1. Introduction

Melanocortins are peptides derived from the pro-opiomelanocortin (POMC) gene, including α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH). Five melanocortin receptors have been identified so far, MC1 – 5R. The melanocortin system is involved in diverse physiological functions, including, most notably, energy balance, pigmentation, sexual function and inflammation. Extensive reviews on the melanocortin ligands and receptors have been published and readers are referred to those recent publications for the pharmacology and physiology of the melanocortin system [1-12]. This review will summarise advances made in 2002 – 2003.

Recent clinical studies on obese patients carrying melanocortin-4 receptor (MC4R) variants further strengthen the role of MC4R in energy balance. Farooqi et al. found that complete loss of function variants are associated with a more severe phenotype of obesity than those variants leading to only partial loss of function [13]. Branson et al. further showed that binge eating is characteristic of patients with MC4R variants [14]. Additional studies indicated that many of the MC4R variants found in obese patients tend to have defects in plasma membrane targeting, which is consistent with the notion that reduced MC4R surface expression can be a cause of obesity [15-17]. These results further predict additional mutations in the MC4R promoter region may also cause obesity by reducing surface expression.

The role of MC3R and MC4R in cachexia has been evaluated in mice. The MC4R knockout (KO) mice resist the loss of lean body mass caused by tumour
growth, while the M C3R KO mice showed enhanced wasting [18]. These data suggested a differential role of M C3R and M C4R in the development of cachexia and weight gain [18-20].

In the area of analgesia, M C1R gene mediates female-specific κ-opioid analgesia in both mice and humans. Women with two variant M C1R alleles exhibit greater analgesia from κ-opioid than all other groups [21]. This finding demonstrates the involvement of M C1R in pain modulation in addition to its well-known role in pigmentation. Recent epidemiological studies confirmed that M C1R polymorphism clearly contributes to pigmentation along with two other genes [22-24].

The M C1R has been known to play a role in inflammatory response [10]. In addition, M C5R and M C1R immunoreactivity were found in human duodenal mucosa [25]. Further studies are needed to elucidate how other M C receptor subtypes modulate inflammatory response.

2. Patents

2.1 Piperidine- and piperazine-based ligands

Bristol-Myers Squibb has reported [101-104] a new series of piperidine and spiropiperidine derivatives as modulators of M C1R, M C4R, and M C4R. The compounds are related to a dipeptide-heterocycle template exemplified by compounds 1 and 2. In vitro and in vivo data were provided for compound 2 [26]. This melanocortin ligand was shown to be a highly potent and selective M C1R agonist (median inhibitory concentration [IC50] value = 120 nM, effective concentration for half-maximum response [EC50] value = 28 nM) which, even at micromolar concentration, did not activate MC3R and was a weak partial agonist at M C4R and M C5R. When tested in a murine lipopolysaccharide-induced cytokine accumulation model, compound 2 was able to elicit an anti-inflammatory effect; it decreased TNF-α production in a dose-dependent manner [26].

Eli Lilly has expanded its repertoire of M C4R agonists with yet another group of substituted piperazines and 1,4-diazepanes [103]. The structures of the new compounds include the dipeptide D-Tic-D-Phe(4Cl) segment and the piperazine ring modified with various piperidine derivatives. Compounds published are related to compound 3 (EC50 = 4.3 nM at M C4R) and have been claimed for the treatment of obesity, diabetes, and male and female sexual dysfunction.

Merck's collection of patents on M C4R agonists [3] has been supplemented by 4 new applications [106-109]. Previously published compounds [1-3] derived mostly from dipeptide-piperidine, dipeptide-spiropiperidine and dipeptide-piperazine templates and were claimed for the treatment of obesity, diabetes mellitus and sexual dysfunction. Recent compounds are also piperidine derivatives, 4-substituted N-acylpiperidines. Although, in the structures of compounds claimed in WO 0307949 [109], the dipeptide-piperidine template is retained, as in compound 4, compounds of the other patents [106-108] have the piperidine moiety substituted with isonicotinic acid or cyclopentane-carboxylic acid or 3-carboxy-pyrolidine derivatives, exemplified by compound 5. The new agonists have been claimed for the treatment of obesity, diabetes mellitus and sexual dysfunction but no specific biological data has been given.

Recently, Merck has also detailed [27] its efforts directed towards the design and syntheses of new M C4R agonists based on structural motifs other than the piperidine and piperazine templates. A series of pyridazinone derivatives, such as compound 6 (IC50 = 33 nM and EC50 = 177 nM at hM C4R), has been reported. These compounds could provide new leads for the development of M C4R agonists suitable for the treatment of obesity.

Amgen has recently joined other pharmaceutical companies in pursuit of low molecular weight hM C4R agonists based on the Tic-D-Phe(4Cl) dipeptide-piperazine/piperidine template. Two patents published [110,111] cover a huge number of substituted N-acylpiperidines and 1-acylpiperazines related to compounds 7 and 8, respectively. Claims have been made for the treatment of obesity, diabetes, cancer, inflammation, and Alzheimer's diseases. Separately, two other groups of piperazine derivatives related to compounds 9 and 10, with a succinamide core in place of Phe(4Cl), have been reported [28] to be potent and selective M C4R agonists and antagonists.

Similarly, Neurocrine has disclosed [112,113] ligands for M C3R and M C4R having structures related to compounds 11 and 12 in which the dipeptide-piperazine template has been retained. Compound 12 was reported to be a selective M C4R agonist with an EC50 value of 24 nM at M C4R and an IC50 value of > 3000 nM at hM C1R, hM C3R and hM C5R [29]. Claims have been made for a broad range of therapeutic applications, including eating disorders and sexual dysfunctions. These Neurocrine substituted phenyl piperazines and cyclohexyl piperazines [112,113], together with Amgen's sulfonamide-substituted phenyl piperazines [111] and Eli Lilly's substituted piperidyl piperazines [105], substantially expand the family of melanocortin ligands based on the dipeptide-piperazine template [3].

Another application from Neurocrine [114] has claimed substituted-pyroles of structures similar to compound 13 for the treatment of eating and skin disorders; no biological data have been reported. The novel pyrrole template of compounds disclosed might offer further opportunities for the new ligand design.

Two recent patents from Proctor and Gamble [115,116] have centred on yet another series of 4,4-disubstituted N-acylpiperidines as agents suitable for treating eating disorders. These compounds, represented by compound 14, are the structure-activity relationship (SAR) extensions of Merck's previously discussed compound 15 and feature various replacements for the Tic and [1,2,4]triazole-1-ylmethyl moieties. The 4,4-disubstituted N-acylpiperidine derivatives with different substitutions in the same positions have been the subject of the above-cited recent patent disclosures from Bristol-Myers Squibb [101,102] and Merck [109].

Taisho has claimed [117-119] peptide and low molecular weight M C4R antagonists (dipiperazine derivatives) for the
treatment of anxiety and depression. Anxiolytic and anti-depressant activities have been reported [30] for MCL-0020, Ac-D-Nal(2')-Arg-Nal(2')-NH₂, upon intracerebroventricular injection in mice. This short peptide is a high affinity ligand for M C 4 R (IC₅₀ = 11.63 nM) and is 860-fold selective over M C 1 R and 89-fold selective over M C 3 R. A non-peptidic compound (16), MCL-0129, has been shown to elicit similar effects when administered subcutaneously or orally [31]. MCL-0129 binds to M C 4 R with an IC₅₀ value of 7.9 nM and displays no apparent affinity for M C 1 R and M C 3 R, even at 1 µM concentration. Recently reported by Amgen [32] are low molecular weight M C 4 R antagonists based on the same (piperazinyl-ethyl)piperazine template; compound 17 (IC₅₀ = 220 nM at M C 4 R) represents the Amgen series.

2.2 Guanidine-based ligands

Chiron has claimed another series of guanidine-containing M C 4 R agonists for a number of therapeutic interventions [120-122]. In the previously reviewed patents [3], claims were made for guanidinobenzamide and guanidine compounds derived from 2(S)-methylpiperazines and (+)-isocampherlamines. The latest applications centred on structures exemplified by compound 18, 5-guanidino-isindoled derivatives and compound 19, guanidinobenzamides derivatives. No specific biological data were given for compounds published but it was stated that a significant reduction in food intake and body weight was observed when these compounds were administered intraperitoneally to the ob/ob mice. Improvements in blood glucose, insulin and free
Fatty acid levels were also noted. Claims were for the treatment of obesity and Type 2 diabetes.

In a separate patent, Chiron claimed an intranasal route for delivering MC4-R agonists to mammalian subjects [123]; guanidine compounds described above were included.

Melacure has previously published [1-3] hydroxyaminoguanidines and aminoguanidines as melanocortin receptor ligands. Recent patents [124-126] have claimed another set of aminoguanidines as agonists or antagonists for melanocortin receptors, thus containing substitutions with benzylidene or 1-phenylpyrrole moieties. The newer compounds, exemplified by compounds 20 and 21, have been tested for their effects on food intake, body weight and inflammation but no in vivo data have been provided. Only limited in vitro inhibition constant (K)<sub>i</sub> binding affinities were reported. Compound 20 appeared to be the most selective MC1R and MC4R ligand: K<sub>i</sub> values of 0.5 µM at MC1R, 5.8 µM at MC3R, 0.01 µM at MC4R and 4.9 µM at MC5R. The newer compounds have been claimed as useful in treating a broad range of clinical conditions, including inflammation and cardiac diseases.

2.3 Other ligands

Ortho-McNeil has claimed [127,128] a series of 2,3-diaryl-5-anilino[1,2,4]thiadiazoles related to compound 22. This compound was reported [33] to be an MC4R agonist (IC<sub>50 </sub>= 22 nM) but its agonist potency and selectivity profile were not disclosed. Although with intraperitoneal administration, compound 22 was able to significantly reduce food intake in fasted rats; it was not effective when orally dosed. Selected compounds were also evaluated for their ability to promote neurite outgrowth and/or for their stimulatory or inhibitory effect on human sebocyte differentiation and lipid production. Some of the compounds tested were superior to α-MSH in eliciting these effects. Compounds centred around compound 22 were claimed as melanocortin receptor modulators for a broad range of metabolic, CNS and dermatological diseases, including obesity, Type 2 diabetes, erectile disfunction, acne and dry skin.

Proctor & Gamble has reported [129] a series of conformationally restricted, peptide-like compounds as MC4R and/or MC3R modulators. These are dipeptide-heterocyclic derivatives such as compound 23. They are listed for a number of therapeutic applications: Type 2 diabetes mellitus, coronary artery disease, hypertension and dyslipidemia, among others, but no specific biological data are provided. The subsequent broad patent application [130] claims substituted cyclic agents (piperidines, piperazines and ketopiperazines) with structures similar to compound 24. Another application [131] features analogues of MT-II and SHU-9119, mainly with Tyr in place of His, that might be suitable for treating diseases mediated by the MC4R or MC3R.

Merck has claimed [34,132] high affinity, selective, peptide MC4R antagonists for the treatment of cachexia, anorexia and bulimia. The structures of these cyclic compounds, lactam macrocycles, are similar to the structures of peptide MC4R agonists discussed in an earlier review [3]. The most interesting MC4R antagonist is a compound called MBP-10, cyclo[CO-CH<sub>2</sub>-CH<sub>2</sub>-CO-D-Nal(2′)-Arg-Trp-Lys]-NH<sub>2</sub>, of ~125-fold higher antagonist selectivity for hMC4R than hMC3R (K<sub>i</sub> = 0.5 nM, binding constant [K<sub>i</sub>] = 6.2 nM at in vivo conditions).
Ligands of the melanocortin receptors, 2002 – 2003 update

hMC4R and \( K_i = 150 \text{ nM}, K_b = 775 \text{ nM} \) at hMC3R.) This small cyclic peptide does not activate hMC1bR, hMC3R or hMC4R, even at micromolar concentrations, and is a weak agonist at hMC5R (EC50 = 530 nM.) An acute increase in food intake was observed when MBP-10 was injected centrally in satiated mice [35]. This peptide also reduced the inhibition of food intake induced by central injection of the cytokine IL-1\( \beta \) in the mouse [35].

A recent patent [133] from Palatin on metallopeptides claims rhenium-complexed peptides as MC3R and/or MC4R agonists for the treatment of sexual disfunction in mammals. A representative compound Ac-Nle-Ala-His-D-Phe-Arg-Trp-Cys-NH\(_2\) was reported to be a potent mouse MC4R agonist (EC50 = 21 nM) and a weak mouse MC3R antagonist (pA2 = 5.6, \( K_i = 2.5 \text{ nM} \); partial agonist.) The second compound, Ac-His-D-(pl)Phe-Ang-Trp-Cys-NH\(_2\), is also a potent mouse MC4R agonist (EC50 = 25 nM) but a potent mouse MC3R antagonist (pA2 = 7.25, \( K_i = 56 \text{ nM} \).) These small peptides have been claimed for the treatment of obesity and the control of appetite.

Millennium has claimed [137] a large number of MC4R-binding compounds, such as substituted 1,4,5,6-tetrahydro-pyrimidines related to compound 26. They are claimed as agonists, antagonists and modulators of MC4R, useful for the treatment of disorders associated with pigmentation, bone or weight loss.

Finally, Schering has claimed [138] usage of MC4R agonists (compounds not specified) in combination with phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction and other disorders. Similarly, co-administration of melanocortin receptor agonists (MC1R or MC4R agonists) with phosphodiesterase inhibitors has been claimed by Bristol-Mayers Squibb [139] for the treatment of inflammatory, immune and neurodegenerative diseases and/or stroke. Action Pharma APS has also claimed [140] a method for the treatment and prevention of inflammation, infection or cancer in which \( \alpha \)-MSH and erythropoietin are co-administered.

3. Expert opinion

In the last 15 months, MC4R agonists have again dominated the patent literature of melanocortin receptor ligands. A number of laboratories previously involved in the pursuit of non-peptide MC4R agonists for the treatment of sexual disfunction in mammals. A representative compound Ac-Nle-Ala-H is-D-Phe-Arg-Trp-Cys-NH\(_2\) was reported to be a potent initiator of penile erection (PE) in rats following intravenous or intranasal administration. The MC1R-specific agonist Ac-Nle-Ala-H is-D-Phe-Arg-Cys-Trp-NH\(_2\) was not able to initiate PE. Several complexes with analogues possessing D-Nal(2') in place of D-Phe (MC3R/MC4R antagonists) effectively inhibited the PE responses elicited by MT-II.

Another patent [134] has disclosed compounds similar to compound 25, with non-peptide ring structures in place of Arg-Trp segment of the previously reported [3] biologically active metallopeptides.

In addition, Palatin has also claimed cyclic and linear peptides as useful agents for decreasing food intake and for stimulating sexual response [135]. The cyclic compounds are mainly derivatives of MT-II or SHU-9119 with Ser(BzI) in place of His and Phe(4Cl) in place of Phe. The linear compounds are related to 7'-amino-heptanoyl-Ser(BzI)-D-Phe(4Cl)-Arg-Trp-NH\(_2\) (\( K_i = 1 \text{ nM} \) at M C4R.)

University of Florida has reported [36,37,136] two tetrapeptides of unusual pharmacology at the brain melanocortin receptors M C3R and M C4R. The first compound, Ac-Anc-D-Phe-Ang-Trp-NH\(_2\), Anc (amino-2-naphthyl carboxylic acid) is a potent mouse M C4R agonist (EC50 = 21 nM) and a weak mouse M C3R antagonist (pA2 = 5.6, \( K_i = 2.5 \text{ nM} \); partial agonist.) The second compound, Ac-His-D-(pl)Phe-Ang-Trp-NH\(_2\), is also a potent mouse M C4R agonist (EC50 = 25 nM) but a potent mouse M C3R antagonist (pA2 = 7.25, \( K_i = 56 \text{ nM} \).) These small peptides have been claimed for the treatment of obesity and the control of appetite.

Millennium has claimed [137] a large number of MC4R-binding compounds, such as substituted 1,4,5,6-tetrahydro-pyrimidines related to compound 26. They are claimed as agonists, antagonists and modulators of MC4R, useful for the treatment of disorders associated with pigmentation, bone or weight loss.

Finally, Schering has claimed [138] usage of MC4R agonists (compounds not specified) in combination with phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction and other disorders. Similarly, co-administration of melanocortin receptor agonists (MC1R or MC4R agonists) with phosphodiesterase inhibitors has been claimed by Bristol-Mayers Squibb [139] for the treatment of inflammatory, immune and neurodegenerative diseases and/or stroke. Action Pharma APS has also claimed [140] a method for the treatment and prevention of inflammation, infection or cancer in which \( \alpha \)-MSH and erythropoietin are co-administered.

3. Expert opinion

In the last 15 months, MC4R agonists have again dominated the patent literature of melanocortin receptor ligands. A number of laboratories previously involved in the pursuit of non-peptide MC4R agonists have claimed an additional series of compounds. Several other laboratories have also joined the field by publishing their MC4R agonists. Similar to the previously disclosed low molecular weight compounds [1-3], the majority of the new agonists are derivatives of piperidines, spiro-piperidines or piperazines (Amgen, Bristol-Myers Squibb, Eli Lilly, Merck, Neurocrine, Procter and Gamble) or substituted guanidines (Chiron and M elacure.). These compounds are claimed for the treatment of obesity and/or erectile dysfunction and appear to reflect an unwavering commitment of the pharmaceutical research community towards the development of drugs for these two therapeutic areas. Multiple nonspecific claims are almost routinely attached to the new melanocortin ligands. At the present time, it is impossible to discuss the usefulness of these compounds for potential clinical interventions because, with only a few exceptions, the results of their
The and in patients with erectile dysfunction when given intra-
lar weight MC4R agonist. of leptin and insulin, when administered intranasally to nor-
would be superior to non-selective MC agonists, which
MC4R agonists may be effective to treat erectile dysfunction.
In addition, rodent pharmacological data suggest that
MC4R antagonists are piperazine-based compounds as well
M C4R antagonists might be suitable for treating cachexia
human studies, peptides, such as LH-RH agonists, somatostatin and vasopressin
ties are not yet available for these hypotheses, it is
likely that some drug discovery efforts directed towards compo-
ments from Amgen and Taisho might prompt medicinal chemists to revisit the pipeline
and MC5R have been reported [41-46]. Moreover, M elacure's
In conclusion, advances have been made towards further
of the role of α-M SH in inflammation and certain skin disorders [10,11] may intensify
medicinal chemistry efforts directed towards MC1R ligands
and perhaps M C3R and M C5R ligands suitable for treating
theses conditions; whereas, the recent reports [2,47] on antimi-
crobes aureus and Candida albicans may encourage efforts focused on the development of α-M SH derivatives as a novel class of
anti-infective agents (they may not necessary be M CR ligands, since it is not yet known if the M CR exist in yeast).
In conclusion, advances have been made towards further understanding of the role of α-M SH in various clinical condi-
tions, in particular eating disorders and erectile dysfunction. Yet, in spite of the intensive basic research and drug discovery efforts, the development of clinically useful agents for these two therapeutical areas remains a challenge.

Bioavailability and high cost of production. Yet, PT-141 and
bioavailability and high cost of production. Yet, PT-141 and
bioavailability and high cost of production. Yet, PT-141 and
bioavailability and high cost of production. Yet, PT-141 and
bioavailability and high cost of production. Yet, PT-141 and
Ligands of the melanocortin receptors, 2002 - 2003 update

Bibliography

Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.


• Review of the patent literature on ligands for the melanocortin receptors.


• Review of the patent literature on MCR4 ligands.


27. STURM RA, TEASDALE RD, BOX NF et al.: A non-peptide MC4R agonist is reported.


31. PAN K, SCOTT MK, LEE DHS et al.: A new template for MCR4 agonists is reported.


**Patents**

Patents of special note have been highlighted as of considerable interest (**) to readers.


**A new template for MCR4 agonists is reported.**

Ligands of the melanocortin receptors, 2002 - 2003 update

Affiliation
Maria A. Bednarek† & Tung M Fong
†Author for correspondence
Merck Research Laboratories, PO Box 2000
R 30G-140, Rahway, NJ 07065, USA
Tel: +1 732 594 4798; Fax: +1 732 594 8080;
E-mail: maria_bednarek@merck.com