 489. **Kamiji and Inui** (2007) Neuropeptide Y receptor selective ligands in the treatment of obesity. ***28*** 664.

SB 334867, Selective Non-Peptide OX_1 Antagonist

SB 334867
Cat. No. 1960

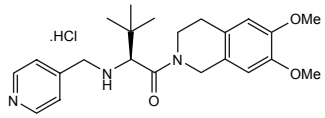


SB 334867 is a selective non-peptide orexin OX_1 receptor antagonist (pK_b values are 7.2 and < 5 for inhibition of intracellular Ca^{2+} release in CHO cells expressing human OX_1 and OX_2 receptors respectively). The compound blocks orexin A-induced grooming and feeding following systemic administration *in vivo*.

Haynes *et al* (2000) A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. Regul.Peptides ***96*** 45. **Duxon** *et al* (2001) Evidence that orexin-A-evoked grooming in the rat is mediated by orexin-1 (OX_1) receptors, with downstream 5-HT_{2C} receptor involvement. Psychopharmacology ***153*** 203. **Porter** *et al* (2001) 1,3-Biarylureas as selective non-peptide antagonists of the orexin-1 receptor. Bioorg.Med.Chem.Lett. ***11*** 1907. **Smart** *et al* (2001) SB-334867-A: the first selective orexin-1 receptor antagonist. Br.J.Pharmacol. ***132*** 1179.

TCS OX2 29, Potent and Selective OX_2 Antagonist

TCS OX2 29
Cat. No. 3371



TCS OX2 29 is a potent orexin 2 receptor (OX_2) antagonist (IC_{50} = 40 nM) that displays > 250 fold selectivity over OX_1 and over 50 other receptors, ion channels and transporters.

Hirose *et al* (2003) *N*-acyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline: The first orexin-2 receptor selective non-peptidic antagonist. Bioorg.Med.Chem.Lett. ***13*** 4497.

Treatment with an OX_1 receptor antagonist has been shown to reduce food consumption in rats, although this effect may be related to the involvement of these peptides in sleep regulation and the possible sedative consequences of blocking orexin function.[188] As with NPY and MCH, fasting upregulates orexin gene expression in the hypothalamus,[180] although orexins are far less effective than other peptides in stimulating food intake. They are also strongly linked to the regulation of sleep-activity cycles, which may restrict the utility of orexin interventions in treating obesity.

Galanin and Galanin-like peptide

Galanin (GAL) is a 29 amino acid neuropeptide (30 in man) that is unrelated to any known family of neuropeptides. While widely distributed throughout the periphery and brain, GAL expression is particularly dense in the PVN.[189] Three galanin receptors (GAL_{1-3}) have been characterized in rat, mouse and human, with GAL_1 being the predominant form in the brain.[189] Central administration of GAL rapidly stimulates feeding in satiated rats and has a relatively short duration of action.[190] The PVN is the most sensitive site of action, but dose-related increases in food intake have been obtained after administration into other hypothalamic nuclei, as well as the lateral, third and fourth ventricles. The effects of galanin were reported to be selective for more palatable foods, with some arguing for selective enhancement of fat intake, but such actions remain controversial.[189,191] There is evidence for the expression of galanin receptors by arcuate NPY/AgRP and POMC/CART neurons, while leptin can downregulate hypothalamic galanin gene expression and block galanin-induced hyperphagia. Whether GAL constitutes an important orexigenic signal in the daily pattern of feeding has not been clearly established. The GAL receptor antagonists C7 and M40 inhibit GAL-induced feeding, but generally fail to suppress feeding in different behavioral paradigms when administered alone.[191,192] Infusion of GAL antisense oligonucleotides in the PVN inhibits feeding[193] but, unlike NPY, continuous GAL infusion is ineffective in increasing food intake and body weight gain.[194] Galanin knockout mice do not exhibit any marked alteration in food intake, metabolism or body weight. However, male GAL-/-NPY-/- double knockout mice are unexpectedly hyperphagic, heavier, and gain more weight than wild type mice when fed a high fat diet. These animals also have elevated serum insulin and leptin levels. Although GAL-/-NPY-/- knockouts are no more sensitive to the intake suppressing actions of exogenous leptin than wild type mice, they do display enhanced weight loss and adipose reduction in response to chronic leptin administration in the pre-obese phase.[195] Such findings suggest that galanin and NPY have complementary functions in the regulation of metabolic hormones that maintain energy homeostasis. Additional studies are necessary to determine whether GAL plays more than a modulatory role in the normal regulation of feeding behavior.

Galanin-like peptide (GALP) is a 60 amino acid neuropeptide which shares a partial sequence with

Table 4 | Anorexigenic neuropeptides. Commonly used doses, agonists and antagonists.

Peptide	Dose	Agonists	Antagonists	References
α-MSH	1 nmol i.c.v. 10 μg	**NDP-MSH (Nle^4,D-Phe^7-α-MSH)**, **MT-II**, **THIQ**	AgRP **SHU 9119** MC_4: **HS 014** **HS 024** **MCL 0020** **JKC 363**	213, 307, 316
CART	0.38 nmol	–	–	219
NT	10 μg	**JMV 449** JMV 94	SR 48692 **SR 142948**	225, 317, 318

(Bold text denotes compounds available from Tocris)

Galanin (porcine), Endogenous Galanin Receptor Agonist

Galanin (porcine)
Cat. No. 3008

Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-His-Ala-Ile-Asp-Asn-His-Arg-Ser-Phe-His-Asp-Lys-Tyr-Gly-Leu-Ala-NH_2

Endogenous porcine galanin receptor agonist (pK_i values are 9.63, 9.49, 9.02, 8.98, 8.01 and 8.14 at $hGAL_1$, $rGAL_1$, $hGAL_2$, $rGAL_2$, $hGAL_3$ and $rGAL_3$ respectively). Significantly increases food intake under free access conditions and also has roles in learning and memory, anxiety and sexual behavior.

Branchek *et al* (2000) Galanin receptor subtypes. TiPS. ***21*** 109. **Tachibana** *et al* (2008) Central administration of galanin stimulates feeding behavior in chicks. Comp.Biochem.Physiol.A.Mol.Inter.Physiol. ***151*** 637. **Brewer and Robinson** (2008) Galanin stimulation of feeding is blocked by the addition of a response element. Behav.Neurosci. ***122*** 949.

galanin.[196] *In vitro* GALP is an agonist for all three galanin receptors, but displays slight preference for GAL_3 and GAL_2 over GAL_1.[196,197] To date, there is considerable evidence of GALP playing a role in food intake and energy metabolism.[189,198,199]

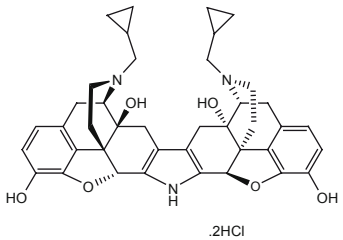
Opioid Peptides

Opioid peptides consist of three principal families, each with distinct precursors: endorphins (POMC), enkephalins (pre-pro-enkephalin), and dynorphins (pre-pro-dynorphin). These neuropeptides act at several opioid receptors (μ-, δ- and κ-opioid receptors), for which they display varying affinity. The link between opioids and feeding was first indicated by the finding that the general opioid receptor antagonist naloxone could exert an anorectic effect in rats[200] – an effect since replicated in many species, including humans. Subsequently, opioid receptor agonists were shown to stimulate feeding, beginning with the demonstration of hyperphagia following systemic morphine administration.[201,202] With the gradual characterization of a large number of opioid peptides and receptor subtypes, the involvement of these systems in appetite has been consolidated (for a comprehensive overview, Bodnar and Klein (2004)[203]). Feeding is reliably induced following central administration of opiates and the endogenous opioids. Thus, β-endorphin, dynorphin and enkephalin analogs (e.g., DADL, DPDPE, DSLET, DALA) reliably increase food intake following injection into PVN, VMH, ventral tegmental area (VTA) and nucleus accumbens (NAcc). Other opioids, such as leumorphin, deltorphin, endomorphins and α-neoendorphin, have also been shown to exert orexigenic activity.[204,205] Changes in opioid activity are also detected within the brain in response to nutritional status. For example, food deprivation increases enkephalin levels in the PVN, dynorphin levels are closely correlated with circadian feeding patterns (increasing with nocturnal intake), and hypothalamic levels of β-endorphin and dynorphin are elevated in obese Zucker rats.[204] Additionally, agonists have been reported to increase operant responding for ingesta. In contrast to the actions of opioid receptor agonists, antagonists reliably suppress feeding, as well as blocking the hyperphagic actions of opioids. Antagonists selective for μ-, δ- and κ receptors all have acute anorectic effects, although there are some differences between receptor subtypes. μ and κ antagonists have been the most consistently effective across different experimental conditions. In addition to acute intake suppression, antagonists will reduce intake to slow the excessive weight gain seen in dietary obesity and will suppress eating and body weight in genetically obese rodents.

There is good evidence for interactions between opioids and other feeding-related systems. For example, naloxone will block the hyperphagic actions of centrally administered PYY_{3-36}, NPY, OXA and AgRP.[204,205] The μ antagonist β–FNA blocks eating induced by the $MC_{3/4}$ receptor antagonist SHU 9119, while β–endorphin-induced feeding is blocked by the $MC_{3/4}$ receptor agonist MT-II.[204] While the contribution of different opioid receptors to appetite regulation remains to be fully explored, there is general agreement that opioids are closely linked to the processes that underlie the hedonic evaluation of foods.[206-208] Generally, opioid agonist and antagonist effects are enhanced when animals are fed palatable foods[209] with high fat diets stimulating opioid release in brain and altering opioid receptor densities.[204] In humans, opioid receptor blockade will reduce the palatability of food and can suppress intake in binge eaters.[210] In summary, the clear involvement of opioids in the affective aspects of appetite may provide an important focus for future research: to identify how

nor-Binaltorphimine Dihydrochloride, Selective κ-Opioid Receptor Antagonist

***nor*-Binaltorphimine dihydrochloride**
Cat. No. 0347



nor-Binaltorphimine is a selective κ-opioid receptor antagonist that reduces food intake induced by food-deprivation and opioid receptor agonists. The antagonist reduces meal size and frequency, increases energy expenditure and improves satiation in obese Zucker rats.

Portoghese *et al* (1994) Structure-activity relationship of N17′-substituted norbinaltorphimine congeners. Role of the N17′-basic group in the interaction with a putative address subsite on the κ opioid receptor. J.Med.Chem. ***37*** 1495. **Feng** *et al* (1997) Nor-binaltorphimine precipitates withdrawal and excitatory amino acid release in the locus ceruleus of butorphanol- but not morphine-dependent rats. J.Pharmacol.Exp.Ther. ***283*** 932. **Jarosz and Metzger** (2002) The effect of opioid antagonism on food intake behavior and body weight in a biobehavioral model of obese binge eating. Biol.Res.Nurs. ***3*** 198.

HS 014, Selective MC_4 Receptor Antagonist

HS 014
Cat. No. 1831

Ac-Cys-Glu-His-D-2-Nal-Arg-Trp-Gly-Cys-Pro-Pro-Lys-Asp-NH_2

HS 014 is a potent and selective melanocortin MC_4 receptor antagonist (K_i values are 3.16, 54.4, 108 and 694 nM for cloned human MC_4, MC_3, MC_1 and MC_5 receptors respectively). The antagonist increases food intake in rats and nociception in mice following central administration. It also inhibits IL-1β-induced Fos expression in the paraventricular hypothalamus.

Schioth *et al* (1998) Discovery of novel melanocortin$_4$ receptor selective MSH analogues. Br.J.Pharmacol. ***124*** 75. **Bellasio** *et al* (2003) Melanocortin receptor agonists and antagonists modulate nociceptive sensitivity in the mouse formalin test. Eur.J.Pharmacol. ***482*** 127. **Whitaker and Reyes** (2008) Central blockade of melanocortin receptors attenuates the metabolic and locomotor responses to peripheral interleukin-1β administration. Neuropharmacology ***54*** 509.

the putative orexigenic and anorexigenic signals discussed in other sections ultimately modulate the motivation to eat and guide behavior.

Anorexigenic Hypothalamic Neuropeptides

α-Melanocyte-stimulating hormone

α-Melanocyte-stimulating hormone (α-MSH) is a 13 amino acid peptide derived from the precursor POMC. α-MSH reduces food intake by activating MC_3 and MC_4 receptors. A biologically unique feature of this melanocortin family is the existence of an endogenous antagonist (AgRP; see above), in addition to the endogenous agonist for the target receptors. Thus, α-MSH and AgRP/NPY neurons are believed to act as a dynamic system *in vivo*. Intraventricular administration of α-MSH inhibits feeding and reduces body weight. Similarly the MC_4 agonist MT-II exerts a potent anorectic action following central injection in food-deprived animals and in *ob/ob* mice, as well as reversing NPY-induced hyperphagia. Dietary obesity is associated with reduced MC_4 density, while fasting upregulates MC_4 receptors and downregulates POMC mRNA expression.[211] Blockade of the MC_4 receptor with AgRP or synthetic antagonists (e.g. SHU 9119) increases food intake.[212] Similarly, MC_4 knockout mice are obese, display hyperphagia, hyperinsulinemia and hyperglycemia[212,213] and are insensitive to the anorectic actions of MT-II. MC_3 knockout mice additionally have increased fat mass and reduced lean mass, while combined deletion of both MC_3 and MC_4 produces a heavier phenotype than MC_4 deletion alone.[214] In humans, several families have been identified with mutant MC_4 related to early onset obesity and the defect is evident in 4% of extremely obese children. Furthermore, children with defects in the genes regulating POMC translation or processing are hyperphagic and obese.[215] POMC knockout mice are also obese but the condition is reversible through administration of a stable analog of α-MSH. Overall, these findings suggest that the melanocortin system is amongst the most promising targets for future research.

CART

In 1995, Douglass *et al*[216] found that a particular mRNA was upregulated by acute administration of cocaine or amphetamine. They named this transcript 'cocaine- and amphetamine-regulated transcript' (CART) and the two encoded peptides are referred to as CART peptides. CART is found in many feeding-related brain regions and co-localizes with other neurotransmitters that affect appetite, such as POMC-derived peptides in the medial hypothalamic regions and MCH in the LH. In the ARC, CART neurons are directly stimulated by leptin[26] and CART inhibits NPY-induced feeding.[217] Intraventricular and intra-accumbens administration of CART causes a rapid inhibition of feeding.[218] Conversely, CART antibodies enhance feeding, suggesting that CART exerts a tonic inhibitory control on feeding.[219] Chronic administration of CART, not only inhibits food intake, but causes weight loss in both lean and obese Zucker rats.[220] This weight loss is reversed after discontinuing CART administration. Moreover, fasting causes a reduction in CART mRNA in the ARC nucleus.[221]

These complementary effects need to be placed alongside some less straightforward findings, which suggest that CART may not be solely anorexigenic. Most notably, intra-hypothalamic injection of CART has been found to induce feeding rather than suppress it. Also problematic is the fact that intake suppression with CART is often accompanied by the induction of non-specific behavioral effects that are incompatible with the normal expression of feeding. These effects

CART (62-76) (rat, human), Neuromodulating Neuropeptide Fragment

CART (62-76) (rat, human)
Cat. No. 3339

Tyr-Gly-Gln-Val-Pro-Met-Cys-Asp-Ala-Gly-Glu-Gln-Cys-Ala-Val

Cart (62-76) is a cocaine- and amphetamine-regulated transcript (CART) peptide fragment that inhibits food intake. The peptide attenuates NPY-induced feeding and decreases food intake in food-restricted goldfish, and induces anxiogenic-like effects in the elevated plus-maze test. It modulates the activity of the striatal noradrenergic, and corticostrial and hypothalamic serotoninergic system, with no major effect on dopaminergic pathways in rat brain.

Volkoff and Peter (2000) Effects of CART peptides on food consumption, feeding and associated behaviors in the goldfish, *Carassius auratus*: actions on neuropeptide Y- and orexin A-induced feeding. Brain Res. ***887*** 125. **Vaarmann and Kask** (2001) Cocaine and amphetamine-regulated transcript peptide (CART$_{62-76}$)-induced changes in regional monoamine levels in rat brain. Neuropeptides ***35*** 292. **Colombo** *et al* (2003) Effects of ghrelin and other neuropeptides (CART, MCH, orexin A and B, and GLP-1) on release of insulin from isolated rat islets. Pancreas ***27*** 161.

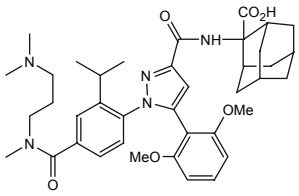
include increased (stimulant-like) locomotor activity, unnatural body postures, movement-related tremor and altered oral motor function.[222] CART has been interwoven into the increasingly complex models of energy and body weight regulation, but it seems that there are many factors to be satisfactorily resolved before these accounts can be accepted.

Neurotensin

Neurotensin (NT) is a 13 amino acid neuropeptide, initially implicated in memory function, but subsequently ascribed a role in a wide range of psychological processes. Several observations strongly suggest a role of NT in brain anorexigenic circuitry. NT neurons and terminals are present in those hypothalamic sites that have been implicated in feeding behavior and body weight regulation.[223] Central administration of NT decreases food intake in a variety of experimental paradigms. Neurotensin receptor 1 knockout mice (NTS1-/-) display a marginal increase in weight gain over the wild type, particularly in males, but only after several weeks. The degree of weight gain was correlated with increased food intake, again with a slow onset.[224] It has been proposed that NT may mediate the feeding effects of leptin, since leptin receptors are expressed by NT neurons in the hypothalamus and NT gene expression is decreased in genetically obese *ob/ob* mice. Central leptin administration also increases NT gene expression in the hypothalamus.[223] Further, immunoneutralization of NT or NTS antagonists reverse leptin-induced intake suppression. However, overweight NTS1-/- show no differences from wild type in relation to leptin levels or other metabolic indices.[224] Interestingly, i.c.v. NT blocks MCH-induced hyperphagia but not the feeding induced by NPY, suggesting some complex functional interactions between the anorectic NT and orexigenic peptide systems.[225]

SR 142948, Highly Potent NT Receptor Antagonist

SR 142948
Cat. No. 2309



SR 142948 is a potent non-peptide neurotensin (NT) receptor antagonist that binds with high affinity (IC_{50} = 0.32-3.96 nM). The compound attenuates amphetamine-induced hyperactivity and is orally active *in vivo*.

Gully *et al* (1997) Biochemical and pharmacological activities of SR 142948A, a new potent neurotensin receptor antagonist. J.Pharmacol.Exp.Ther. ***280*** 802.
Quere *et al* (1998) X-ray structural characterization of SR 142948, a novel potent synthetic neurotensin receptor antagonist. Bioorg.Med.Chem.Lett. ***8*** 653.
Marie-Claire *et al* (2008) Effects of the selective neurotensin antagonist SR 142948A on 3,4-methylenedioxymethamphetamine-induced behaviours in mice. Neuropharmacology ***54*** 1107.

Conclusion

This overview presents some of the basic evidence implicating these putative orexigenic and anorexigenic peptides in the complex regulation of appetite, body weight and energy homeostasis. The list of candidate signals will no doubt grow further, and there is a range of non-peptide transmitters that we have not discussed but which are strongly linked to these processes. We must also recognize that current emphasis on hypothalamic processes within the brain masks crucial influences of extra-hypothalamic circuitry. A fuller understanding of the behavioral and motivational aspects of eating control will require greater knowledge of those factors. It is also apparent that, in relation to several of the peptides discussed here, the evidence for a primary – or even an actual role – in feeding is sometimes to be questioned. It is essential that more thorough analyses of behavior accompanies the highly technical assays that link a peptide to a regulatory process largely on the basis of anatomical localization and whether food intake is stimulated or suppressed after non-physiological, exogenous administration. The research literature in this area is overwhelming in its scope and scale; it is hoped that the brevity of these notes will illuminate rather than conceal.

List of Abbreviations

AMY	amygdala
ARC	arcuate nucleus
nor-BNI	*nor*-binaltorphimine
BS	brain stem
DH	dorsal hippocampus
DMN	hypothalamic dorsomedial nucleus
DRN	dorsal raphe nuclei
β-FNA	β-funaltrexamine
LC	locus ceruleus
LH	lateral hypothalamus
NAcc	nucleus accumbens
NTS	nucleus of the solitary tract
PVN	paraventricular nucleus
SN	substantia nigra
SON	supraoptic nucleus
THAL	thalamus
VMN	hypothalamic ventromedial nucleus
VRN	ventral raphe nucleus
VTA	ventral tegmental area

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Peptide Receptor Compounds Available from Tocris

Bombesin Receptors

3237 BIM 23042
Selective neuromedin B receptor (BB_1) antagonist

1839 BIM 23127
NMB receptor antagonist. Also U-II receptor antagonist

3422 [D-Phe^{12},Leu^{14}]-Bombesin
Bombesin receptor antagonist

1789 GRP (human)
Endogenous GRP receptor agonist

0823 ICI 216,140
Potent Bombesin/Gastrin releasing peptide antagonist

2602 PD 176252
GRP (BB_2) and NMB (BB_1) receptor antagonist

Calcitonin and Related Receptors

3419 AC 187
Potent and selective amylin receptor antagonist

3418 Amylin
Endogenous peptide agonist for amylin receptors (AMY_{1-3})

Cholecystokinin (CCK) Receptors

CCK_1 Receptor

2411 A-71623
Potent and selective CCK_1 agonist. Suppresses feeding

3423 AR-R 15849
Potent and selective CCK_1 agonist

3456 Anti-CCK_1
Antibody recognizing CCK_1

3457 Anti-CCK_1 (mouse)
Antibody recognizing mouse CCK_1

2304 Devazepide
Selective, orally active CCK_1 receptor antagonist

2190 SR 27897
Potent and selective CCK_1 antagonist

CCK_2 Receptor

3458 Anti-CCK_2
Antibody recognizing CCK_2

2607 CI 988
Potent and selective CCK_2 antagonist

3006 Gastrin I (human)
Selective CCK_2 agonist

1018 LY 225910
Potent CCK_2 antagonist

1524 LY 288513
Selective CCK_2 antagonist

2608 PD 135158
Potent and selective CCK_2 antagonist

1408 YM 022
Highly potent, selective non-peptide CCK_2 antagonist

Non-selective CCK

1323 Butabindide oxalate
Potent, competitive inhibitor of CCK-inactivating serine protease

1150 CCK Octapeptide, non-sulfated
Non-sulfated form of CCK octapeptide

1166 CCK Octapeptide, sulfated
C-terminal octapeptide of CCK

Galanin Receptors

2699 AR-M 1896
Selective GAL_2 agonist

3466 Anti-GAL_1 (C Term)
Antibody recognizing GAL_1 (C´ terminus)

3467 Anti-GAL_1 (internal)
Antibody recognizing GAL_1 (internal region)

3468 Anti-GAL_2
Antibody recognizing GAL_2

3469 Anti-GAL_3
Antibody recognizing GAL_3

3008 Galanin (porcine)
Galanin receptor agonist

1450 Galanin (1-15) (porcine, rat)
Galanin receptor agonist peptide

2696 Galanin (1-29) (rat, mouse)
Non-selective galanin receptor agonist

1179 Galanin (1-30) (human)
Modulator of neurotransmission

1451 Galanin (2-29) (rat)
Selective GAL_2 peptide agonist

3425 M40
Potent, non-selective galanin receptor antagonist

2697 M617
Selective GAL_1 agonist

2698 M871
Selective GAL_2 antagonist

Ghrelin Receptors

3033 Cortistatin-8
Ghrelin receptor antagonist

3374 Cortistatin 14
Endogenous neuropeptide; binds GHS-R and sst_1 - sst_5

1463 Ghrelin (human)
Endogenous ghrelin receptor agonist

1465 Ghrelin (rat)
Endogenous ghrelin receptor agonist

1346 des-Gln^{14}-Ghrelin (rat)
Endogenous ghrelin receptor ligand

2260 [Des-octanoyl]-Ghrelin (human)
Major circulating form of ghrelin; devoid of activity at ghrelin receptor but is active *in vivo*

1922 **[D-Lys^3]-GHRP-6**
Ghrelin receptor antagonist
2261 **L-692,585**
Potent, non-peptide ghrelin receptor agonist
1946 **[D-Arg^1,D-Phe^5,D-Trp^{7,9},Leu^{11}]-Substance P**
Potent ghrelin receptor full inverse agonist. Also antagonist at other neuropeptide receptors. Anticancer *in vitro*
2308 **Tabimorelin hemifumarate**
Potent, orally active ghrelin receptor agonist

Glucagon and Related Receptors

GIP Receptors

2084 **GIP (human)**
Potent insulinotropic gut hormone
2257 **GIP (1-39)**
Highly potent insulinotropic peptide

Glucagon Receptors

2216 **des-His^1-[Glu^9]-Glucagon (1-29) amide**
Glucagon receptor antagonist
2311 **L-168,049**
Potent, orally active human glucagon receptor antagonist

Glucagon-Like Peptide 1 Receptors

2081 **Exendin-3 (9-39) amide**
Potent GLP-1 receptor antagonist
1933 **Exendin-4**
Potent GLP-1 receptor agonist
3266 **GLP-1 (9-36) amide**
Metabolite of GLP-1-(7-36) (Cat No. 2082)
1851 **Glucagon-like peptide 1 (1-37) (human, rat)**
Endogenous pancreatic peptide
2082 **Glucagon-like peptide 1 (7-36) amide (human, rat)**
Potent insulinotropic peptide
2094 **Oxyntomodulin**
Endogenous gut peptide; modulates feeding and metabolism

Glucagon-Like Peptide 2 Receptors

2258 **GLP-2 (human)**
Endogenous hormone; displays intestinotrophic activity
2259 **GLP-2 (rat)**
Endogenous hormone; displays intestinotrophic activity

Growth-hormone Releasing Hormone Receptors

1187 **GRF (ovine)**
Stimulates growth hormone release

Secretin Receptors

1918 **Secretin (human)**
Gastrointestinal peptide
1919 **Secretin (rat)**
Gastrointestinal peptide

Insulin and Insulin-like Receptors

1819 **Demethylasterriquinone B1**
Selective insulin RTK activator
3435 **Insulin (human) recombinant, expressed in yeast**
Endogenous peptide agonist
2768 **PQ 401**
IGF-IR inhibitor

Leptin Receptors

2985 **LEP (116-130) (mouse)**
Synthetic leptin peptide fragment

Malanin-concentrating Hormone Receptors

3434 **[Ala^{17}]-MCH**
Potent, non-selective MCH receptor agonist

Melanocortin Receptors

1831 **HS 014**
Selective MC_4 receptor antagonist
1832 **HS 024**
Highly potent MC_4 receptor antagonist
3426 **JKC 363**
Potent and selective MC_4 receptor antagonist
3476 **Anti-MC_2**
Antibody recognizing MC_2
3477 **Anti-MC_3**
Antibody recognizing MC_3
3438 **MCL 0020**
Selective MC_4 receptor antagonist
2566 **Melanotan II**
High affinity melanocortin receptor agonist
2584 **α-MSH**
Endogenous melanocortin receptor agonist
3013 **[Nle^4,D-Phe^7]-α-MSH**
Melanocortin receptor agonist
3424 **γ1-MSH**
Selective MC_3 receptor agonist
3420 **SHU 9119**
MC_3 and MC_4 receptor antagonist
3032 **THIQ**
Potent and selective MC_4 receptor agonist

Neuropeptide Y Receptors

2707 **BIBP 3226 trifluoroacetate**
Mixed NPY Y_1 and NPFF receptor antagonist
1700 **BIIE 0246 formate**
Potent, selective non-peptide NPY Y_2 antagonist
2177 **BVD 10**
Highly selective Y_1 antagonist; devoid of Y_4 agonist activity
2035 **BWX 46**
Highly selective Y_5 agonist
2199 **CGP 71683 hydrochloride**
Highly selective and potent non-peptide NPY Y_5 receptor antagonist
1486 **GR 231118**
Potent NPY Y_1 antagonist/NPY Y_4 agonist. Binds to NPFF receptors
1382 **L-152,804**
Potent, selective non-peptide NPY Y_5 antagonist
1153 **Neuropeptide Y (human, rat)**
Influences feeding and sexual behavior
1173 **Neuropeptide Y (porcine)**
Influences feeding and sexual behavior
1177 **Neuropeptide Y 13-36 (porcine)**
Y_2 receptor agonist
1176 **[Leu^{31},Pro^{34}]-Neuropeptide Y (human, rat)**
NPY Y_1 receptor agonist
3436 **[D-Trp^{34}]-Neuropeptide Y**
Potent NPY Y_5 agonist; stimulates feeding *in vivo*
2155 **NTNCB hydrochloride**
Potent and selective non-peptidic Y_5 antagonist
1154 **Pancreatic Polypeptide (human)**
NPY Y_4 agonist; involved in gastrointestinal tract function
1365 **[cPP$^{1-7}$,NPY$^{19-23}$,Ala^{31},Aib^{32},Gln^{34}] -hPancreatic Polypeptide**
Potent, selective neuropeptide Y Y_5 agonist
2200 **PD 160170**
Selective non-peptide NPY Y_1 antagonist
1618 **Peptide YY (3-36)**
Selective Y_2 receptor agonist
3432 **S 25585**
Potent, selective NPY Y_5 antagonist

Neurotensin Receptors

1998 **JMV 449**
Potent neurotensin receptor agonist
2309 **SR 142948**
Highly potent NT receptor antagonist

Opioid Receptors

μ Receptors

Agonists

1171 **DAMGO**
Selective μ agonist
1055 **Endomorphin-1**
Potent and selective μ agonist

Antagonists

1560 **CTAP**
Selective and potent μ antagonist
1578 **CTOP**
Highly selective, potent μ antagonist

δ Receptors

Agonists

1431 **DPDPE**
Selective δ agonist
0764 **SNC 80**
Highly selective non-peptide δ agonist

Antagonists

0899 **BNTX maleate**
Standard $δ_1$ selective antagonist
0820 **ICI 174,864**
δ selective peptide antagonist

κ Receptors

Agonists

2134 **Salvinorin A**
Highly potent and selective κ-opioid agonist
0495 **(±)-U-50488 hydrochloride**
Standard selective κ agonist

Antagonists

0347 ***nor*-Binaltorphimine**
Standard κ selective antagonist
0794 **DIPPA hydrochloride**
Selective irreversible κ antagonist

1282 GNTI dihydrochloride
Potent, selective κ antagonist

NOP Receptors

Agonists

1780 NNC 63-0532
Potent non-peptide NOP agonist; brain penetrant
0910 Nociceptin
Endogenous NOP agonist

Antagonists

2598 (±)-J 113397
Potent and selective NOP antagonist
1552 UFP-101
Potent, selective silent antagonist for NOP

Orexin Receptors

OX_1 Receptors

1960 SB 334867
Selective non-peptide OX_1 antagonist
1963 SB 408124
Selective non-peptide OX_1 antagonist

OX_2 Receptors

2142 [Ala^{11},D-Leu^{15}]-Orexin B
Potent, selective OX_2 receptor agonist
3483 Anti-OX_2
Antibody recognizing OX_2
3371 TCS OX2 29
Potent and selective OX_2 antagonist

Non-selective OX

1455 Orexin A (human, rat, mouse)
Endogenous agonist at OX_1 and OX_2
1456 Orexin B (human)
Endogenous agonist at OX_1 and OX_2
1457 Orexin B (mouse)
Endogenous agonist at OX_1 and OX_2
3482 Anti-OX_1 and OX_2
Antibody recognizing OX_1 and OX_2

Tachykinin Receptors

NK_1 Receptors

2400 FK 888
High affinity NK_1 receptor antagonist
1669 GR 73632
Potent, selective NK_1 agonist
0868 L-732,138
Potent, selective NK_1 antagonist
1145 L-733,060 hydrochloride
Potent NK_1 antagonist
3479 Anti-NK_1
Antibody recognizing NK_1
1635 RP 67580
Potent and selective NK_1 antagonist
1784 Spantide I
Selective NK_1 antagonist
1178 [Sar^9,Met(O$_2$)^{11}]-Substance P
Potent, selective NK_1 agonist

NK_2 Receptors

1668 GR 64349
Potent, selective NK_2 agonist
1667 GR 94800
Potent, selective NK_2 antagonist
1274 GR 159897
Non-peptide, potent NK_2 antagonist
1632 MEN 10376
Potent, selective NK_2 antagonist
1640 [bAla^8]-Neurokinin A(4-10)
NK_2 agonist
3228 [Lys^5,MeLeu^9,Nle^{10}]-NKA(4-10)
Selective NK_2 agonist

NK_3 Receptors

1376 SB 218795
Potent, selective non-peptide NK_3 antagonist
1393 SB 222200
Potent, selective non-peptide NK_3 antagonist. Brain penetrant
1068 Senktide
Tachykinin NK_3 agonist

Other Tachykinin Receptors

1152 Neurokinin A (porcine)
Endogenous tachykinin peptide
1156 Substance P
Sensory neuropeptide, inflammatory mediator
1946 [D-Arg^1,D-Phe^5,D-Trp^{7,9},Leu^{11}]-Substance P
Substance P analog and broad spectrum neuropeptide receptor antagonist/inverse agonist. Anticancer *in vitro*

Other Peptide Receptors

3339 CART (62-76) (rat, human)
Neuromodulating neuropeptide fragment; inhibits food intake *in vivo*

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TOCRIS bioscience
www.tocris.com

UK:
Phone: + 44 (0)117 916 3333
Fax: + 44 (0)117 916 3344
customerservice@tocris.co.uk
Tocris House, IO Centre, Moorend Farm Avenue,
Avonmouth, Bristol, BS11 0QL, UK

US:
Phone: 800-421-3701
Fax: 800-483-1993
customerservice@tocrisusa.com
16144 Westwoods Business Park,
Ellisville, Missouri 63021 USA