INTRODUCTION

The incidence of obesity has increased substantially since the 1970’s with 65% of the adult US population currently categorized as overweight or obese [1, 2]. As a result of this alarming trend we can anticipate corresponding increases in the incidence of obesity related pathologies such as type II diabetes, cardiovascular disease and certain forms of cancer [3, 4]. In spite of an increased awareness of its prevalence and consequences, obesity remains a complex, difficult to treat condition. While bariatric surgery represents a potential, though risky [5], alternative for morbidly obese individuals, there are few non-surgical treatment options which have demonstrated effective and durable weight loss. Two currently approved anti-obesity agents, sibutramine (Meridia, Abbott Laboratories) and orlistat (Xenical, Roche), have been shown to be efficacious as has the recently approved rimonabant (Accomplia, Sanofi – Aventis) [6, 7], particularly when prescribed in conjunction with a behavioral modification program [8, 9]. However, due to either limited efficacy or side effects these therapeutics have not seen widespread use. The urgent need for novel and more efficacious anti-obesity therapeutics has stimulated an intensive exploration of the biochemical pathways which control appetite, food intake, energy storage, and energy expenditure. One of the most therapeutically promising targets controlling these pathways is the melanocortin-4 receptor (MC4R). The purpose of this review is to detail the advances in the development of MC4R specific agonists focusing on the progress made since the previous excellent review in 2003 by Goodfellow and Saunders [10]. Specific attention has been paid to the development of novel small molecule and peptide agonists and their demonstration as agents controlling food intake or body weight.

THE MELANOCORTIN PATHWAY

Discovery of the constituent parts of the melanocortin system has occurred as a slow process over more than a century. Examination of systems controlling pigmentation began in the 1850’s with the description by Addison of a hyperpigmentation disorder followed by the identification of a pigmentation factor in the tadpole pituitary in the early 1900’s [11]. Subsequently, the active melanocortin peptides corticotrophin (ACTH) (1), α-MSH (2), β-MSH (3) and γ-MSH (4) were isolated and sequenced beginning in the 1950’s, while the genes encoding the pro-opiomelanocortin precursor and the five melanocortin receptors were cloned in the 1970’s and 1990’s, respectively [11-21]. Utilizing these peptides as well as mice deficient in the individual receptors, the melanocortin system has been implicated in the control of pigmentation, behavior, exocrine gland secretion, inflammation, steroidogenesis, sexual function, as well as food intake and energy expenditure [22]. Interest in the central nervous system effects of melanocortins has existed since their discovery. In the 1950’s, direct intrathecal administration of ACTH and α-MSH was found to produce a “stretching crisis” in dogs [23, 24]. Later work examined the effects of melanocortins (MSH and ACTH) on other behavioral responses in rodents including open field behavior and acoustic startle [25], learning of appetitive behaviors [26], motivation and food and water consumption [27]. Although food intake was examined in some of these studies, peripheral administration of the highly unstable melanocortin peptides did not provide a clear and reproducible effect. The unambiguous demonstration of a melanocortin effect on food intake was provided by Vergoni and colleagues who utilized central administration of corticotrophin into either the lateral ventricle or directly into the ventromedial hypothalamus, to illustrate a profound inhibition of food intake in fasted rats or nocturnal feeding of normally fed rats, respectively [28]. The effect was extended to α-MSH [29] and was found to be dependent on acetylation of the amino terminus as the desacetyl peptide was not found to influence food intake [30]. That ACTH mediated inhibition of food intake was centrally mediated was confirmed by illustrating an anorectic activity following intracerebroventricular but not subcutaneous administration [31]. The development of novel peptide tanning agents NDPαMSH (5) and MTII (6) based on the α-MSH sequence provided improved tools for further understanding the effect of melanocortins on food intake and body weight [32-34]. The cyclic peptide MTII was shown by Fan and colleagues to have approximately five fold higher potency at the mouse MC4R versus the rat MC3R while the antagonist SHU9119 (7) [35] was about ten fold more potent at the MC4R [36]. Following central administration to mice, MTII reduced twelve hour cumulative food intake and these effects could be completely reversed by SHU9119 administration suggesting a specific role for the MC4R in the control of food intake. Due to instability or the presumption that peptides are incapable of crossing the blood brain barrier and accessing the MC4R, the majority of studies with these agonists have utilized direct intracerebroventricular administration. However, these studies were the first to illustrate an anorectic effect of stable MC4R agonist peptides following peripheral (intraperitoneal, i.p.) administration.

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Since the majority of the in vivo studies described above have been carried out using rodent models, the utility of MC4R agonists as therapeutics for human obesity remains unproven. To date, only one study in nonhuman primates has illustrated that treatment with ACTH/MSH 4-10, a more recent 12 week trial conducted by these authors failed to reproduce the effect of the agonist. The reported failure to achieve weight loss in overweight POMC deficient children following a three-month course of treatment with nasally administered ACTH 4-10, further strengthens the above possibility [49]. Nevertheless, these results should be interpreted cautiously since ACTH/MSH 4-10 lacks potent activity at the MC4R [50] and, unlike enzymatically resistant ligands such as NDPαxMSH and MTII, undergoes rapid degradation under physiological conditions. Furthermore, the administration of peptides by the nasal route is generally characterized by low bioavailability, short duration of action and a great degree of inter- and sub-ject variability in its actions. In addition, a study of nasally administered MSH 4-10 indicated that this peptide does not follow linear pharmacokinetics under these conditions [51]. Unequivocal demonstration of therapeutic utility can only be demonstrated in clinical trials using predictable and reproducible administration of an optimized MC4R agonist, a number of which are in preclinical development.

**MELANOCORTIN 4 RECEPTOR AGONISTS**

The growing conviction that the anorexigenic action of existing (non-selective) melanocortin ligands is mediated through the MC4R has stimulated the search for peptides and small molecules with selectivity for this receptor subtype. While peptide drugs have traditionally been perceived as less attractive than their small molecule counterparts, several factors have led to the recognition of peptide MSH ligands as viable candidates for the treatment of obesity. Several non-selective peptides such as α-MSH [29] and the cyclic MTII [36] have demonstrated proof-of-concept efficacy in rodent models of feeding suppression and offered excellent starting points for structure-activity studies designed to enhance their potency and selectivity. While the earlier in vivo studies utilized intracerebroventricular (ICV) administration to achieve a reduction in food intake, several investigators have observed anorectic effects of melanocortin peptides following their peripheral administration suggesting these peptides may be capable of crossing the blood brain barrier [36, 52-55]. Further efforts have also illustrated that MTII is capable of accessing central MC4Rs following peripheral administration and activating the stretching, yawning, and grooming complex in rodents and stimulating yawning in humans [56, 57]. These efforts proved that modified, stable peptides could recapitulate the observed activity of centrally administered melanocortins.

1 ACTH: Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Lys-Lys-(+24AA)

2 α-MSH: Ac-Ser1-Tyr2-Ser3-Met4-Glu5-His6-Phe7-Arg8-Trp9-Gly10-Lys11-Pro12-Val13-NH2

3 β-MSH(5-22): Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-His-Phe-Arg-Trp-Gly-Ser-Pro-Lys-Asp

4 γ-MSH: Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Gly-Phe

5 NDP-α-MSH: Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2

[36]. Simultaneously with these findings, Huszar and colleagues published their studies characterizing MC4R deficient mice which illustrated a phenotype including mature onset obesity with hyperphagia, hyperinsulinemia and hyperglycemia [37]. Additional studies by Marsh and colleagues used these mice to illustrate the requirement for the MC4R in the previously observed effect of MTII on food intake [38]. These findings further solidified the preclinical validation of the MC4R as a novel target for obesity.

Although the majority of work on the melanocortins has utilized the endogenous agonists, the role of the endogenous antagonists in the validation of this target should not be understated. Mice carrying the lethal yellow gene were first characterized by Cuenot in 1905 [39] and later by Castle in 1942 [40] who illustrated that this strain of mice carried a gene defect which resulted in a substantial increase in adiposity. Nearly ninety years later, the protein encoded by the Agouti (A') locus [13], was cloned and found to antagonize both the skin MC1R as well as the brain MC4R explaining both the yellow and obese phenotypes of the Agouti mouse [41]. A second endogenous antagonist targeting the central nervous system MC3R and MC4R, Agouti Related Protein (AGRP), was subsequently identified and shown to be intimately involved in the central control of food intake and body weight [16]. The identification of these genes further coupled the melanocortin system to the control of body weight and food intake but at the same time also presented a difficulty. Would an agonist for the MC4R need to compete with an endogenous antagonist in order to function as an efficacious therapeutic? On the other hand, attempts to selectively disrupt the interaction of the antagonist with its receptor have been considered as an alternative approach to developing a therapeutic for obesity [42].

Since the majority of the in vivo studies described above have been carried out using rodent models, the utility of MC4R agonists as therapeutics for human obesity remains unproven. To date, only one study in nonhuman primates has illustrated that central administration of a melanocortin agonist, NDPαxMSH, is capable of decreasing food intake in a phylogenetically higher species [43]. Thus far, the best evidence for connection to humans is provided by clinical case histories which link mutations in either the melano-cortin prohormone pro-opioimelanocortin, POMC, its processing enzyme, prohormone convertase 1, or the MC4R to monogenic forms of human obesity. Krude et al. documented examples of two distinct POMC gene defects responsible for early-onset obesity, adrenal insufficiency and red hair pigmentation [44]. Several reports have documented mutations in the MC4R in obese subjects as well as a high correlation between mutations and the incidence of binge eating disorders among obese patients [45]. Farooqi and coworkers were not only able to illustrate that symptoms such as morbid obesity, hyperphagia and hyperinsulinemia resulted from mutations within the MC4R, but remarkably, also demonstrated a qualitative relationship between the deficiency in receptor signaling capacity and the severity of these symptoms [46]. Based on these findings it is clear that the MC4R is intimately involved in the control of body weight in humans. However, with regard to target validation, the obesity resulting from the absence of this receptor or its endogenous ligands must, at best, be considered as validation of this receptor as a target for cachexia and wasting disorders (reviewed in this series by Chen and Foster) and not for obesity.

Despite the circumstantial weight of the above findings we have as yet no “proof of concept” evidence to suggest that administration of a MC4R agonist to humans will produce a therapeutically relevant weight loss in obese patients. While an encouraging initial report by Fehm [47] demonstrated statistically significant decreases in body fat in normal-weight males following six weeks of twice daily nasal administration of ACTH/MSH 4-10, a more recent 12 week trial conducted by these authors failed to reproduce the effect in obese males [48]. Taken together, the two studies may suggest that, in contrast to the normal-weight cohorts, the obese subjects in the latter study were somehow resistant to the effects of the agonist. The reported failure to achieve weight loss in overweight POMC deficient children following a three-month course of treatment with nasally administered ACTH 4-10, further strengthens the above possibility [49]. Nevertheless, these results should be interpreted cautiously since ACTH/MSH 4-10 lacks potent activity at the MC4R [50] and, unlike enzymatically resistant ligands such as NDPαxMSH and MTII, undergoes rapid degradation under physiological conditions. Furthermore, the administration of peptides by the nasal route is generally characterized by low bioavailability, short duration of action and a great degree of intra- and inter-subject variability in its actions. In addition, a study of nasally administered MSH 4-10 indicated that this peptide does not follow linear pharmacokinetics under these conditions [51]. Unequivocal demonstration of therapeutic utility can only be demonstrated in clinical trials using predictable and reproducible administration of an optimized MC4R agonist, a number of which are in preclinical development.
Efforts to develop linear, selective MC4R peptide agonists have in most instances utilized truncated versions of the original NDP-αMSH peptide and shared the essential His-DPhe-Arg-Trp tetrapeptide pharmacophore. Studies by Benoit et al. [58] conducted with Ro27-3225 (8), a modestly selective MC4R agonist demonstrated a suppression of food intake in both wild type and db/db mice and also established, that in contrast to non-selective melanocortin agonists [59] the reduction in food intake seen with Ro27-3225 did not involve a conditioned taste aversion (CTA). The Roche group carried out systematic modifications on this pentapeptide in order to improve its potency and MC4R vs. MC1R selectivity. Replacement of the guanidine group of Arg⁸ with several non-basic surrogates such as cyanoguanidine and acyl-guanidine maintained \textit{in vitro} activity of the parent peptide but failed to improve selectivity [60]. Additional structure activity studies directed at the DPhe⁷ and Trp⁹ identified several substitutions which produced only modest enhancements in MC4R potency and/or selectivity [61]. The above observations are essentially in agreement with a series of reports by Haskell-Luevano and coworkers who also noted that: 1) the guanidine group of Arg⁸ was not critical to melanocortin agonist activity [62], 2) that the indole side chain of Trp⁹ could be replaced by 2’-naphthyl group [63] and 3) that para substitution of D-Phe⁷ with a halogen group was tolerated [64]. While modifications of D-Phe⁷, Arg⁸ and Trp⁹ resulted in at best modest improvements in MC4R potency and selectivity, several groups reported various modifications to His⁶ which dramatically enhanced these properties. Substitution of Lys for His⁶ by Nijenhuis and co-workers in a heptapeptide sequence (Ac-Nle-Gly-His-DPhe-Arg-Trp-Gly-NH₂) enhanced the MC4R vs. MC3R and MC5R selectivity as a result of decreased affinity at the latter two receptor subtypes [65]. A series of spirocyclic 2-amino-tetraline-2-carboxylic acids (ATC) and 1-amino-4-phenyl-cyclohexane-1-carboxylic acids (APC) introduced by the Roche group at the His⁶ position exemplified by peptide 9 demonstrated low nanomolar potency at the MC4R with excellent selectivity vs. MC-1R [66, 67]. Replacement of the N-terminal histidine with an amino-2-naphthylcarboxylic acid capping group in a tetrapeptide by Haskell-Luevano and coworkers resulted in not only enhanced MC4R selectivity vs. MC1R and MC5R but also in a conversion to a weak MC3R antagonist [68]. The Merck group recently disclosed a series tetrapeptides in which a 1, 2, 3, 4-tetrahydro-3-isoquinolinecarboxylic acid (THIQ) capping group was used to replace the N-terminal His⁶ [69]. Aromatic substitution of D-Phe⁷ produced a number of analogs with excellent MC4R binding, a range of intrinsic efficacy, and excellent selectivity against the MC1R, MC3R and MC5R subtypes. The tetrapeptide THIQ(p-OMe)DPhe-Arg-Trp-NH₂ displayed high potency for the MC4R (Ki = 17 nM) but low relative efficacy (38% at human and 20% at rat MC4R). Despite the low relative efficacy of this peptide, intracerebroventricular administration was found to reduce cumulative overnight food intake as well as feeding duration. A similar strategy was used by the Procter and Gamble group who utilized 4-chlorophenylalanine based capping groups in place of His⁶ (10, 11) to dramatically enhance potency and selectivity over MC1R and MC3R [70, 71].
While the MTII lactam lacks significant MC4R selectivity (MC1R = MC4R > MC3R = MC5) [72], it provided a highly versatile scaffold for further structure-activity studies designed to produce potent and specific MC4R agonists. Substitution of the His residue with an appropriate surrogate group or fine-tuning of the macrocyclic constraint have been associated with profound increases MC4R selectivity. The Roche group incorporated a number of conformationally constrained moieties from the linear series into a lactam scaffold exemplified by 12 and achieved excellent potencies as well as MC4R vs. MC1R selectivities of 100-fold or greater. Peripheral administration (i.p.) of a peptide containing the APC modification, Ro28-0956, produced a reduction in food intake and body weight in ob/ob mice, an effect not observed in MC4R knockout mice [73, 74]. Furthermore, intraperitoneal or intranasal administration of this peptide for a period of 37 days produced a 10% reduction in body weight in ob/ob mice.

A series of MC4R selective cyclic peptides disclosed by Merck also utilized the MTII core scaffold [75]. The desired balance between MC4R potency and selectivity was achieved through systematic optimization of the lactam ring size from 20 to 23 atoms with the 23 membered lactam 13 and 21 membered lactam 14 demonstrating low nanomolar binding, subnanomolar EC50 values and excellent selectivity with respect to MC3R and MC5R.
MC4R selective peptide from this series was also independently disclosed by Hruby and coworkers who reported similar in vitro activity [76]. A further survey of the patent literature also revealed claims of MC4R selective cyclic peptides from the Procter and Gamble Corporation which were based on a lactam scaffold incorporating a tyrosine in place of His as exemplified by structure 15 [77].

The Eli Lilly group reported two series of disulfide containing cyclic peptides based on the β-MSH sequence exemplified by the cyclic nonapeptide 16. Peptides in this series exhibited sub-nanomolar Kᵢ and EC₅₀ values at MC4R as well as excellent selectivity against MC5R, and relatively modest selectivity against MC1R. Administration of 16 either by direct intracerebroventricular or subcutaneous injection was found to decrease food intake and body weight as well as increase fat utilization in obese Long-Evans rats [78]. A significant inhibition of food intake was observed in wild type but not MC4R deficient mice establishing in vivo specificity for this receptor. Furthermore, 16 was found to stimulate stretching, yarning and grooming in wild type but not MC4R deficient mice confirming that peptides of this series were capable of crossing the blood brain barrier and activating this receptor [79].

Extensive SAR studies demonstrated that the strong positive charge contributed by the exocyclic Arg³ residue (17) was essential to the subnanomolar potency of this series [80]. Further minimization of the pharmacophore through reduction of the ring size from a 23 to a 21 membered macrocycle yielded the smaller hexapeptide series 18 with improved potency and selectivity [72]. Introduction of steric constraint by substitution of penicillamine for cysteine (R¹ = CH₃) resulted in improvements in MC4R potency and selectivity as did substitution with a halogen (R² = F, Cl) at the para-position of D-Phe⁷. Representative members of these series were shown to have robust activity in rodent models of diet induced obesity. Fourteen days of daily subcutaneous administration of peptides 16-18 to high fat diet-induced obese rats at doses of 0.075 and 0.3 μmoles/kg produced a dose dependent reduction in food intake and body weight. Furthermore, these metabolic effects were attributed to reductions in fat rather than lean mass [78, 80].

SMALL MOLECULES, HEMI-PEPTIDES, AND NON-PEPTIDES

The evolution of peptide agonists to hemi-peptide and then to non-peptide congeners has been the subject of several excellent recent reviews [10, 81, 82]. The material in this section will not attempt to cover the subject matter of the past reviews or to survey the growing body of nearly 100 patents/applications in the MC4R agonist/ligand arena. Rather, this section will endeavor to highlight examples of the progression of peptide agonists to their non-peptide counterparts. Additionally, an attempt will be made to capture the
compounds reported in the literature with either demonstrated exposure after oral administration or reported efficacy in models of food consumption.

Researchers from Merck were among the first to report on the discovery and development of hemi-peptide agonists for MC4R. Their initial disclosure nicely describes the design and optimization of dipeptide capped privileged structures [83]. The authors pictorially suggest that the privileged structure element is a surrogate for the tryptophan and arginine residues of the His-Phe-Arg-Trp core sequence 19 required for activity at the melanocortin receptors. Their optimum compound 20 (“THIQ”) was shown to have good potency (IC\textsubscript{50} 1.2 nM, EC\textsubscript{50} 2.1 nM), selectivity, and to be active in models of erectogenic function. Compound 20 has a reported bioavailability of 14% in rats and 16% in dogs and was also reported to significantly inhibit food intake after oral administration (species and dose not given). Following these reports, Dyck and colleagues reported that 20 induced short term inhibition of food intake in fasted mice following intracerebroventricular (icv) administration [84]. Cepoi and colleagues also reported that icv administration of 20 to mice at doses up to 32 nanomoles transiently decreased food intake for up to six hours following an overnight fast [85]. Importantly, these authors illustrated that the effects of 20 on food intake were absent in MC4 deficient mice. Unlike MTII however, 20 was not able to increase oxygen consumption following central administration and was not effective following intraperitoneal (i.p.) administration suggesting this compound was unable to cross the blood brain barrier. Nordheim and colleagues have further examined the effect of 20 on food intake and cardiovascular responses in Sprague Dawley rats [86]. Similar to the effects of Cepoi, these authors were unable to observe an effect of 20 on 24 hour ad lib food intake following peripheral administration at doses up to 10 mg/kg (i.p.) but mentioned that a short term effect could be observed following dosing just prior to the dark phase. These authors did observe a modest increase in mean arterial pressure and heart rate four hours after administration but no increase in core body temperature.

The (pCl)-Phe-THIQ dipeptide capped privileged structure approach has been employed by other workers in the field. Lilly has disclosed a similar approach yielding sulfonamide 21 which afforded a K\textsubscript{i} of 220 nM and an EC\textsubscript{50} of 16 nM [87]. The bioavailability for this molecule in Fischer 344 rats was 30% with a T\textsubscript{1/2} of 1.7 hours. Amgen has reported additional aryl piperazines in patent applications [88, 89] with compounds 22 and 23 being representative. Compound 22 was reported to significantly decrease food intake in fasted mice following systemic dosing at less than 30 mg/kg [88]. Oral administration of compound 23 at doses of 25 to 100 mg/kg was found to produce a dose dependent decrease in food intake for up to 6 hours in fasted mice [90]. No effect of this compound was observed on locomotor activity suggesting its effect on food intake was not mediated by an adverse effect.

In an effort to mitigate unwanted side effects afforded by compound 20, workers at Merck replaced the THIQ residue with piperazine and piperidine moieties and the triazole group with an amido functionality, generating second generation analogs 24 (MB243) [91] and 25 (RY764) [92]. Compound 24 afforded excellent potency at MC4R (IC\textsubscript{50} 16 nM, EC\textsubscript{50} 11 nM) and a good selectivity profile. In-vivo efficacy was observed in the obese rat model with a significant reduction in body weight seen after four days of oral administration at a dose of 20 mg/kg. A bioavailability of 9% and 17% was seen in the rat and dog, respectively. Compound 25 (RY764, IC\textsubscript{50} 8 nM, EC\textsubscript{50} 11 nM) has a better exposure profile than compound 24 with an observed bioavailability of 32% and 50% in the rat and dog, respectively [92]. Again this compound demonstrated in vivo activity in the obese rat model with a significant reduction in food intake observed following oral dosing at 20 mg/kg. Oral administration of compound 25 was further found to reduce food intake in wild type mice following an overnight fast while this effect was absent in MC4R deficient mice.

Researchers at Palatin have departed from privileged structure based ligands with a nice example of a peptidomimetic (26)[93]. Their compounds are derived from piperazines which are appropriately decorated with the phenylalanine and two of the important side-chains found in the HFRW sequence; namely, the arginine guanidine and the tryptophan aryl moiety. These molecules have been reported to have significant activity in a mouse model of obesity with an observed reduction in food intake after a 3 mg/kg i.p. dose. Unfortunately, no oral pharmacokinetic or efficacy data were disclosed.

Interesting examples of non peptide MC4R agonists have been reported by workers at Glaxo (27-28) [94, 95] and Johnson and Johnson (29) [96]. Compound 27 is a guanidine-substituted quinazolinone and the substitution pattern is suggestive of some type of β-turn mimic. The patent data described these compounds
as selective agonists for MC4R but gives no binding or functional data. Experimental descriptions included in the patent application indicate that activity for the series described may be present in mouse models of obesity and compound 27 is reported to have both plasma and brain exposure after oral administration. Compound 28 is derived from a trisubstituted diazepinedione and represents a shift away from traditional peptide based privileged structures and bears little resemblance to commonly described \( \beta \)-turn mimics. This compound has good potency for MC4R and has been described in a poster presentation to afford a decrease in food consumption after oral dosing of 25 mg/kg in fatty Zucker rats [95]. Compound 29, with no amide bonds represents the farthest departure from a peptide [96]. This trisubstituted thiadiazole is reported to have a binding affinity of 22 nM and is a functional agonist. Compound 29 was found to have activity in a rat model of obesity when administered subcutaneously at doses of 10 mg/kg. Interestingly, the most potent compound reported in this paper did not show in-vivo activity.

**CONCLUSION**

Despite the wealth of data establishing the relationship of MC4R signaling with control of energy intake and expenditure, and the extensive efforts which have been directed toward developing potent and selective MC4R agonist ligands, relatively little progress has been made toward a promising and clinically useful anti-obesity agent. Similar to the experience with the hormone leptin, the journey from the validation of a relevant pathway to a safe and efficacious clinical candidate can be long and unpredictable. This review summarizes the major efforts in pursuit of this goal by industrial and academic groups. While both small molecule and peptide based strategies have been employed, both face technically difficult paths forward. Mimicking the actions of an endogenous, centrally acting peptide ligand with an orally available small molecule is enormously challenging. Other than the serendipitous exception of the morphine alkaloids, few examples of agonists to peptide receptors (e.g. growth hormone secretagoue, ORL-1, cholecystokinin A) exist in medicinal chemistry. The use of a peptide-based therapeutic on the other hand, while promising a more direct path to the clinic, suffers from the usual limitations associated with this treatment paradigm including short half life, low CNS exposure and the need for parenteral administration. Regardless of the molecule chosen to test this hypothesis, limitations specific to the melanocortins may arise including the effect of the endogenous antagonist AGRP on the long term efficacy of any MC4R agonist. Additionally, agonists acting on the MC4R have effects other than food intake and energy expenditure such as penile erection that may impact its use in obese men (See Shadiack et al., Review in this issue).

Ultimately, the most daunting obstacle in our quest for an effective anti-obesity agent may be posed by our bodies’ own evolutionary predisposition to fat storage. The ability to store energy in the form of fat once conferred an evolutionary advantage through periods when food was in limited supply [97]. Will the resulting maladaptive consequences of the so-called “thrifty gene” also limit the long term efficacy and durability of a therapeutic weight loss agent? Despite these concerns it is hoped that continued work to discover and develop drugs directed at novel anti-obesity targets including the MC4R will lead to important medical advances and provide patients with a solution to this chronic disease.

**REFERENCES**


