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The role of melanocortins in body weight regulation: opportunities for the treatment of obesity

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Abstract

Five G-protein-coupled melanocortin receptors (MC_1–MC_5) are expressed in mammalian tissues. The melanocortin receptors support diverse physiological functions, including the regulation of hair color, adrenal function, energy homeostasis, feed efficiency, sebaceous gland lipid production and immune and sexual function. The melanocortins (adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), β-MSH and γ-MSH) are agonist peptide ligands for the melanocortin receptors and these peptides are processed from the pre-prohormone proopiomelanocortin (POMC). Peptide antagonists for the melanocortin MC_1, MC_3 and MC_4 receptors include agouti-related protein (AgRP) and agouti. Diverse lines of evidence, including genetic and pharmacological data obtained in rodents and humans, support a role for the melanocortin MC_3 and MC_4 receptors in the regulation of energy homeostasis. Recent advances in the development of potent and selective peptide and non-peptide melanocortin receptor ligands are anticipated to help unravel the roles for the melanocortin receptors in humans and to accelerate the clinical use of small molecule melanocortin mimetics.

Keywords: Melanocortins; Melanocortin receptor; Neuropeptide; ACTH (adrenocorticotropic hormone); AgRP (agouti-related protein); POMC (proopiomelanocortin); Energy homeostasis; Obesity; Sexual function

1. Introduction

Melanocortins were discovered as bioactive substances of the pituitary that modulate skin color in frogs (Smith, 1916). Since these initial findings, a wealth of discoveries further advanced our understanding of the broad-based physiological functions of melanocortins and it is anticipated that melanocortin-based drug-development will find useful applications. Potential clinical indications pursued with melanocortin ligands include: the treatment of obesity, sexual dysfunction, skin cancer, acne, inflammatory disease, neuronal regeneration, pain and memory dysfunction. In this review, we will summarize current pharmacological and genetic evidence, which justifies the pursuit of the development of small molecule mimetics of the melanocortins, and we will address some possible therapeutic applications, with a focus on the treatment of obesity and sexual dysfunction.

2. Melanocortins and their receptors

2.1. Melanocortins

The proopiomelanocortin (*POMC*) gene encodes a 31–36-kDa pre-prohormone, from which seven mature peptide hormones [adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), β-MSH, γ-MSH, corticotropin-like intermediate lobe peptide (CLIP), β-lipotropin, and β-endorphin (Fig. 1)] are derived via post-translational cleavage by various prohormone convertases. POMC processing occurs in a tissue-specific manner yielding four distinct melanocortin peptides (ACTH, α-, β- and γ-MSH), with the core sequence (-Met-Glu or Gly-His-Phe-Arg-Trp-; Bertagna, 1994). Processing of POMC in the

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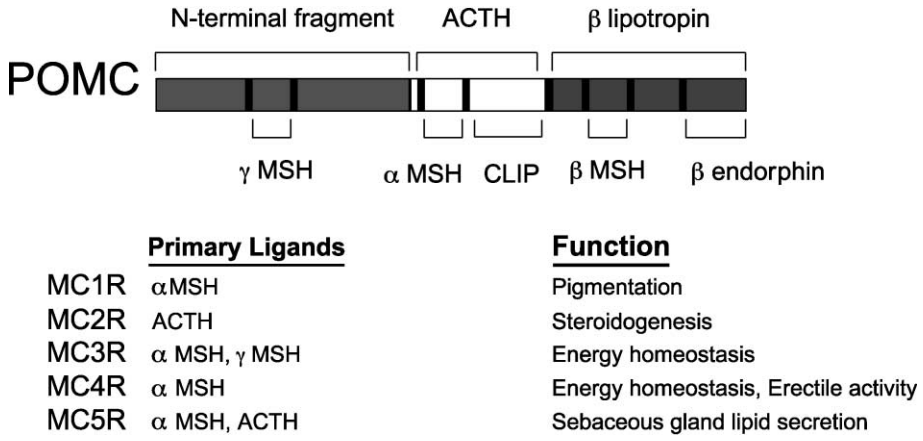

Fig. 1. POMC structure and processed peptides. G-protein-coupled melanocortin receptors (MCRs), their proposed ligands and functions.

anterior lobe of the pituitary gland yields ACTH, a 39-amino-acid peptide known to act upon the adrenal to stimulate corticoidsteroidgenesis. The 13-amino-acid peptide, α-MSH, represents the most amino terminal portion of ACTH. The 12-amino-acid peptide, γ-MSH, is derived from the N-terminal fragment of POMC, while β-MSH is processed from β-lipotropin. Both α- and γ-MSH peptides are synthesized in the intermediate lobe of the pituitary. α-MSH can be further processed by amidation of the C-terminus and acetylation of the N-terminus and can stimulate pigmentation in skin melanocytes. POMC is also expressed in various regions of the brain, gut, placenta, and pancreas and may be processed to form β-MSH (central nervous system (CNS), pituitary) and β-lipotropic hormone (pituitary).

2.2. Melanocortin receptors

Molecular cloning identified five G-protein-coupled receptors which, when activated by one or more melanocortins, signal via $G\alpha_s$ to increase intracellular cAMP (for review, see Wikberg, 1999). The α-MSH responsive receptor on melanocytes is designated the melanocortin MC_1 receptor and the ACTH receptor in the adrenal gland is termed melanocortin MC_2 receptor. A large number of alleles of the melanocortin MC_1 receptor affect skin and hair color (Valverde et al., 1995). Three other melanocortin receptors have been characterized (MC_3–MC_5). The five melanocortin receptors form a subfamily of G-protein-coupled receptors, which are about 42–67% identical to each other at the amino acid level (Table 1). Interspecies homology among mammals for each receptor is in the range of 75–94%, with the melanocortin MC_4 receptor being the most conserved and the melanocortin MC_1 receptor the least. The melanocortin receptors are most homologous to the cannabinoid receptors, and they are among the smallest G-protein-coupled receptors (296 to 361 amino acids; Tatro, 1996). All melancortin receptors contain the conserved DRY motif at the junction of transmembrane 3, contain sites for N-linked glycosylation in the extracellular N-terminal domain, and contain a C-terminal cysteine that may function as a fatty acid acylation site. The melanocortin receptors lack several conserved features found in most G-protein-coupled receptors including one or both cysteine residues in the first and second extracellular loops and the prolines usually found in the fourth and fifth transmembrane domains.

Table 1
Homology among the human melanocortin receptors and their relative potency of activation by various melanocortins

Receptor	Homology (%)				Potency of agonist activation
	MC_1	MC_2	MC_3	MC_4	
MC_1					α-MSH = ACTH > β-MSH>γ-MSH
MC_2	42				ACTH
MC_3	50	49			α-MSH = β-MSH = γ-MSH = ACTH
MC_4	53	48	64		α-MSH = ACTH>β-MSH>γ-MSH
MC_5	47	47	61	67	α-MSH>ACTH>β-MSH>γ-MSH

3. Expression patterns

3.1. POMC and hypothalamic neuronal pathways

The *POMC* gene is primarily expressed in the pituitary and CNS. In the pituitary, POMC mRNA is synthesized in the anterior and neurointermediate lobes, and due to differential processing, the corticotroph cells in the anterior lobe secrete ACTH and β-lipotropin, whereas the melanotroph cells of the intermediate lobe secrete α-MSH, β-MSH, CLIP, β-endorphin and γ-lipotropin (Smith and Funder, 1988). In the brain, POMC cell bodies are found in the hypothalamic arcuate nucleus and nucleus of solitary tract in the caudal brainstem (Jacobowitz and O'Donohue, 1978; Watson et al., 1978; Joseph et al., 1983). POMC neurons project broadly to many brain regions, including those important for regulating

energy homeostasis such as various hypothalamic and brainstem nuclei (Jacobowitz and O'Donohue, 1978; Bagnol et al., 1999; Fig. 2). POMC mRNA is also detectable in the spinal cord and dorsal root ganglion, raising the possibility that POMC peptides can be made in other central and peripheral sites (Plantinga et al., 1992; Van der Kraan et al., 1999; Jeannotte et al., 1987). There appear to be multiple forms of the POMC transcripts. Hypothalamus and pituitary POMC mRNA encode a secreted protein while peripheral tissues express a truncated POMC mRNA without coding for a signal sequence (Jeannotte et al., 1987; Clark et al., 1990).

Within the hypothalamus, the integrating center for energy balance, POMC neurons have extensive interactions with other pathways (Fig. 2). Melanocortinergic terminals are found in various hypothalamic regions such as paraventricular, dorsomedial hypothalamic nucleus, arcuate nucleus and lateral hypothalamic area (Bagnol et al., 1999; Elias et al., 1999). The POMC neurons in the arcuate nucleus express leptin receptors, through which leptin regulates POMC expression (Hakansson et al., 1998; Schwartz et al., 1997; Mizuno et al., 1998). The arcuate nucleus POMC neurons also express neuropeptide Y_1 and Y_5 receptors, receive neuropeptide Y innervations and interact with neuropeptide Y/agouti-related protein (AgRP) neurons locally (Broberger et al., 1997, 1999; Fuxe et al., 1997; Bagnol et al., 1999; Csiffary et al., 1990). In addition, POMC is co-localized with another anorexic peptide cocaine- and amphetamine-regulated transcript (CART), but not with neuropeptide Y/AgRP neurons in the arcuate nucleus (Hahn et al., 1998; Elias et al., 1998a,b; Mihaly et al., 2000). These cells have been shown to send projections to sympathetic preganglionic neurons in the thoracic spinal cord, presumably involved in the regulation of energy expenditure (Elias et al., 1998a,b).

3.2. Melanocortin MC_1–MC_5 receptor expression

Melanocortin MC_1 and MC_2 receptors are expressed primarily in a few peripheral tissues. The melanocortin MC_1 receptor was first identified in melanoma cells, but is also expressed in normal melanocytes, (Chhajlani and Wikberg, 1992; Loir et al., 1999), and keratinocytes (Chakraborty et al., 1999; Table 2). A number of other tissue/cell types have been reported to express the melanocortin MC_1 receptor including the pituitary, testis, corpus luteum, placenta, macrophages, endothelial cells, glioma cells and astrocytes (for references, see Wikberg, 1999). The presence of melanocortin MC_1 receptor mRNA and immunoreactivity were also reported in the periaqueductal grey, but not detectable in other brain regions (Xia et al., 1995). The melanocortin MC_1 receptor is expressed in the same tissues as the endogenous antagonist encoded by *agouti*. Indeed, several *extension* mouse mutants are defective in melano-

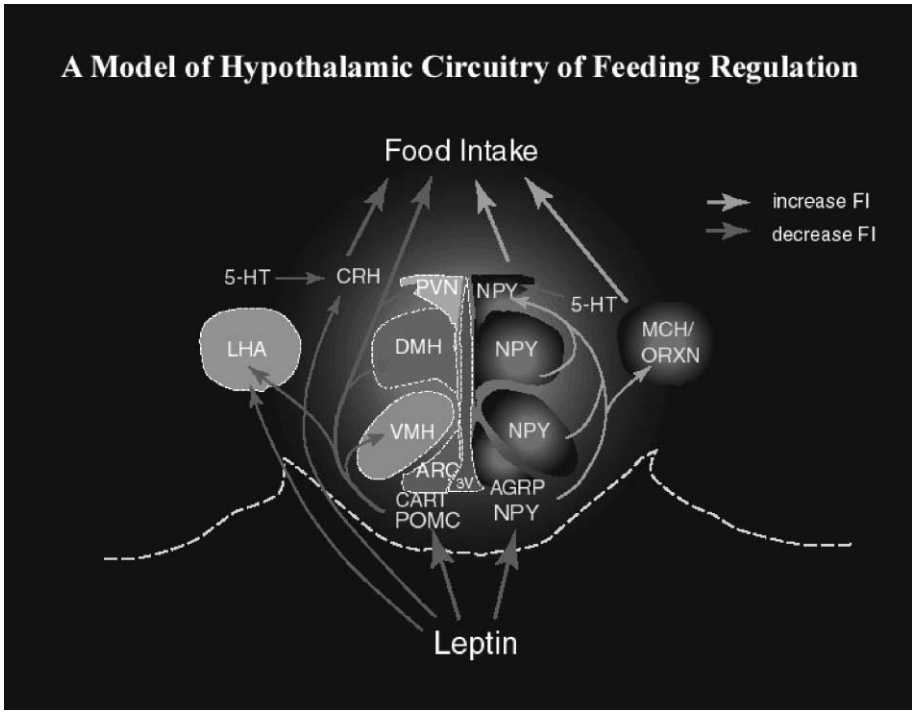

Fig. 2. Schematic representation of hypothalamic nuclei involved in the control of food intake, energy expenditure and diverse endocrine functions. Leptin can modulate leptin receptor function on hypothalamic neurons expressing CART (cocaine- and amphetamine-regulated transcript) and POMC (proopiomelanocortin) (red) or AgRP (agouti-related peptide) and NPY (neuropeptide Y) (green). These neurons project to the arcuate nuclues (ARC), ventral medial hypothalamus (VMH), paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). Serotonin and CRH (corticotropin-releasing hormone) are among the neuronal pathways that can modulate the activity of this neuronal circuitry.

Table 2
Expression of melanocortin receptors[a]

Receptor	Human tissues	Additional rodent tissues[b]
MC_1	Skin (melanocyte, sebocyte), monocytes, placenta, testis, ovary, brain	
MC_2	Adrenal, skin, testis	Adipose, thymocyte, B lymphocyte
MC_3	Brain (hypothalamus), placenta, gut, heart, testis	Brain (pituitary, ventral tegmental)
MC_4	Brain (wide spread)	Spinal cord
MC_5	Skin (lachrymal, sebaceous, eccrine, apocrine glands), adrenal, adipose, lymphocyte, pituitary, lung, kidney, ovary, uterus, breast, testis	Brain, liver, heart, muscle, eye, bone, adrenal, pancreas, prostate, harderian gland

[a] Summary of data was from LifeSpan BioSciences GPCR database, http://www.lsbio.com/.
[b] Only lists tissues if expression of melanocortin receptor was observed in rodents and not reported in human samples.

cortin MC_1 receptor function, leading to lack of responsiveness to α-MSH and alterations in pigmentation. The decreased melanocortin MC_1 receptor tone alters the ratio of eumelanin (brown/black) to phaeomelanin (yellow/red) pigment production, causing red hair in humans and lack of pigmentation in skin following exposure to UV light (reviewed by Schaffer and Bolognia, 2001). In addition, various melanoma cell lines which are responsive to α-MSH express melanocortin MC_1 receptor. The melanocortin MC_1 receptor is also expressed in inflammatory cells such as neutrophils and monocytes, dermal microvascular endothelial cells and the melanocortin MC_1 receptor may mediate at least some of the anti-inflammatory actions of α-MSH. The melanocortin MC_2 receptor is expressed most abundantly in the adrenal cortex, in both the zona fasciculata (source of glucocorticoids) and the zona glomerulosa (source of the mineralocorticoids) where the melanocortin MC_2 receptor mediates the action of ACTH (Xia and Wikberg, 1996). Melanocortin MC_2 mRNA was also detected in a few scattered cells in the adrenal medulla, however, the function of these cells is unknown. In addition to the adrenal gland, the melanocortin MC_2 receptor is expressed in white adipose tissue (Boston and Cone, 1996), skin (Slominski et al., 1996), and mononuclear leukocytes (Johnson et al., 2001). The melanocortin MC_2 receptor is expressed on adipocytes of various mammals and mediates the lipolytic actions of ACTH; however, in primates, neither ACTH nor α-MSH appears to mediate lipolysis.

Melanocortin MC_3 and MC_4 receptors are expressed in brain and both are involved in regulating energy metabolism. A comparison [Nle^4,D-Phe^7]α-MSH (α-NDP-MSH) radioligand binding to mouse brain sections showed that melanocortin MC_3 receptor binding sites appear to be more abundant than melanocortin MC_4 receptor binding sites in mouse brain (Fig. 3). The highest melanocortin MC_3 receptor expression level was found in the hypothalamic regions and limbic system, including the ventromedial hypothalamic nucleus, arcuate nucleus, preoptic nucleus, lateral hypothalamic area and posterior hypothalamic area (Roselli-Rehfuss et al., 1993). Melanocortin MC_3 receptor mRNA is also present in the septum, hippocampus, thalamus, amygdala, and brainstem, including the central linear nucleus of raphe and ventral tegmental area (Roselli-Rehfuss et al., 1993). Receptor autoradiography revealed intense melanocortin MC_3 receptor binding in the shell of the nucleus accumbens (Lindblom et al., 1998). It is note-

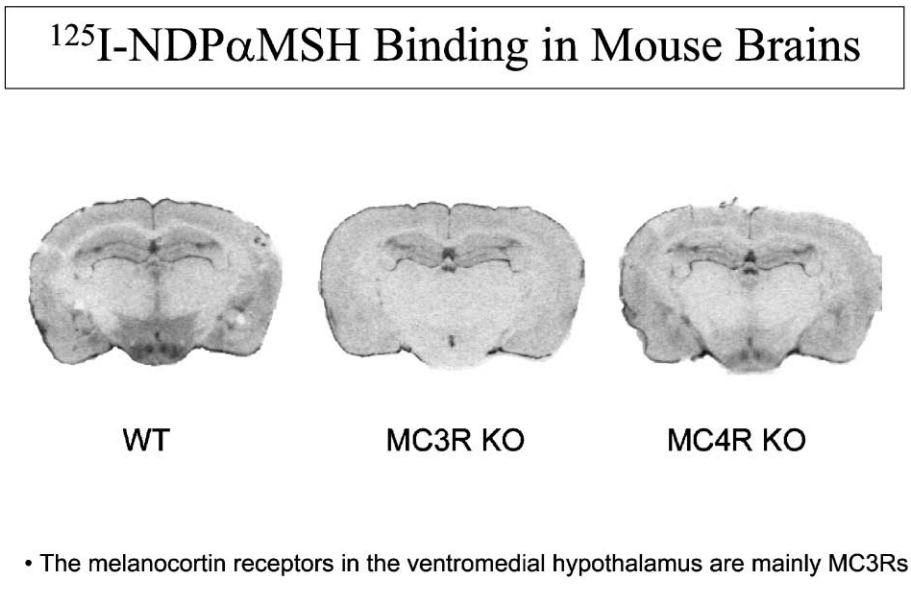

Fig. 3. Representation of ^{125}I-α-NDP-MSH binding in coronal mouse brain sections of C57Bl/6J/129 Svj hybrid wildtype, *Mc3r* − / − and *Mc4r* − / − mice.

worthy that the POMC and AgRP neurons in the arcuate nucleus selectively express melanocortin MC_3 receptors, but not melanocortin MC_4 receptors, suggesting a role for this receptor in the feedback regulation of melanocortinergic circuitry in the brain (Bagnol et al., 1999; Jegou et al., 2000). It has been reported that the melanocortin MC_3 receptor is expressed in several peripheral tissues such as the placenta, gut, and heart, stomach and pancreas and at lower levels in testis, ovary, muscle and kidney (Gantz et al., 1993; Chhajlani, 1996). Melanocortin MC_3 receptor mRNA was also detected in the early postnatal rat pituitary (Lorsignol et al., 1999). The altered body composition in *Mc3r* knock-out mice (see below) confirms a role for melanocortin MC_3 receptors in regulating energy homeostasis. Since γ-MSH preferentially activates melanocortin MC_3 receptors and intracerebroventricular (i.c.v.) administration of γ-MSH reduces blood pressure and heart rate, it appears that the melanocortin MC_3 receptor may also regulate cardiovascular functions (Versteeg et al., 1998).

In rodent brain, melanocortin MC_4 receptor mRNA appears to be less abundant, though more widely expressed than melanocortin MC_3 receptor mRNA. The melanocortin MC_4 receptor is widely distributed in virtually all the major brain regions including the cerebral cortex, hypothalamus, thalamus, brainstem, spinal cord (Mountjoy et al., 1994; Mountjoy and Wild, 1998; Van der Kraan et al., 1999; Cowley et al., 1999). Diverse lines of evidence implicate the melanocortin MC_4 receptor in regulating food intake and energy metabolism. Of particular interest is the observation that the highest level of melanocortin MC_4 receptor expression is observed in the hypothalamus, especially in the paraventricular nucleus and in the dorsal motor nucleus of the vagus in the caudal brainstem (Mountjoy et al., 1994). Such a distribution pattern correlates well with the brain sites displaying high sensitivity to melanocortin-regulated feeding behavior (Kim et al., 2000a; Williams et al., 2000). The melanocortin MC_4 receptor is thought to play a major role in regulating body weight since *Mc4r* −/− mice are obese, melanocortin MC_4 receptor agonists administered i.c.v. inhibit food intake, and obese humans have been identified with mutations in the melanocortin MC_4 receptor gene (see next sections).

Numerous tissues express the melanocortin MC_5 receptor. For example, melanocortin MC_5 receptor mRNA is detected in fat cells, kidneys, lung, lymphnodes, leukocytes, mammary glands, ovary, pituitary, testis, uterus, stomach, spleen, skeletal muscle, skin, bone marrow, esophagus, and spinal cord as well as in several exocrine and endocrine glands, including prostate glands, pancreas, adrenal gland, and thymus (Chhajlani, 1996; Van der Kraan et al., 1998; Chen et al., 1997; Labbe et al., 1994; Akbulut et al., 2001). High levels of expression of the melanocortin MC_5 receptor in several exocrine glands, notably the lacrimal, harderian and sebaceous glands, suggest a role in sebaceous gland lipid production. Low levels of melanocortin MC_5 receptor expression were also reported in brain (Chhajlani et al., 1993; Labbe et al., 1994; Fathi et al., 1995; Griffon et al., 1994), but the physiological function of the melanocortin MC_5 receptor in the brain remains unclear.

4. Genetics

4.1. Use of rodent genetic models to study the function of melanocortin receptors in the regulation of body weight

During the 1990s, a series of pharmacological and genetic experiments conclusively demonstrated that melanocortins modulate body weight through effects on food intake and energy expenditure (for review, see Cone, 1999). Initial data suggesting a role for melanocortins in body weight regulation came from an analysis of the obese agouti mouse. Agouti protein (also known as agouti signaling protein (ASIP) in humans) is a 131-amino-acid peptide, which is a competitive antagonist of the melanocortin MC_1 receptor. In mammals, agouti is expressed primarily in the skin where it acts in a paracrine manner to regulate fur pigmentation by spatial and temporal antagonism of the melanocortin MC_1 receptor. However, certain agouti mice, which contain mutations that lead to ectopic expression of agouti in the brain, develop obesity; apparently by antagonism of the melanocortin MC_4 receptor and possibly the melanocortin MC_3 receptor (Lu et al., 1994; Chen et al., 2000b). Klebig et al. thus proposed that the melanocortin MC_3 receptor and possibly the melanocortin MC_4 receptor would be likely candidates for ligand–receptor antagonism by agouti in these mice (Klebig et al., 1996; Tatro, 1996). Following the discovery of the agouti gene, a homologous gene was identified by database searching which encodes a protein termed agouti-related protein (AgRP; Shutter et al., 1997). AgRP is expressed in the adrenal gland, subthalamic nuclei, and the hypothalamus (Bicknell et al., 2001; Shutter et al., 1997). AgRP is an endogenous antagonist of the melanocortin MC_3 receptor and possibly an inverse agonist at melanocortin MC_4 receptors (Ollmann et al., 1997; Fong et al., 1997; Nijenhuis et al., 2001). I.c.v. injections of AgRP in rodents increase food intake for a surprisingly long time (Lu et al., 2001; Hagan et al., 2000). As predicted from the AgRP pharmacology, transgenic mice overexpressing *AgRP* are obese (Ollmann et al., 1997). Additional confirmation of the importance of the melanocortins in mediating body weight came with the construction of *POMC* knock-out mice, whose obesity can be reversed by treatment with a metabolically stable derivative of α-MSH (Yaswen et al., 1999). Finally, based on coat color selection, several genes have been identified that impact the function of the agouti protein. These include the mahogany protein, a single transmembrane domain polypeptide also known as attractin. Mahogany may function to support the action of agouti at the melanocortin MC_1 receptor, possibly by facilitating the presentation of agouti protein to its receptor (Miller et al., 1997; Nagle et al., 1999; Barsh et al., 2000; Kuramoto et al., 2001; Gunn and Barsh, 2000).

Confirmation of the role of melanocortin MC_4 receptor in obesity came from the analysis of *Mc4r* knock-out ($-/-$) mice (Huszar et al., 1997). Not only was the *Mc4r* $-/-$ mouse severely obese, but *Mc4r*+/ $-$ heterozygous mice displayed a milder obesity, suggesting that the extent of melanocortin MC_4 receptor signaling is important in maintaining normal body weight. *Mc4r* $-/-$ mice were hyperphagic, and display reduced oxygen consumption, indicative of a metabolic defect and may show altered metabolic behavior in response to dietary fat exposure (Ste. Marie et al., 2000; Chen et al., 2000a; Butler et al., 2000, 2001). Not surprisingly, given their severe obesity, the *Mc4r* $-/-$ mice develop hyperinsulinemia and hyperleptinemia, known risk factors for, or a possible consequence of obesity (Huszar et al., 1997). *Mc4r* $-/-$ mice are no longer sensitive to the elevation in metabolic rate induced by treatment with the potent non-selective melanocortin MC_1, MC_3, MC_4 and MC_5 receptor agonist, MTII (Chen et al., 2000a). *Mc4r* $-/-$ mice also have a reduced response to the anorectic actions of MTII, suggesting that most of the actions by melanocortins to modulate body weight are mediated by melanocortin MC_4 receptors (Marsh et al., 1999; Chen et al., 2000a). Interestingly, both the *Mc4r* and the *POMC* knock-out mice have significant increases in body length (Yaswen et al., 1999; Huszar et al., 1997).

The melanocortin MC_3 receptor is expressed predominantly in the hypothalamus where it is more abundant than the melanocortin MC_4 receptor (Roselli-Rehfuss et al., 1993), and an analysis of *Mc3r* $-/-$ mice suggests that the melanocortin MC_3 receptor plays a complementary role to the melanocortin MC_4 receptor in mediating melanocortin effects on body weight. Young *Mc3r* $-/-$ mice are not hyperphagic or significantly overweight, but they have increased adiposity and have an increased feed efficiency (Butler et al., 2000; Chen et al., 2000a). A satisfactory explanation for this phenotype has not yet been provided, although it does not appear that either motor activity, altered thyroid function or other endocrine abnormalities provide a mechanistic explanation for the *Mc3r* $-/-$ mouse. In conclusion, it appears that the melanocortin MC_4 receptor regulates food intake and energy expenditure, while the melanocortin MC_3 receptor regulates feed efficiency and partitioning of nutrients into fat. Kim et al. (2000a) described evidence for a role of the melanocortin MC_3 and MC_4 receptors in the regulation of the fasting-induced suppression of the hypothalamic–pituitary–thyroid axis. In addition, central melanocortin MC_3 and MC_4 receptors can regulate insulin action (Fan et al., 2000; Obici et al., 2001). In non-obese rats, 7-day central infusion of α-MSH enhanced insulin action on glucose uptake and reduced intra-abdominal fat, while the melanocortin MC_3/MC_4 receptor antagonist SHU9119 had the opposite effect. These data are consistent with a model in which central melanocortin receptors regulate energy intake, energy expenditure, and increase insulin sensitivity.

Although melanocortin MC_1 and MC_5 receptors are expressed at low levels in the brain, there is no evidence that these receptors play a role in mediating the effects of melanocortins on energy homeostasis. Indeed, the yellow agouti mutant mice lacking the melanocortin MC_1 receptor (the extension mutants) have an altered coat color, but do not have altered body weight (Robbins et al., 1993). Similarly, *Mc5r* $-/-$ mice have altered lipid production in various exocrine tissues leading to the defects in maintaining thermoregulation when wet, but no noticeable effects on body weight have been noted (Chen et al., 1997).

4.2. Human genetics and the melanocortin receptors

The characterization of a variety of rodent obesity models with altered melanocortin signaling suggests that melanocortins may play a significant role in regulating body weight in humans. If so, this suggests that agonists of melanocortin action would provide an effective anti-obesity therapy. Indeed, human genetic data provide conclusive evidence for the notion that the POMC/melanocortin MC_4 receptor pathway is an important modulator of body weight (see Table 3).

Two genome-wide scans found evidence for linkage of obesity to 2p21, a locus which includes POMC (Comuzzie et al., 1997; Hager et al., 1998). In a follow-up study, polymorphisms in *POMC* were used to map the 2p21 obesity locus to *POMC* with 95% confidence (Hixson et al., 1999). Another study of 87 early onset obese Italian children revealed that 3 had mutations in one of their *POMC* alleles, suggesting that defects in *POMC* may contribute to obesity (Del Giudice et al., 2000). In contrast, a study of 264 French sib-pairs, 379 unrelated obese patients, and 370 non-obese diabetic patients found no association between obesity and *POMC* mutations (Delplanque et al., 2000). In addition, QTL analysis of *POMC* to obesity in 212 patients failed to find any heterozygous mutations that are a major cause of early onset obesity (Echwald et al., 1999). However, POMC-derived peptides are clearly involved in regulating human body weight since two severely obese patients have been identified that are homozygous for *POMC* inactivation (Krude et al., 1998). Predictably, the phenotype of these patients includes ACTH insufficiency (no serum ACTH to activate the melanocortin MC_2 receptor), red hair (no α-MSH for eumelanin production eliminating dark hair and tanning via the melanocortin MC_1 receptor activation), and obesity (lack of α-MSH agonist tone).

Several investigators have found that up to 4% of severely obese humans has defects in the *MC4R* gene (Farooqi et al., 2000). Gu et al. (1999) described three allelic variants in an analysis of 190 obese patients. One of the novel allelic variants was functionally deficient when expressed in HEK293 cells, suggesting that its defect could account for the severe obesity (BMI>57) observed in this patient. Reminiscent of the *Mc4r*+/ $-$ heterozygous mice that are obese, these data suggest that haploinsufficieny for the melanocortin MC_4 receptor in humans may lead to obesity (Vaisse et al., 1998; Yeo et al., 1998; Farooqi et al.,

Table 3
Linkage analysis of human melanocortin pathway genes to obesity

Gene	Phenotype of study group	Reference
POMC	0/63 severely obese had a mutation in *POMC*	Dubern et al., 2001
	12/96 obese children had a mutation in *POMC*	Hinney et al., 1998
	2 severely obese individuals are *POMC* −/−	Krude et al., 1998
	Genome-wide scans finds linkage to *POMC*	Comuzzie et al., 1997
	Genome-wide scans finds linkage to *POMC*	Hager et al., 1998
	Obesity QTL linked to *POMC*, 95% confidence	Hixson et al., 1999
	3/87 early onset obese individuals have heterozygous *POMC* mutations	Del Giudice et al., 2000
	No linkage in 264 obese sib-pairs	Delplanque et al., 2000
	QTL analysis of 212 obese found no mutations associated with obesity	Echwald et al., 1999
MC4R	4/63 severely obese have heterozygous missense mutations	Dubern et al., 2001
	All 283 non-obese lack the mutations	
	RFLP analysis of 124 Quebec families found association with %fat	Chagnon et al., 1997
	Analysis of family members of patients with four *MC4R* mutations	Sina et al., 1999
	identified 19/43 were carriers of the mutation and obese	
	10 individuals with deletions of *MC4R* were not obese	Cody et al., 1999
	11/446 have heterozygous missense mutations leading to early onset obesity	Farooqi et al., 2000
	4% of morbidly obese has heterozygous missense mutations	Vaisse et al., 2000
	7/190 obese have *MC4R* mutations, only 1 is functionally inactive	Gu et al., 1999
	No association of mutations with obesity in 50 Japanese	Ohshiro et al., 1999
MC3R	Sequenced 2kb region of *MC3R* in 124>40 BMI obese and 85 average weight females	Li et al., 2000
	No variants in gene associated with obesity	
	Allelic frequency of two missense mutations the same in 308 diabetics and 218 normal patients	Hani et al., 2001
MC5R	RFLP analysis of 124 Quebec families found association with BMI	Chagnon et al., 1997
AGRP	1/63 severely obese has heterozygous missense mutation	Dubern et al., 2001
	Similar frequency seen in 283 controls	
ASIP	No mutations found in 12 lean or 12 obese Pima Indians	Norman et al., 1999

2000; Vaisse et al., 2000). The clearest evidence indicating a role for the melanocortin MC_4 receptor in obesity was obtained in families in which both nonsense and frameshift mutations in *MC4R* lead to dominantly inherited obesity (Gu et al., 1999; Hinney et al., 1999). Sina et al. (1999) also suggested that *MC4R* haploinsufficieny leads to obesity since he observed that in 19 family members, 4 individuals heterozygous for *MC4R* mutations were obese. Single strand conformational polymorphism (SSCP) analysis of 306 obese Germans revealed several mutations that appear to dominantly confer obesity. These included a 4-bp frameshift at codon 211, a nonsense mutation at codon 35, which apparently results in a dominant form of obesity, in as well as nine missense mutations in the *MC4R* gene that result in obesity (Hinney et al., 1999). However, Cody et al. (1999) found no evidence for haploinsuficiency in an analysis of patients with deletions of *MC4R*. This group noted that 10 individuals with deletions of *MC4R* were, on average, not different in their distribution of body weights than 17 individuals who had similar deletions on chromosome 18 that did not extend into *MC4R*. A modest ($N = 50$) study in Japan also failed to find any association with melanocortin MC_4 receptor mutations and obesity (Ohshiro et al., 1999).

In separate reports, an association between obesity and the genes encoding the antagonists of the MC receptors, AgRP or ASIP (Norman et al., 1999; Dubern et al., 2001) was not observed. In addition, sequencing of 124 extremely obese (BMI>40) and 85 normal weight women failed to find any *MC3R* alleles that were associated with obesity (Li et al., 2000) nor was any linkage found between *MC3R* and diabetes phenotype in two French family large cohorts (Hani et al., 2001). There is one report associating mutations in *MC5R* with obesity (Chagnon et al., 1997), but there are no reports of *MC1R, MC2R, MC3R, ASIP,* or *AGRP* mutations associated with obesity.

5. Receptor pharmacology

α-MSH, γ-MSH and ACTH are three major melanocortin peptides that bind and activate melanocortin MC_1, MC_3, MC_4 and MC_5 receptors, while ACTH is the only high affinity natural agonist for the melanocortin MC_2 receptor. The binding affinity for several natural ligands is listed in Table 4. The precise affinity may vary depending on the species origin of each receptor. For example, the melano-

Table 4
EC50 (nM) of ligands in activating melanocortin receptor-mediated cAMP increase, or binding affinity (nM) in the case of antagonists (underlined) (Cone et al., 1996; Huang et al., 2000; Kiefer et al., 1998; Tota et al., 1999; Yang et al., 1997, 1999)

	MC_{1b}	MC_2	MC_3	MC_4	MC_5
α-MSH	4	>1000	1	2	20
γ_2-MSH	40	>1000	6	300	600
ACTH-(1–24)	11	1	7	4	41
AgRP	>100	>100	1	1	>40
Agouti	3	100	190	50	>1000

cortin MC_5 receptor exhibits more profound species-dependent ligand binding affinity than other subtypes (Huang et al., 2000). In general, the melanocortin MC_2 receptor subtype is differentiated from other subtypes by its poor affinity for α-MSH. The melanocortin MC_3 receptor can be distinguished from other subtypes due to its moderate affinity for γ-MSH. However, this selectivity is not substantial, and therefore, any attempt to use γ-MSH as an melanocortin MC_3 receptor-selective ligand in pharmacological studies should be approached cautiously.

5.1. Peptide and non-peptide melanocortin receptor ligands; perspectives on the clinical development of melanocortin MC_4 receptor-selective compounds

As discussed in earlier sections, the central role of the melanocortin system in human physiology suggests that selective modulation of the melanocortin receptors represents a plausible strategy for pharmacological intervention in a diverse range of clinical indications. Both pharmacological and genetic criteria converge in support of melanocortin MC_4 receptor's pivotal role in feeding and energy homeostasis. More recently, a separate indication for melanocortin active drugs has emerged in the treatment of erectile dysfunction (Wessells et al., 2000a,b).

At a first approximation, a therapeutically successful melanocortin MC_4 receptor agonist should be highly selective and exhibit minimal, if any, activation at the remaining melanocortin receptors or other targets. The agent should have appropriate pharmacokinetic and pharmacodynamic profiles consistent with oral, once-daily dosing and adequate receptor occupancy to active melanocortin MC_4 receptors. As an agonist is sought, desensitization or loss of response with chronic drug treatment must be assessed. In addition, consideration must be given to unwanted, but potentially mechanism-based side effects that might include modulation of the cardiovascular system, the immune system and the CNS.

The development of novel and selective peptide agonists and antagonists for melanocortin receptors closely followed the identification of various melanocortin receptor subtypes (Table 5). α-MSH, a 13-amino-acid peptide, Ac-Ser^1-Tyr^2-Ser^3-Met^4-Glu^5-His^6-Phe^7-Arg^8-Trp^9-Gly^{10}-Lys^{11}-Pro^{12}-Val^{13}-NH_2, is a nonselective agonist at four melanocortin receptors, MC_1 and MC_3–MC_5. Extensive structure–function studies on this peptide hormone eventually resulted in a more potent and enzyme-resistant analog, α-NDP-MSH, that contains the "active core" fragment of melanocortin peptides with D-Phe substitution in position 7 (Sawyer et al., 1980). This high affinity but nonselective agonist, and its derivative labeled with the radioactive iodine, quickly became valuable research tools in studies on melanocortin receptors in vitro and in vivo. Subsequently, a smaller peptide, the lactam derived from the (4–10)-fragment of α-NDP-MSH was identified as an even more potent nonselective agonist at melanocortin MC_1, MC_3, MC_4 and MC_5 receptors, Ac-Nle^4-cyclo(5β->10ε)(Asp^5-His^6-D-Phe^7-Arg^8-Trp^9-Lys^{10})-NH_2 named MTII (Al-Obeidi et al., 1989). A rather conservative replacement of phenylalanine with 2-naphthylalanine in the MTII lactam ring yielded a high affinity antagonist for melanocortin MC_3 and MC_4 receptors and an agonist for melanocortin MC_1 and MC_5 receptors, Ac-Nle^4-cyclo(5β->10ε)(Asp^5-His^6-D-(2′)Nal^7-Arg^8-Trp^9-Lys^{10})-NH_2, named SHU9119 (Hruby et al., 1995). I.c.v. administration in rats of MTII reduced food intake and conversely administration of SHU9119 increased food intake and body weight (Fan et al., 1997; Grill et al., 1998; Murphy et al., 1998; Marsh et al., 1999; Chen et al., 2000a;

Table 5
Synthetic ligands for the melanocortin receptors (Adan et al., 1999; Bednarek et al., 2001a,b; Benoit et al., 2000; Schioth et al., 1997)

	Binding affinity, IC_{50} (nM)				cAMP activation, EC_{50} (nM)			
	hMC_1	hMC_3	hMC_4	hMC_5	hMC_1	hMC_3	hMC_4	hMC_5
α-MSH	4.3	19	19	120	0.45	0.73	1.6	19
NDP-α-MSH	0.26	3	3.7	1	0.35	0.12	0.14	0.33
MTII	0.4	1.6	0.07	0.89	0.22	0.74	0.45	2.9
SHU9119	0.7	0.23	0.06	0.09	0.15	antagonist K_B = 2.15 nM	antagonist K_B = 0.39 nM	0.12
MBP10	8900[a]	150	0.5	540	>3000[a]	antagonist K_B = 775 nM	antagonist K_B = 6.2 nM	530
D-Tyr^4-MTII	n.d.	204[b]	3.8 nM[b]	n.d.	n.d.	20.3 [b,*]	0.4 [b,*]	n.d.
Agonist #15	n.d.	490	4.3	4600	11[a]	50	0.56	1900
HS014	n.d.	25	1.5	16	n.d.	n.d.	n.d.	42
HS024	n.d.	2.6	0.57	0.39	n.d.	n.d.	n.d.	0.22
Ro27-3225	n.d.	n.d.	n.d.	n.d.	8	675	1	5800
Ro27-4680	n.d.	n.d.	n.d.	n.d.	42	not active	16 partial agonist	340
HP228 #	1.62	73.9	74.2	53.4	n.d.	n.d.	n.d.	n.d.

#, binding affinities are K_i values.
n.d., not determined.
[a] At MC1bR.
[b] rat receptors.
* β-galactosidase activity assay.

Vergoni and Bertolini, 2000; Adan and Gispen, 2000), while chronic antagonist treatment increased body weight (Skuladottir et al., 1999; Kask et al., 1998b). Moreover, the MTII peptide administered subcutaneously was shown to be a potent initiator of erections in men with psychogenic erectile dysfunction (Wessells et al., 1998, 2000a,b). Several analogs of SHU9119 were reported which are high affinity antagonists for the melanocortin MC_4 receptor with improved selectivity with respect to melanocortin MC_1, MC_3 and MC_5 receptors (Bednarek et al., 2001a). The most specific peptide was cyclo($COCH_2CH_2CO$-D-(2′)Nal^7-Arg^8-Trp^9-Lys^{10})-NH_2, named MBP10, a competitive antagonist at melanocortin MC_4 receptors with 125-fold selectivity over the melanocortin MC_3 receptor. This peptide had virtually no agonist potency at melanocortin MC_1, MC_3 and MC_4 receptors and only weak potency at melanocortin MC_5 receptors. Compounds with structures similar to that of MBP10, but with D-phenylalanine in position 7 instead of 2-naphthylalanine, were potent melanocortin MC_4 receptor agonists of improved selectivity over the other melanocortin receptors; e.g. agonist #15, cyclo($NHCH_2CH_2CO$-His^6-D-Phe^7-Arg^8-Trp^9-Glu^{10})-NH_2 (Bednarek et al., 2001b). The D-Tyr^4 analog of MTII is also an agonist with higher affinity for melanocortin MC_4 receptors than for melanocortin MC_3 receptors (Adan et al., 1999).

Several peptides cyclized via disulfide bridges increased food intake and body weight in rats. These compounds, HS014, HS024 and others, are melanocortin MC_4 receptor antagonists with moderate selectivity over melanocortin MC_3 receptors. The HS014 peptide, Ac-cyclo(*S*-*S*)(Cys^4-Glu^5-His^6-D-(2′)Nal)^7-Arg^8-Trp^9-Gly^{10}-Cys^{11})-Pro^{12}-Pro^{13}-Lys^{14}-Asp^{15}-NH_2, (Kask et al., 1998a), additionally, is a partial agonist at melanocortin MC_1 and MC_5 receptors, while the HS024 compound, Ac-cyclo(*S*-*S*)(Cys^3-Nle^4-Arg^5-His^6-D-(2′)Nal)^7-Arg^8-Trp^9-Gly^{10}-Cys^{11})-NH_2 (Kask et al., 1998b; Andersson et al., 2001), does not display agonist activity at melanocortin MC_1 and MC_3 receptors.

The linear peptide Ro27-46580, $CH_3CH_2CH_2CO$-His^6-D-(2′)Nal^7-Arg^8-Trp^9-Sar^{10}-NH_2, a selective melanocortin MC_4 receptor antagonist, also increased food intake in rodents when administered centrally (Benoit et al., 2000). A peptide of a related structure with D-Phe in position 7 was reported to be MC4R selective agonist, $CH_3CH_2CH_2CO$-His^6-D-Phe^7-Arg^8-Trp^9-Sar^{10}-NH_2, Ro27-3225 (Benoit et al., 2000). Another linear analog of α-MSH with the highest affinity for melanocortin MC_1 receptors, HP228, Ac-Nle^4-Gln^5-His^6-D-Phe^7-Arg^8-D-Trp^9-Gly^{10}-NH_2, was evaluated in clinical trials (Abou-Mohamed et al., 1995). HP-228 (30 μg/kg i.v.) resulted in cutaneous flushing, but had no significant effect on respiration or hemodynamics (Weinger et al., 1998).

Within the past several years, significant advances have been made in the design of peptidyl-privileged structure agonists for seven transmembrane receptors, including C5a receptor, ghrelin receptor and somatostatin sst1, sst2, sst4 and sst5 receptors (De Laszlo et al., 1997; Patchett et al., 1995; Berk et al., 1999). In addition to the above, non-peptide agonists have been identified for the angiotensin AT_1, CCK_1, bradykinin B_2 and vasopressin V_2 receptors by making structural changes to antagonist ligands (Patchett and Nargund, 2000 and references therein). The design of peptidyl-privileged structure agonists is based upon the well-known observation of commonly recurring structural units in receptor ligands. Termed privileged structures, both agonists and antagonists have been designed by their judicious derivatization (Evans et al., 1988).Tetrahydroisoquinoline melanocortin agonists, including the highly selective melanocortin MC_4 receptor agonists **1** and **2** (Fig. 4), are the first peptidyl-privileged structures to be described (Patchett et al., 1999; Van der Ploeg et al., submitted). Compound ***2*** is a potent melanocortin MC_4 receptor agonist and shows >200-fold binding and functional selectivity versus melanocortin MC_1, MC_3 and MC_5 receptors (Van der Ploeg et al., submitted; Table 6). In published patent applications, compounds such as **3**, **4**, **5** and **6** are claimed as melanocortin receptor agonists (Fig. 5; Melacure patent Kaulina et al., 2001; Trega patents Dines et al., 1999 and Hitchen

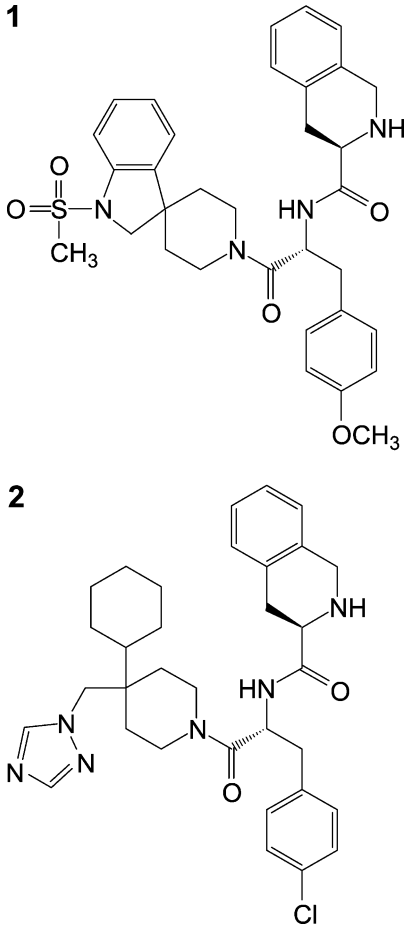

Fig. 4. Peptidyl-privileged structure agonists for melanocortin MC_4 receptor (MC4R).

Table 6
Binding IC_{50} and functional EC_{50} values for melanocortin MC_4 receptor agonist **2**

	IC_{50} (nM)[a]	EC_{50} (nM)[b]	%Activation at 10 μM[c] (%)
hMC1R	2100	1300	84
hMC2R	>10,000	–	0
hMC3R	540	1200	29
hMC4R	0.92	2.1	96
hMC5R	230	530	58

hMC1R = human melanocortin MC_1 receptor, etc.

[a] IC_{50} values were determined in a radioligand ([^{125}I]NDP-α-MSH) binding assay using cell membranes.

[b] EC_{50} values were determined by measuring cAMP concentrations post-incubation of compound **2** with intact cells expressing the melanocortin receptors.

[c] %Activation refers to levels of cAMP stimulation post-incubation at 10 μM in comparison with α-MSH.

et al., 2001). Activity data at the various melanocortin receptors for these compounds are awaited. Compounds **3** and **4** have been reported to reduce feeding and body weight following their i.c.v. administration.

The development of highly selective ligands represents an important step toward defining the biological function of melanocortin receptors. For example, while the nonselective agonist MTII is pro-erectile in humans (Wessells et al., 2000b), it has thus far been unclear which specific melanocortin receptors mediate this effect. Using the tretrahydroisoquinonline melanocortin MC_4 receptor agonist, we were able to provide proof for the involvement of the melanocortin MC_4 receptor in erectile function in rodents (see next section; Van der Ploeg et al., submitted).

5.2. Receptor mutagenesis

Mutational analyses have been carried out to determine the structure–function relationship of melanocortin receptors. Earlier studies focused primarily on receptor mutational analysis. Studies identifying receptor residues whose mutation can result in substantial functional loss, suggested a range of residues that may interact directly with peptide ligands (Yang et al., 1997; Haskell-Luevano et al., 2001). Using a complementary modification approach (i.e. the combination of receptor mutational analysis and ligand modification), Yang et al. (2000) have identified the Asp^{122} residue in the transmembrane domain 3 of the melanocortin MC_4 receptor as the most likely residue interacting specifically with Arg^8 in the α-MSH peptide. In addition, all of these studies are consistent with an overlapping but nonidentical nature of the peptide binding site and the AgRP binding site. Specifically, one loop in the AgRP molecule encompassing RFF111-113 was demonstrated to be the critical component of its binding to the melanocortin MC_4 and MC_3 receptors, and this loop, when taken out of the AgRP context, can still bind to the melanocortin MC_4 receptor with moderate affinity (Tota et al., 1999).

6. Neurophysiology of melanocortins

POMC-derived peptides are among the most abundant neuropeptides in the brain (Adan and Gispen, 2000; Cone, 1999; Vergoni and Bertolini, 2000). In this section, we will

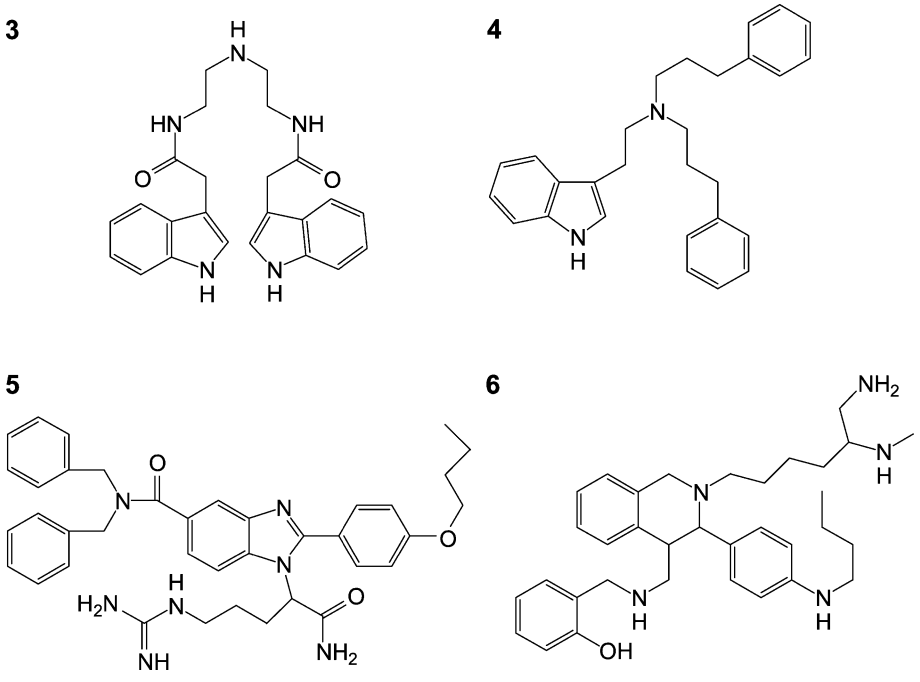

Fig. 5. Non-peptide melanocortin receptor agonists.

only discuss the neurophysiology of melanocortins, while the physiological role of β-endorphin, β-lipotropin and CLIP has been extensively reviewed elsewhere (Heijnen et al., 1991; Loh, 1992).

Due to the overall relatively low abundance of melanocortin MC_3 and MC_4 receptors in brain, neurophysiological studies of the melanocortin system has been attempted only recently. Cowley et al. (1999) investigated the synaptic transmission in the paraventricular nucleus of rat hypothalamic slices. Melanocortin receptor agonists were shown to increase the inhibitory postsynaptic current under voltage clamp conditions. Whether melanocortin receptor agonists act presynaptically by enhancing γ-aminobutyric acid (GABA) release or act postsynaptically by potentiating $GABA_A$ receptor, channel opening remains to be investigated. Taking a different approach, we investigated neuronal activity in slice preparations in the presence of melanocortin peptides (Fong and Van der Ploeg, 2000). These studies suggest that α-MSH postsynaptically inhibits the spontaneous firing rate of a subpopulation of ventral medial hypothalamic and paraventricular nucleus neurons exhibiting a continuous firing pattern (Fig. 6). These neurons are not regulated by a 5-HT_2 receptor agonist or by neuropeptide Y receptor agonist ligands. In the arcuate nucleus, approximately 44% of the AgRP neurons express melanocortin MC_3 receptors and 31% of the POMC neurons expresses melanocortin MC_3 receptors (Bagnol et al., 1999). By studying the POMC neurons in the arcuate nucleus directly, it was found that a relatively selective melanocortin MC_3 receptor agonist (D-Trp8-γ-MSH, melanocortin MC_3 receptor binding affinity = 7 nM, melanocortin MC_4 receptor binding affinity = 600 nM) at low concentration led to increased miniature IPSC frequency in 3 of the 4 neurons, hyperpolarization in 9 of 15 neurons, and reduced firing rate (Cowley et al., 2001).

Taken together, melanocortins appear to exert their functions either at the synaptic level (increasing inhibitory postsynaptic current or increasing the spontaneous miniature IPSC frequency) or at the neuronal level (reducing the spontaneous firing rate). The net effect will be reduced neuronal excitability for melanocortin MC_3/MC_4 receptor expressing neurons or those neurons receiving GABA inputs. Such neurophysiological effects may represent the neural substrate of melanocortin-mediated satiety.

7. Erectile function and the melanocortin MC_4 receptor

Erectile dysfunction is defined as the inability to initiate or maintain an erection that is sufficient for satisfactory sexual intercourse (Lue, 2000). Penile erection is driven by a spinal reflex that can be initiated by the activation of penile afferent nerves (tactile stimuli), but also by visual, olfactory, and imaginary stimuli. The reflex involves both autonomic and somatic efferents in the spinal cord (SPN, DRC, IML) and is modulated by supraspinal influences present in the medulla/pons (nucleus paragigantocellularis), midbrain (periaqueductal grey), hypothalamus (medial preoptic area) and forebrain (amygdala, hippocampus) (Giuliano et al., 1995). Centrally, several neurotransmitters that

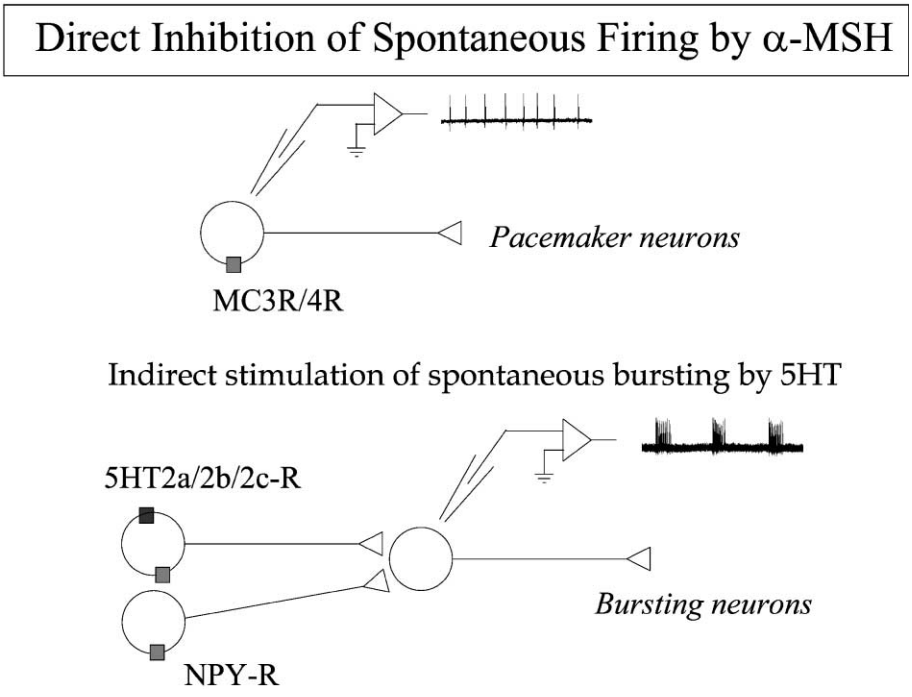

Fig. 6. Schematic representation of results obtained for extracellular single-cell recordings of PVN and VMH neurons noting their response to α-MSH, the non-specific 5HT2 agonist DOI and the agonist NPY.

modulate penile erection have been described, including dopamine, acetylcholine, nitric oxide (NO), and oxytocin which promote penile erection; the opioid enkephalin peptides which are inhibitory and, serotonin which may be either facilitatory or inhibitory (Steers, 2000). From the perspective of the peripheral nervous system and innervated tissue, the functional state of the penis is controlled by the precise balance between tumescence or detumescence provoking factors through control of the smooth muscle of the corpora cavernosa (detumescence or flaccidity and tumescence or erection). While the different steps of neurotransmission and intracellular transduction of neural signals in penile smooth muscle are being elucidated, the role of nitric oxide released from nerve terminals and endothelial cells within the corpus cavernosum has been established as the pivotal mediator of pro-erectile responses. In contrast, norepinephrine serves a major role as the primary factor responsible for anti-erectile responses mediated by α_1-adrenoceptors, which result in penile smooth muscle and blood vessel contraction. Inhibition of the breakdown of cGMP (cGMP-phosphodiesterase type 5 inhibitors) and concomitant reduction in cytosolic calcium released within the corpus cavernosum of the penis have proven to be a safe and effective means to treat erectile dysfunction (Corbin and Francis, 1999; Goldstein et al., 1998). Sildenafil (Viagra, Pfizer), the first orally active phosphodiesterase-5 treatment for erectile dysfunction, has rapidly become the drug of choice partly due to its action as an erection facilitator: sexual arousal must occur for Viagra to be effective, thus simulating a more natural experience.

Recently, melanocortin receptor agonists have gained support as a potential new therapy for the treatment of erectile dysfunction (Wessells et al., 1998, 2000a,b). POMC-derived peptides (ACTH-(1–24), α-MSH; i.c.v. administered) can provoke sexual and grooming behavior in rodents, including genital licking, erection, and ejaculation (Argiolas et al., 2000). In humans, evidence supporting the role of melanocortin receptors in sexual function derives from two, double-blind, placebo-controlled phase I clinical trials, with the nonselective melanocortin receptor agonist MTII. Subcutaneous low-dose administration of MTII was pro-erectile in men with organic (hypercholesterolemia, obesity, hypertension) and psychogenic (no organic cause identified) erectile dysfunction. TheraTech and Palatin are collaborating on the development of oral and intranasal delivery systems for MTII or its analogs (PT-14 and PT-141). Our data show that the melanocortin MC_4 receptor mediates pro-erectile events in rodents (Van der Ploeg et al., submitted). These effects maybe brought about in part by modulation of neuronal circuitry involving mechano receptors in the penis and/or spinal cord erection centers. As expected, the effects of melanocortin MC_4 receptor agonists are lacking in *Mc4r* −/− mice, while *Mc3r* −/− mice respond normally to the action of the melanocortin MC_4 receptor agonists.

8. Conclusions

Over the past decade, significant strides were made in our understanding of the role of melanocortins in diverse physiological functions and the proposed role of the melanocortin MC_3 and MC_4 receptors in energy homeostasis has received significant attention. In this respect, it is relevant to

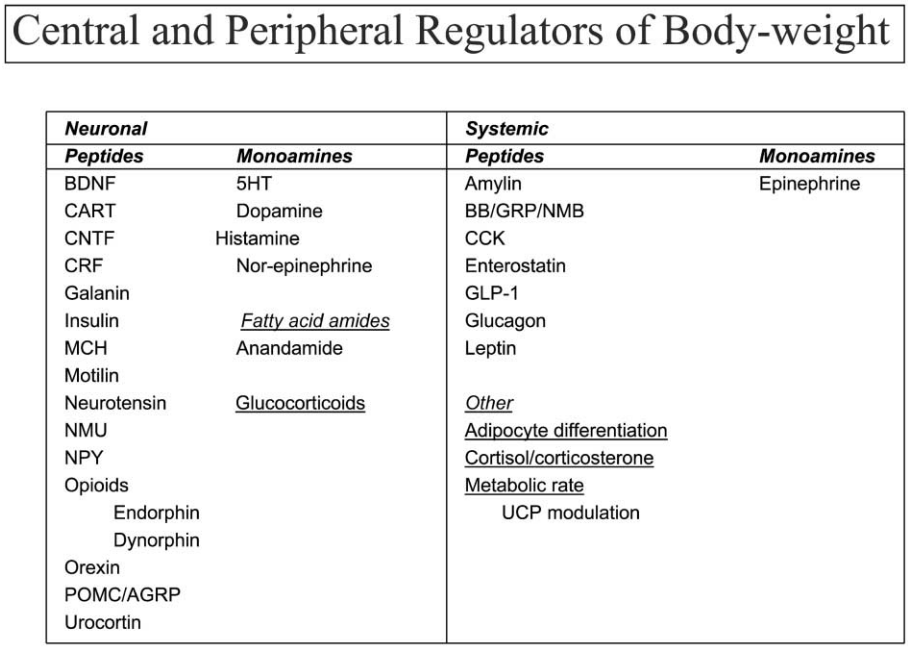

Fig. 7. Schematic outline of central and peripheral modulators of body weight.

outline that numerous CNS mediators (peptides and non-peptides) of energy homeostasis exist (Fig. 7). However, unlike the accumulated data that outlines a role for leptin and the melanocortins in energy homeostasis, the possible therapeutic relevance of most the other neuropeptides in the treatment of eating disorders is not yet supported by both genetic and pharmacological evidence.

The development of selective therapeutics that modulate the function of specific melanocortin receptors may now allow us to put several models to the test. It can therefore be anticipated that in the coming years, investigations into the role of specific melanocortin receptors will be enhanced with observations made in humans addressing the role of unique melanocortin receptors in human physiology.

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