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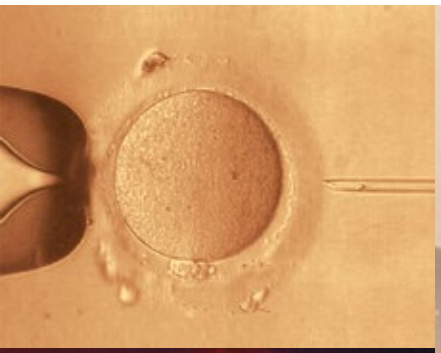

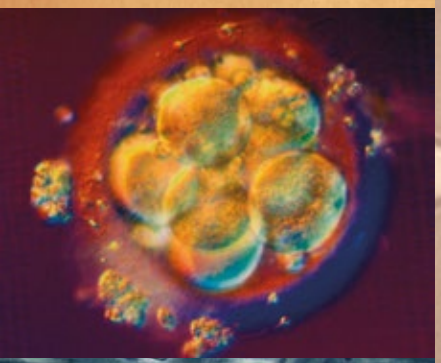

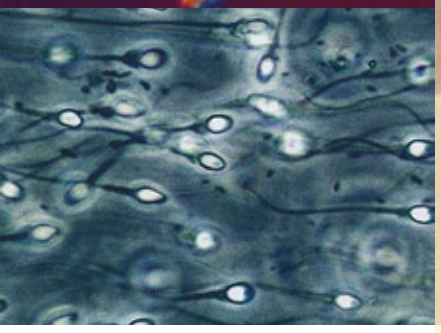

Neuropeptide Regulation of Appetite and Reproduction

Small CJ, Bloom SR, Stanley SA

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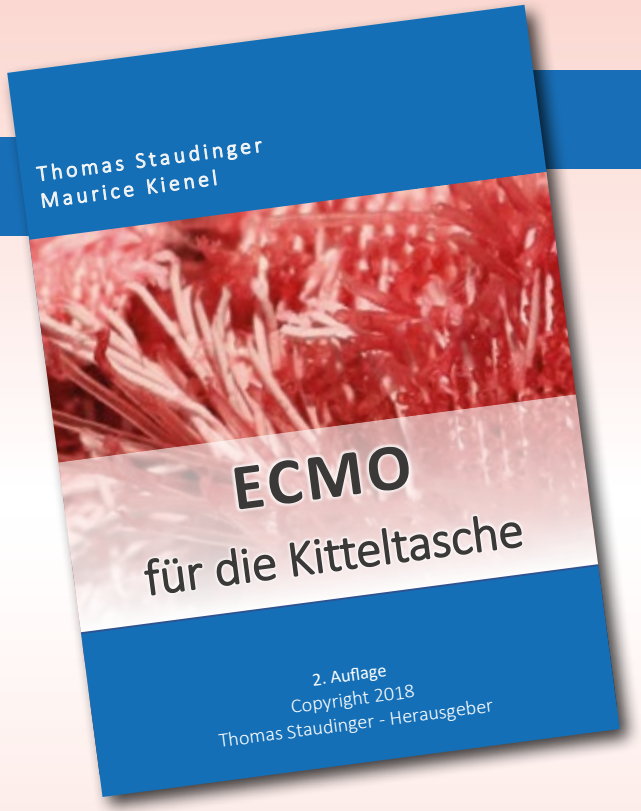

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Neuropeptide Regulation of Appetite and Reproduction*

C. J. Small, S. A. Stanley, S. R. Bloom

It is now recognised that appropriate regulation of reproduction, energy intake and energy expenditure, and thus maintenance of body weight and fertility, relies on complex hypothalamic neuro-circuitry. Feeding and reproductive function are closely linked. During times of under nourishment and falling body fat the reproductive axis is down regulated. Circulating factors and hypothalamic circuits co-ordinate these responses. Leptin has been described to be an important peripheral signal that indicates body fat stores to the hypothalamus and thus links nutrition and reproduction. Leptin acts by altering neuropeptide circuits in the hypothalamus, which alter gonadotrophin releasing hormone (GnRH) release and food intake. The importance of key neuropeptide systems identified in rodents is now being established in man. Notably mutations in the melanocortin MC4 receptor are found in up to 4 % of the morbidly obese whilst in a proportion of patients with anorexia nervosa mutations have been identified in the agoutirelated peptide (AgRP) gene, which codes for an endogenous antagonist of this receptor. Intranasal administration of a melanocortin fragment known to activate the MC4 receptor decreases adiposity in humans. The melanocortin system has been shown to influence the reproductive axis in rodents. However, the role of the melanocortin system in the control of reproduction in humans remains to be established. Since the discovery of leptin, attention has also been focused on peripheral signals that regulate reproduction, food intake and energy expenditure, either directly or via feedback on hypothalamic circuits. Notable new discoveries in this area include the gastric hormone ghrelin. Circulating ghrelin stimulates food intake in rodents and humans although an influence on the reproductive axis is yet to be reported.

***Keywords**: hypothalamus, leptin, melanocortins, ghrelin, food intake*

Neuropeptidregulation von Appetit und Reproduktion.** Mittlerweile gilt es als anerkannt, daß eine entsprechende Regulation der Reproduktion die Energieaufnahme und -abgabe und demnach die Aufrechterhaltung des Körpergewichts und der Fertilität von einem komplexen hypothalamischen Neurokreislauf abhängig sind. Ernährung und Reproduktion stehen in einem sehr engen Verhältnis zueinander. Bei Unterernährung und sinkendem Körperfett ist die reproduktive Funktion verringert, zirkulierende Faktoren und ein hypothalamischer Kreislauf koordinieren diesen Response. Leptin wurde als wichtiges peripheres Signal beschrieben, das im Hypothalamus die Speicherung von Körperfett anzeigt und somit eine Verbindung zwischen Ernährung und Reproduktion darstellt. Leptin wirkt, indem es den Neuropeptid-Kreislauf im Hypothalamus verändert, welcher die Freisetzung des Gonadotropin-releasing-Hormons (GnRH) und die Nahrungsaufnahme modifiziert. Die Bedeutung von Schlüssel-Neuropeptidsystemen, die bei Nagetieren festgestellt wurden, konnte nun auch beim Menschen manifestiert werden. Bemerkenswerte Mutationen im Melanocortin-MC4-Rezeptor wurden bei bis zu 4 % der Patienten mit morbider Adipositas festgestellt, wohingegen bei Patienten mit Anorexia nervosa Mutationen in den Agoutirelated Peptid (AgRP)-Genen entdeckt wurden, die für einen endogenen Antagonisten dieses Rezeptors kodieren. Eine intranasale Verabreichung von Melanocortin, bekannt dafür, den MC4-Rezepor zu aktivieren, führt bei Menschen zu einer Verringerung der Adipositas. Es wurde festgestellt, daß das Melanocortin-System die Reproduktion bei Nagetieren beeinflußt. Wie auch immer, die Rolle des Melanocortin-Systems ist in der Kontrolle der Reproduktionsmedizin fest verankert. Seit der Entdeckung von Leptin wurde die Aufmerksamkeit auch auf periphere Signalwege gelegt, die die Reproduktion, Nahrungsaufnahme und Energieabgabe, entweder direkt oder über Feedback auf den hypothalamischen Kreislauf, regulieren. Beachtliche neue Entdeckungen in diesem Zusammenhang betreffen das aus der Magenschleimhaut stammende Hormon Ghrelin. Zirkulierendes Ghrelin stimuliert die Nahrungsaufnahme bei Nagetieren und beim Menschen, obwohl ein Einfluß auf die Reproduktion bis jetzt noch nicht beschrieben wurde.* ***J Reproduktionsmed Endokrinol 2004; 1(1): 13–9.

***Schlüsselwörter**: Hypothalamus, Leptin, Melanocortin, Ghrelin, Nahrungsaufnahme*

The mechanisms by which adipose tissue mass is signalled to the central nervous system (CNS) are only now being delineated. Circulating peptides and hormones whose levels correlate with fat mass signal to hypothalamic neurones. These in turn initiate the response to control food intake and energy expenditure. Feeding and reproductive function are closely linked. During times of under nourishment and falling body fat the reproductive axis is down regulated. Circulating factors and hypothalamic circuits co-ordinate these responses. Leptin has been described to be an important peripheral signal that indicates body fat stores to the hypothalamus and may link nutrition and reproduction.

The identification of leptin arose from examination of two naturally occurring, obese mutant mice, *ob/ob* and *db/db*. Although originally identified over thirty years ago, the nature of their defect was unclear until 1995 when the *ob* gene product was identified as leptin [1]. Leptin is a 16 kDa, 146 amino acid protein preceded by a secretory sequence that is expressed and secreted from adipose tissue in most mammals including humans. The leptin protein folds into a cytokine-like structure.

Circulating leptin concentrations are directly proportional to adiposity in both animals and man (Fig. 1) correlating better with total fat mass than with body weight [2]. However, circulating levels are higher in females than males, even after controlling for adiposity. Leptin is present in cerebrospinal fluid (CSF), at levels less than a tenth of the circulating concentration. As circulating leptin

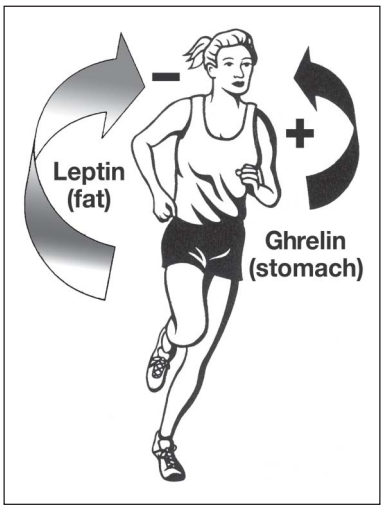

Figure 1. Schematic representation of the role of two circulating hormones that alter appetite and reproductive function. Circulating leptin concentrations are directly proportional to adiposity and acts within the hypothalamus to limit food intake. Ghrelin, a 28 amino acid peptide, was recently identified as the endogenous agonist of the growth hormone secretagogue receptor (GHS-R). Ghrelin is synthesised in the stomach and acts within the hypothalamus to stimulate food intake. Whilst the role of leptin on reproductive function is weil characterized, ghrelin remains to be investigated.

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increases, the CSF:plasma leptin ratio falls, suggesting leptin uptake into the CSF becomes less efficient and that there is a saturable transport mechanism [3].

Within the CNS leptin binding sites have been identified. The leptin receptor gene encodes a single transmembrane receptor belonging to the class I cytokine receptor family. Subsequent work revealed multiple splice variants of OB-R with variable c-terminal portions. The functioning form appears to have a large extracellular domain, of 816 amino acids, and a long intracellular region of 303 amino acids, in contrast to the shorter intracellular domains of the non-functioning receptors. The longer, functioning form of the leptin receptor is less abundant than the short form. Leptin receptor mRNA is found at low levels in almost all tissues examined where the short form is most abundant [4]. However, in the hypothalamus, the long leptin receptor predominates and is found particularly in the ventromedial nucleus (VMN), paraventricular nucleus (PVN) arcuate nucleus (ARC) and dorsomedial nucleus (DMN) areas thought to be important in the regulation of body weight [5]. Within the ARC leptin receptors are abundant on neuropeptide Y (NPY)/ AgRP neurons [6] and α-melanocyte stimulating hormone (α-MSH) α-MSH/cocaine and amphetamine regulated transcript (CART) neurons [7], neuropeptides that control both food intake and GnRH release.

The importance of leptin as a signal of fat mass is seen in the *ob/ob* and *db/db* mice. *Ob/ob* mice fail to produce leptin [1], in the *db/db* mouse truncation of the intracellular domain of the leptin receptor leads to defective signalling and leptin resistance [8]. As leptin levels rise with increasing fat mass it acts to regulate energy homeostasis, to limit energy intake and increase energy expenditure. In the absence of leptin or leptin signalling, this negative feedback does not occur and without a brake on food intake and energy expenditure both *ob/ob* and *db/db* mice become hyperphagic, obese and hypothermic. In the *ob/ob* mouse administration of leptin decreases body weight demonstrating the presence of functional leptin receptors. Leptin deficient humans have been identified [9, 10]. They too lack the negative feedback signal of increasing leptin

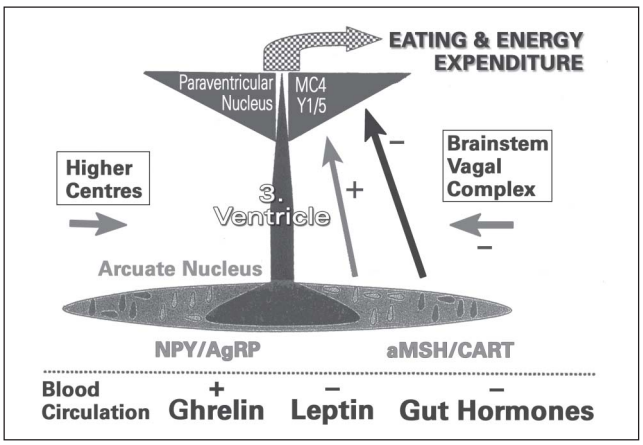

Figure 2. A diagrammatic representation of the hypothalamic circuits that influence food intake and reproductive function. Hypothalamic circuits controlling feeding behaviour, energy expenditure, and GnRH release are extremely complex. The arcuate nucleus (ARC) is a key hypothalamic nucleus, potentially accessible to circulating hormones, for example, leptin and ghrelin. In the ARC, orexigenic neurons co-synthesizing NPY and AgRP and anorectic neurons co-synthesizing melanocortins and cocaine and amphetamine regulated transcript (CART) .These neurons project widely to interact with neurons in other nuclei including the paraventricular nucleus (PVN) and lateral hypothalamus (LH). The ARC nucleus also sends projections to hypothalamic nuclei rich in GnRH neurons, for example, the medial preoptic area.

and are therefore hyperphagic, obese and hyperinsulinaemic and appear to respond to exogenous leptin [11]. Interestingly both the *ob/ob* and *db/db* mice are infertile. In the *ob/ob* mice exogenous leptin completely reverses the obesity syndrome and restores fertility [12].

Leptin falls dramatically in starvation. The genetic absence of leptin as in the *ob/ob* mouse or failure of it's signalling, as in the *db/db* mouse are animal models of low circulating leptin. Many of the neuroendocrine and other abnormalities observed in these mice, namely, the suppression of the gonadal axis [12], somatotrophic axis [13] and immune function [14] and stimulation of the hypothalamo-pituitary adrenal axis, are similar to the consequences of starvation. Prevention of the starvation-induced fall in leptin by replacement blunts these changes [14, 15].

Adequate nutrition is vital for reproduction. Both chronic malnutrition and short-term food deprivation suppress fertility [16] and delay puberty [17, 18] in animals and humans. Negative energy balance, associated with strenuous exercise, may also reduce gonadotrophins. Leptin has been postulated to be a circulating factor, which communicates body fat stores to the CNS hypothalamic pathways. Leptin has been shown to directly modulate GnRH release [19]. In addition, leptin has been found to alter many neurotransmitters and neuropeptides that regulate hypothalamic GnRH release and food intake.

Hypothalamic circuits controlling feeding behaviour, energy expenditure and GnRH release are extremely complex (for review [20]) (Fig. 2). The list of neuropeptide effectors responding to circulating factors is extensive. Many orexigenic signals promote weight gain by stimulating appetite and inhibiting energy expenditure. In addition, many alter GnRH release. The converse is true of anorectic signals. The ARC is a key hypothalamic nucleus, potentially accessible to the circulation and thus leptin. In the ARC orexigenic neurons co-synthesizing NPY and AgRP [21] and anorectic neurons co-synthesizing melanocortins and cocaine and amphetamine regulated transcript (CART) [22, 23] project widely to interact with neurons in other nuclei including the paraventricular nucleus (PVN) and lateral hypothalamus (LH). The ARC nucleus also sends projections to hypothalamic nuclei rich in GnRH neurons, for example the medial preoptic area. The contribution to body weight homeostasis and the reproductive system of key hypothalamic neuropeptides is reviewed below.

Neuropeptide Y

Neuropeptide Y (NPY) is a 36 amino acid neuropeptide that is abundant in the rat CNS, and particularly in hypothalamic nuclei such as the ARC and PVN [20]. NPY is one of the most potent orexigenic peptides identified [24, 25]. CNS injection of NPY activates c-fos expression in the PVN [26]. NPY administration in rats directly into the cerebral ventricles or hypothalamus stimulates food intake [24, 27], whilst chronic administration causes obesity [28]. NPY expression in the ARC is increased by food deprivation [29], by absent or reduced leptin signalling [6, 29] and ghrelin administration [30] and reduced by leptin administration [31]. In addition, immunoneutralisation of endogenous NPY blocks the normal feeding pattern seen in rats [32].

Despite these findings, mice lacking NPY have normal feeding patterns [33]. Other circuits compensate for loss of NPY signalling in this circumstance. *Ob/ob* mice lacking NPY have attenuated hyperphagia and obesity so NPY is necessary for the full manifestation of leptin deficiency [34]. Also Y_2 receptor null mice are obese and hyperphagic, but have normal feeding responses to NPY, suggesting

that this may be an auto-inhibitory receptor [35]. There is also evidence that NPY inhibits energy expenditure by an action on brown adipose tissue [36] and via inhibition of the thyroid axis [37].

There is a considerable body of evidence supporting a role for NPY in the control of the reproductive axis at the hypothalamo-pituitary level. Immunoreactive NPY neurons are found in close proximity to GnRH neurons in the medial pre-optic area [38]. NPY release from the hypothalamus is pulsatile and these are synchronised with GnRH [39]. *In vitro*, NPY stimulates the release of GnRH from medial basal hypothalamic explants [40] and *in vivo* administration of NPY increases plasma gonadotrophins in rodents [41] and in primates [42]. At the level of the pituitary, NPY potentiates GnRH-stimulated gonadotrophin release from anterior hemi pituitaries *in vitro* [43]. In addition CNS administration of NPY antisera or antisense oligonucleotides to NPY mRNA diminishes pulsatile GnRH secretion [44, 45]. The effects of NPY are, however, dependant on the hormonal environment, as in the absence of gonadal steroids, NPY inhibits plasma LH and FSH [46].

Recently, peptide YY (PYY) has been demonstrated to inhibit food intake [47]. PYY is produced by endocrine cells of the gastrointestinal tract and circulating levels are regulated both by body weight and food intake [48]. NPY Y_2 receptors, which bind PYY [49], are regulated by the steroid environment, increasing in the presence of oestrogen and decreasing when progesterone is added [50]. *In vitro*, PYY suppresses GnRH pulse frequency [51] but the effects of PYY on gonadotrophin release *in vivo* are not known.

Opioid Peptides

There is considerable evidence demonstrating the importance of opioid peptides, in particular β-endorphin and dynorphinin [52] in the control of the hypothalamo-pituitary gonadal axis (H-P-G axis) [53]. β-endorphin is derived from pro-opiomelanocortin (POMC). β-endorphin immunoreactive fibres synapse with GnRH-immunoreactive soma and dendrites in the medial preoptic area and are adjacent to GnRH-containing nerve terminals in the median eminence [54]. In contrast to the stimulatory action of NPY, β-endorphin inhibits the release of GnRH from medial basal hypothalamic explants *in vitro*, partly via stimulation of GABA release [55]. In addition, central injection of opioids and agonists at the mu (μ), kappa (κ) and delta (δ) opioid receptors, abolish the preovulatory GnRH and LH surges and inhibit ovulation [56]. ARC POMC mRNA decreases immediately prior to the LH surge in rodents suggesting a tonic inhibitory action on gonadotrophin release by opioid peptides. Reduction of this inhibitory tone contributes to the neural mechanisms which initiating the preovulatory LH surge [57, 58].

Opioid peptides influence appetite. CNS administration of opioid agonists into the third ventricle [59] and intraPVN [60] stimulate food intake whilst μ and κ receptor antagonists suppress food intake [61, 62]. Anatomical and functional evidence suggests interaction between the opioid and NPY systems. NPY immunoreactive neurons are found in close apposition to β-endorphin immunoreactive neurons in the median eminence and synapse with both β-endorphin immunoreactive soma and dendrites [63]. CNS NPY injection stimulates β-endorphin release from the basal hypothalamus [64]. In addition, NPY reduces POMC mRNA [65] and the opiate receptor antagonist naloxone increases preproNPY mRNA [66].

At the level of the gonadotroph, the actions of opioid peptides are diverse. In the presence of high oestrogen, β-endorphin stimulates LH release from the pituitary gland, but is inhibitory when progesterone is present. Thus, β-endorphin might act to potentate the LH surge as circulating levels of oestrogen rise [67].

Gamma Aminobutyric Acid

Gamma aminobutyric acid (GABA) has been demonstrated to influence the control of GnRH and LH secretion in several species. Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme in the synthesis of GABA and GnRH neurons receive synaptic inputs from GAD-containing neuronal processes [68] and themselves possess GABA A and B receptor subunits [69]. In addition, these GAD mRNA expressing cells appear to be steroid sensitive [70]. In the female, there is a 40 % reduction in GAD mRNA content on the afternoon of proestrus. *In vitro*, GABA has diverse effects. It inhibits the release of GnRH from hypothalamic explants [71] but both GABA and the $GABA_A$ receptor agonist muscimol, stimulate basal release of GnRH from immortalised GnRH neurons, GT1-7 cells. The $GABA_B$ receptor agonist, baclofen diminishes potassium induced GnRH release from these cells [72]. *In vivo*, the effects of GABA appear to be steroid dependant. In ovx and ovx, steroid replaced female rodents, central injection of GABA increases plasma LH but the GABA agonist muscimol can suppress LH in certain conditions. In primates, GABA blocks the LH surge and delays puberty and the pubertal delay is reversed by the GABA antagonist, bicuculline [73]. It is possible in certain species that GABA may exert a tonic inhibition of the hypothalamo-pituitary gonadal axis.

Glucagon-like Peptides

Glucagon-like peptides (GLPs), including GLP-1, GLP-2 and oxyntomodulin, are produced by differential post-translational processing of proglucagon in the intestine and the CNS. Glucagon-like peptide 1 (GLP-1) is a 29 amino acid amidated peptide derived from processing of proglucagon in the L cells of the intestine. GLP-1 immunoreactivity is also present in the soma of neurons in the nucleus of the solitary tract and medullary reticular nucleus with projections to the paraventricular and periventricular areas of the hypothalamus.

GLP-1, given ICV, potently inhibits food intake in fasted rats [74]. This effect is blocked by the GLP-1 receptor antagonist exendin (9-39). Exendin (9-39) has no effect on food intake when given alone in fasting rats, but greatly increases food intake in satiated rats, suggesting that endogenous GLP-1 tone is important in maintaining satiety [74]. Similarly GLP-2 [75] and oxyntomodulin [76] have been shown to reduce food intake when injected ICV after an overnight fast or at the start of the dark phase, when rats normally eat rapidly. Intravenous GLP-1 infusion in healthy humans has been shown to reduce food intake from a free-choice meal. GLP-1 receptor null mice have normal feeding patterns [77]. The normal feeding phenotype emphasises the complexity of feeding regulation, with other systems able to compensate for missing signals.

GLP-1 receptors have been identified in the medial and lateral preoptic areas, regions rich in GnRH neurons. GLP-1 stimulates the release of GnRH from the immortalised GnRH cell line GT1-7 and injection into the third ventricle stimulates plasma LH in male rats [78]. The GLP-1 receptor knock-out mouse has delayed puberty suggesting that GLP-1 is important in the control of the hypothalamo-

pituitary gonadal axis [79]. The role of GLP-2 and oxyntomodulin in the control of GnRH release remains to be established.

The Melanocortin peptides and Agouti related peptide (AgRP)

Melanocortins are peptides derived from the precursor polypeptide proopiomelanocortin (POMC). Melanocortin neurons are key mediators of the actions of leptin [80–82]. Five melanocortin receptors have been identified but only the MC_3 and MC_4 receptors are expressed in the CNS [81, 82]. The melanocortin system is unique in biology in having an endogenous antagonist as well as endogenous agonists. The melanocortin alpha-melanocyte-stimulating hormone (alpha-MSH) is an agonist and agouti-related protein (AgRP) is an antagonist at the MC_3 and MC_4 receptors [83, 84]. Evidence from rodent models and man suggests that the balance between activation of hypothalamic MC_4 receptor by alpha-MSH and antagonism by AgRP is crucial in maintaining normal body weight [81, 82, 85]. Administration into the CNS of alpha-MSH reduces food intake, whilst AgRP causes hyperphagia [83] and, on repeated administration, obesity [86]. AgRP is synthesized in the hypothalamus and was identified by its homology to the mouse protein agouti. Agouti expression determines coat colour and is normally confined to hair follicles. When expressed in all cells, in the agouti (A^y/a) mouse, agouti causes an obese and hyperphagic phenotype [80, 81]. It was subsequently found that mice lacking the MC_4 receptor [87], over-expressing AgRP [88] or lacking POMC (and hence producing no alpha-MSH) [89] were also obese and hyperphagic. One can conclude that tonic MC_4 receptor signalling is required to limit feeding and fat accumulation.

The melanocortin system is also important in regulation of energy expenditure. MC_3 and MC_4 receptor null mice have metabolic defects, which promote adiposity [90, 91]. Independent from its feeding effects, chronic AgRP treatment increases epididymal fat pad weight and reduces uncoupling protein 1 in brown adipose tissue, limiting the capacity for thermogenesis [86]. Melanocortin signalling also regulates the thyroid axis, which is stimulated by central melanocortin receptor activation and inhibitited by antagonism [86, 92].

Recent studies in leptin-deficient *ob/ob* mice suggest that, in addition to hypothalamic α-MSH, circulating α-MSH may be an important mediator of stimulation of energy expenditure by leptin. Leptin administration approximately doubled circulating α-MSH concentration. Further, systemic administration of an α-MSH analogue resulted in normalization of the reduced metabolic rate, accelerated weight loss during fasting and partial restoration of thermoregulation during cold challenge [93].

The importance of the melanocortin system in man is now well established. Mutations in POMC [94], prohormone convertase 1 (an enzyme required for POMC processing) [95] and the MC_4 receptor [96] have all been identified in individuals with early onset, severe obesity. The MC4 receptor mutations are particularly important as, like in rodents, obesity is expressed as a dominant trait. Heterozygous mutations were found in 4 % of one large series of morbidly obese individuals but in no non-obese controls [97]. AgRP mutations were also recently identified in individuals with anorexia nervosa [98]. Recent therapeutic trials of a melanocortin fragment ($MSH/ACTH_{4–10}$), administered intranasally, demonstrated a modest reduction in body weight and body fat in normal weigh individuals [99].

Anatomical evidence suggests that the melanocortin system might influence functions other than energy homeostasis. MC_4-R mRNA is expressed at high levels in hypothalamic nuclei regulating feeding and in the medial preoptic nucleus (MPOA), an area rich in GnRH neurons [100]. MC3-R is also expressed within the anterolateral, lateral and MPOA [101]. In addition, both α-MSH [102] and γ-MSH immunoreactivity are also present in these areas [102]. Anterograde tracing studies have demonstrated ARC neurons expressing NPY projecting to both the MPOA and the median eminence [21] where they lie in close proximity to GnRH expressing neurons. Since 95 % of ARC NPY neurons also contain AgRP immunoreactivity, it is likely that AgRP immunoreactive fibres are closely apposed to GnRH neurons [21]. This suggests GnRH neurons may be under multiple regulatory influences by the melanocortin system, α-MSH, γ-MSH and AgRP. AgRP increases GnRH release from medial basal hypothalamic explants and stimulates plasma gonadotrophins and gonadal steroids following ICV injection in male rats [103]. However, agouti mice [80, 81], POMC KO mice [89] and MC_4-R KO mice [87] are all fertile suggesting that the melanocortin system is not essential for reproduction. However, other investigators have suggested some role for the melanocortins in the control of the gonadal axis [103–106].

It is currently unknown whether melanocortin receptors are expressed on GnRH neurones *in vivo*. Recent studies have suggested that both MC_4-R and MC_3-R are expressed in the GnRH clonal cell line, GT_1-7 [107, 108]. There is evidence that both receptors may be involved in regulation of the hypothalamo-pituitary gonadal axis in rodents. The pre-ovulatory surge is diminished by treatment with the relatively MC_4-R specific antagonist, HS014 [109] in ovx, steroid replaced females. However, the MC_3-R preferring γ-MSH increases GnRH release *in vitro* and preoptic area injection of γ-MSH stimulates plasma LH in male rats [108]. Further work is need in this area.

Cocaine and Amphetamine Regulated Transcript (CART)

Hypothalamic cocaine and amphetamine regulated transcript (CART) has been identified as an anorectic neuropeptide [22, 110]. In the ARC nucleus, fasting increases CART mRNA whilst reduced levels in *ob/ob* mice are normalized by leptin treatment. Further, ICV administration of anti CART antibodies stimulates feeding whilst CART inhibits feeding [22, 111]. However, the hypothalamic actions of CART may be more complex than first suspected. Feeding stimulation was recently reported after CART administration directly into hypothalamic nuclei, suggests an additional CART orexigenic circuit [112]. Intra-hypothalamic CART was not associated with movement abnormalities that have been reported in response to ICV CART [22] which may have previously masked feeding stimulation [112].

Anatomical evidence would suggest CART peptide may have a direct action on hypothalamic releasing factor release. *In situ* hybridisation experiments have demonstrated CART mRNA in the parvocellular division of the PVN, an area rich in both TRH and CRH neurons [110]. Immunohistochemistry has also shown high density CART peptide immunoreactivity in this region [113]. CART transcript and peptide are also present in the SON and ARC, hypothalamic nuclei known to project to GnRH neurons [22]. Following ICV injection CART, the majority of c-fos immunoreactive cells were found in the medial parvocellular division of the PVN [110] but activated cells were

also present in the ARC and SON. Central injection of CART peptide may thus activate hypothalamic neuroendocrine circuits [111].

It has recently been demonstrated that CART peptide influences the release of a number of hypothalamic releasing factors and neuropeptides. CART peptide *in vitro* significantly stimulated the release of hypothalamic CRH, TRH and NPY and significantly reduced secretion of GnRH [111]. However, Lebrethon et al showed opposite effects and demonstrated CART to reduce the GnRH interpulse interval *in vitro* [114]. In addition, the leptin-induced increase in GnRH release was blocked using CART antiserum suggesting leptin's actions on GnRH are mediated by CART [115]. As a result of these findings, the actions of central administration of CART on circulating pituitary hormones were investigated. ICV injection of CART significantly stimulated plasma prolactin, ACTH and corticosterone. However, no change in plasma LH was observed [111]. These results suggest CART peptide plays a role in the control of hypothalamo-pituitary axes although its role in the control of the gonadotrophin axis remains to be fully elucidated.

Ghrelin

Ghrelin, a 28 amino acid peptide, was recently identified as the endogenous agonist of the growth hormone secretagogue receptor (GHS-R) [116]. Surprisingly it is predominantly synthesized in the stomach. As well as stimulating growth hormone, several lines of evidence suggest a separate role for ghrelin as a circulating factor, in many ways antagonizing the actions of leptin, to promote food intake and weight gain. Systemic or ICV ghrelin administration potently and dose dependently stimulates feeding in rodents [30, 117, 118]. Although numerous peptides stimulate feeding when given ICV, this was the first identification of a systemically active orexigenic hormone. Ghrelin has an acyl side chain that is essential for biological action [119] and that may facilitate passage into the CNS.

Ghrelin may have a role in stimulating food consumption at an individual meal. The onset and offset of feeding stimulation by systemic ghrelin is rapid in rodents [118], whilst a recent study has reported a dramatic increase in food intake at a single sitting during ghrelin infusion in man [120]. Ghrelin rises on fasting and falls rapidly on refeeding [118] with sharp peaks occurring just pre-meals in man [121]. Further, fasting induced feeding in rodents is inhibited by CNS administration of anti-ghrelin antibodies [30]. However, longer term changes in ghrelin in relation to energy balance suggest that it may form part of a dynamic feedback system with leptin in the regulation of body weight. Chronic administration of ghrelin in rodents stimulates continuing hyperphagia and weight gain [30, 118, 122]. This is independent of GH stimulation. In contrast to GH, ghrelin increases rather than reduces adiposity and is effective in GH-deficient rats [30, 118]. In addition to stimulating hyperphagia systemic ghrelin increases respiratory quotient in rodents, suggesting a reduced fatty acid oxidation and a switch to glycolysis for energy expenditure [117]. These changes favour fat deposition. Circulating ghrelin is reduced in obese individuals [123] and in response to chronic overfeeding [124], but is increased by chronic negative energy balance induced by increased exercise [124] or in anorexia nervosa [125]. Ghrelin appears to act, at least in part, by stimulating the same orexigenic circuits in the hypothalamic ARC that are inhibited by leptin. Ghrelin stimulates neuronal activation [30, 126] NPY [30, 127] and AgRP [128] synthesis in the ARC, whilst antibodies and antagonists to NPY and AgRP inhibit ghrelin-induced feeding [30, 127]. Ghrelin itself is also synthesized at very low concentrations in the ARC. The relative contributions of hypothalamic and circulating ghrelin to energy balance remain to be established. There have been few reports of the effect of ghrelin on reproductive function. Intracerebroventricular administration of ghrelin has been reported to suppress LH pulse frequency in ovx, oestrogen treated female rats [129]. However, bolus ghrelin administration to men does not alter circulating LH or FSH [130]. Ghrelin could be another circulating factor that controls food intake and reproduction.

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