Obesity is a major medical problem with a prevalence that is increasing at an alarming rate.\(^1\) It remains a major risk factor for cardiovascular disease, metabolic diseases like type 2 diabetes mellitus, and certain cancers. There is also an established link between obesity and hypertension. The Normative Aging Study found that adiposity is significantly positively associated with both systolic and diastolic blood pressures and that up to two thirds of hypertension cases are associated with excess adiposity.\(^2\) In addition, evidence from the Framingham Offspring Study suggests that obesity may account for up to 78% of hypertension in men and 64% in women.\(^3\) Obesity is also responsible for increased morbidity from reproductive, skeletal, and gastrointestinal disorders,\(^4\) as well as being negatively associated with psychological well-being and social functioning.\(^5\)

The simple principle that obesity can arise only when energy intake exceeds energy expenditure remains undisputed. Furthermore, rapid changes in the availability, composition, and consumption of energy-dense food, coupled with a downturn in physical activity levels in all aspects of daily life, have undoubtedly contributed to the recent rises in the prevalence of obesity worldwide.

However, in the midst of these dramatic societal changes, many people remain lean.\(^6\) Indeed, the fact that most healthy adults maintain a steady body weight over many years despite huge variations in daily energy intake and expenditure is powerful testament to a system that is under tight homeostatic control. The last 15 years have seen a huge increase in our knowledge of the molecular players that underpin these regulatory systems. Many of the seminal observations in this field have come from obese animal models, both naturally occurring and genetically modified, but have combined synergistically with data from human genetic and physiological studies. We now understand that contained within the brain are a number of signaling pathways that are crucial for the central nervous system to sense peripherally derived signals of both long-term energy stores and more short-term changes in energy expenditure.

One of the most critical of these central pathways is the central melanocortin system, a pathway primarily within the hypothalamus and based around the actions of a family of small peptides (the melanocortins). In this review, we highlight the basic anatomic and functional architecture of the central melanocortin system and review some of the data surrounding the potential physiological roles of the melanocortin peptides. We also describe the convergent data from animal and human studies that have recently given some tantalizing hints into the link between obesity and hypertension. Finally, we discuss evolving, primarily preclinical, data that indicate that melanocortin signaling through the central nervous system may play a part in limiting tissue damage from inflammation and ischemia.

**Architecture of the Melanocortin System**

**Pro-Opiomelanocortin**

It seems likely that pro-opiomelanocortin (POMC) appeared early on in vertebrate evolution, with primitive jawless fish having a POMC coding sequence very similar to that seen in higher mammals.\(^7\) In humans, the POMC gene consists of 3 exons, and although POMC mRNA can be detected in a number of tissues, the gene is expressed at physiologically significant levels in a limited range of tissues.\(^8\) These include the skin,\(^9\) corticotrophs of the anterior pituitary, the hypothalamus, and the brainstem.

POMC is an archetypal polypeptide precursor, with the 241-amino acid propeptide being functionally inert. It is extensively postranslationally processed, undergoing a series of proteolytic cleavages and chemical transformations to generate a series of smaller biologically active peptides (Figure 1). The precise repertoire of POMC-derived products from any particular tissue is dependent largely on the range of processing enzymes expressed in that tissue.\(^10\) POMC is cleaved by a family of serine proteases called prohormone convertases (PCs), with PC1 and PC2 understood to be particularly important in POMC processing. PC1 is ubiquitously expressed in POMC-containing tissues and cleaves n-terminal fragments, joining peptide, adrenocorticotropic (ACTH), and \(\beta\)-lipotropin (\(\beta\)-LPH), whereas PC2 is selectively expressed in the hypothalamus but not the pituitary and...
further cleaves n-terminal fragment, ACTH, and β-LPH to form γ-, α-, and β-melanocyte-stimulating hormone (MSH), respectively.13 α-, β-, and γ-MSH and ACTH are collectively known as the melanocortins. The name "melanocortin" derives from the early studies of peptides extracted from pituitary glands that demonstrated that these peptides were able to bring about dramatic changes in melanin pigmentation and stimulate glucocorticoid production.12 This family of peptides possess structural similarity with a characteristic invariant tetrapeptide motif (His-Phe-Arg-Trp) at their core.13

Melanocortin Receptors

The actions of the melanocortin peptides are mediated by 5 melanocortin receptors (MC1-R through MC5-R).14 These receptors exhibit homology, all being G protein–coupled, 7-transmembrane domain receptors. MC1-R is expressed on a range of cell types within the skin, including melanocytes, keratinocytes, and cells of the immune system.14,15 MC2-R is the classic ACTH receptor, expressed in the cortex of the adrenal gland. MC2-R binds only ACTH and has no affinity for the other melanocortin peptides,16 although ACTH itself is recognized by the other 4 melanocortin receptors. The MC3-R is expressed in the brain, chiefly within the hypothalamus, cortex, thalamus, and limbic system.17 It has also been detected in the gut, placenta, kidney, and heart.18 MC4-R is expressed widely throughout the mammalian central nervous system. It is highly expressed in regions of the hypothalamus known to be involved in the control of energy homeostasis19 and is found within the brainstem and spinal cord.20 MC5-R is expressed more ubiquitously in many peripheral tissues but appears to have a role in pheromone- and sebum-producing exocrine glands.21

Central Melanocortin System

Contained within the arcuate nucleus of the hypothalamus are 2 separate populations of neurons that express POMC or both NPY and agouti-related protein (AgRP).22,23 POMC neurons project to many other regions of the brain, including other hypothalamic regions such as the paraventricular nucleus that are involved in energy homeostasis (paraventricular nucleus) (Figure 2).24 Caudally, projections extend to the thalamus and the medial amygdala; POMC neurons also send descending projections to the brainstem and spinal cord. It is these arcuate neurons, together with their downstream second-order neurons expressing MC3-R and MC4-R, that make up the central melanocortin system. The fed state is characterized by increased POMC neuronal activity with inhibition of AgRP neurons. This increase in melanocortin tone in regions of the brain expressing MC4-R decreases food intake and increases energy expenditure. In contrast, states of negative energy balance such as fasting are characterized by inactivation of POMC neurons (therefore reducing melanocortin levels) but stimulation of AgRP activity. The resultant decrease in MC4-R signaling stimulates feeding and reduces energy expenditure.

An intact central melanocortin signaling pathway is critical for normal energy homeostasis, with defects in synthesis, processing, and action of POMC peptides resulting in obesity (reviewed by Coll et al22). For example, genetic deletion of MC4-R in mice and humans results in severe hyperphagic obesity, with an increase in both fat and lean mass.23 Indeed, MC4-R mutations are responsible for up to 5% of cases of severe childhood obesity and up to 2.5% of adult obesity.24,25 A study of the general population in the United Kingdom suggested a mutational frequency of 1 in 1000,26 making MC4-R deficiency one of the most common single-gene disorders. Of course, this still means that the majority of obese people cannot ascribe their obesity to defective melanocortin receptor functioning, with many complex interactions between environment and genes yet to be untangled, but these studies have played a major role in highlighting the importance of this pathway in human physiology.

Melanocortins and the Sympathetic Nervous System

As befits a system that controls vital homeostatic processes in an involuntary manner, regulation of the sympathetic nervous system is complex, with output being an integration of many inputs. Emerging data indicate that one of these many inputs...
may arise from melanocortin signaling, with studies from rodents indicating a close functional and anatomic link between the central melanocortin system and the sympathetic nervous system. Many of these studies have focused on adipose depots, both thermogenic brown adipose tissue and white adipose tissue, the principal storage depot of surplus energy. Intracerebroventricular administration of the MC4-R agonist produces a dose-dependent increase in sympathetic nerve activity to brown adipose tissue, whereas intracerebroventricular AgRP can suppress sympathetic activity to brown adipose tissue.

Noguieras et al have also demonstrated that bidirectional modulation of central melanocortin tone can have a powerful influence on peripheral lipid metabolism that is quite independent of its effects on food intake. Pharmacological blockade with the melanocortin antagonist SHU9119 caused an increase in triglyceride concentration in epididymal white adipose tissue, an increase in total body fat mass, and a drive toward a decreased metabolic use of fats. Conversely, treatment with the melanocortin agonist MT-II increased the expression of genes implicated in lipid catabolism. Repeating identical antagonist administration experiments in mice engineered to be deficient in β1-, β2-, and β3-adrenoceptors did not bring about the increase in body weight or lipogenic activity seen in the wild-type animals, highlighting the role of the sympathetic nervous system in mediating the peripheral effects of central melanocortin activity.

Direct anatomic evidence to further support this functional link has come from studies using the pseudorabies virus as a transneuronal retrograde tracer. This virus has the ability to be taken up by the terminals of postganglionic sympathetic neurons in peripheral tissue and transported in a retrograde fashion right back to preganglionic neurons higher in the central nervous system. Building on previous studies using this technique to explore the central nervous system origins of the sympathetic nervous system outflow to brown adipose tissue, Bartness et al combined injection of this viral tracer with in situ hybridization to identify MC4-R mRNA and convincingly demonstrated that a high percentage of MC4-R-bearing neurons project to fat tissue.

In addition to these metabolic links, strands of evidence from murine and more latterly human physiology studies have now converged to give a molecular link between obesity and hypertension. Early evidence suggesting a role for melanocortin peptides in autonomic cardiovascular control came from the identification of high levels of MC4-R expression in areas of the paraventricular nucleus that provide descending projections to autonomic preganglionic neurons. Subsequently, the ability of leptin to increase mean arterial pressure and lumbar sympathetic nerve activity was convincingly shown to be mediated through melanocortin activity. Further pharmacological studies demonstrated that sustained administration of an MC3/4-R agonist increased mean arterial pressure despite hypophagia, whereas in contrast, central infusion of the MC3/4-R antagonist SHU9119 caused a marked decrease in heart rate and mean arterial pressure. A similar infusion of melanocortin antagonist to spontaneously hypertensive rats caused a >20-mm Hg drop in mean arterial pressure, despite also causing weight gain, insulin resistance, and hyperleptinemia, indicating that, at least in this model of hypertension, an increase in endogenous melanocortin tone appears to contribute to the elevation in arterial pressure.

This pharmacological evidence was further supported by studies of MC4-R–deficient (Mc4r-null) mice. These mice are not hypertensive on either a standard or high-salt diet. Their basal average heart rate is also significantly lower than that of wild-type mice both during daylight hours and in the hours of darkness when, because of their reverse circadian rhythm, mice are more active (Figure 3). Furthermore, although intracerebroventricular administration of α-MSH to wild-type and Mc3r+/− mice led to a significant increase in mean arterial pressure, this response was not seen in Mc4r-null mice.

Building on these data, Greenfield and colleagues have recently extended our knowledge of the melanocortin system in humans by a detailed phenotypic analysis of adults heterozygous for complete loss-of-function mutations in MC4R. The prevalence of hypertension was significantly lower in MC4-R–deficient subjects compared with equally overweight control subjects. Furthermore, compared with controls, MC4-R–deficient subjects had a lower increase in heart rate on waking, a lower heart rate during euglycemic hyperinsulinemia, and a lower 24-hour urinary norepinephrine excretion, all in keeping with reduced activity of the sympathetic nervous system. During sleep, there was no difference in the high-frequency component of heart rate variability (regarded as a measure of parasympathetic activation) between the 2 study groups. Of note, total cholesterol was no different between the 2 groups (4.9±0.8 versus

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**Figure 3.** Basal 24-hour average mean arterial pressure (MAP) and heart rate (HR) in male 17- to 19-week-old MC4-R(−/−), MC4-R(+/−), and wild-type (WT) mice on days 11, 12, and 13 after implantation of telemetry probe (n=5 to 7 per group). *P<0.05 vs MC4R(−/−) mice. Reproduced with permission from Tallam et al. Copyright © 2005 American Heart Association. All rights reserved.
5.0 ± 1.0 mmol/L, MC4r-deficient versus obese control mice, respectively). The same group also went on to examine the effects of increased central melanocortin tone by studying the effects of a subcutaneous infusion of a synthetic peptide agonist highly selective for MC4-R on 28 overweight or obese volunteers. The maximum tolerated dose led to a significant increase in both systolic and diastolic blood pressures (9.3 ± 1.9 and 6.5 ± 1.1 mm Hg, respectively; Figure 4). Thus, by combining data from careful phenotyping of patients with congenital deficiency in melanocortin tone with data from pharmacological studies, these authors were able to show that both decreases and increases in central melanocortin signaling influence blood pressure in humans and that the effects were not explained by changes in circulating insulin levels or insulin sensitivity. This study now gives a potential mechanistic explanation to the well-established, but poorly understood, effects of weight loss and obesity on human hypertension.

Further studies are currently underway to determine further whether MC4r-deficient obese adults are protected from the adverse cardiovascular consequences that normally accompany obesity. We await the outcome of studies investigating left ventricular mass, cardiac output, arterial stiffness, and endothelial function with great interest (personal communication, Dr I. Sadaf Farooqi, MBBS, PhD, Cambridge, UK, 2009).

**γ-MSH, Sodium Homeostasis, and Hypertension**

γ-MSH was the last of the melanocortin peptides to be characterized, and its true physiological role is somewhat less well defined compared with its more famous “older sibling,” α-MSH. Nevertheless, it is clear from animal model systems that γ-MSH does have an effect on the cardiovascular system, albeit one that is somewhat distinct from that of α-MSH. Administration of γ-MSH can increase mean arterial pressure and heart rate in wild-type, Mc3r−/−, and Mc4r−/− mice. The hypertensive effect of intravenous γ-MSH is not blocked by intracarotid delivery of potent melanocortin antagonists but can be abrogated after intracerebroventricular administration of the sodium channel blocker benzamil in both Mc3r−/− and Mc4r−/− mice. Such observations have led to speculation that γ-MSH may act on a receptor quite distinct from 1 of the 5 classic melanocortin receptors.

Animal data also indicate that γ-MSH has a role in sodium homeostasis and can act as a natriuretic. Rats and mice given a high-salt diet respond by doubling the γ-MSH content of the pituitary intermediate lobe and their circulating concentration of γ-MSH. Mice lacking the processing enzyme PC2 (Pc2 null) are rendered γ-MSH deficient as a result of impaired secondary POMC processing and, unlike their wild-type littermates, have lost the ability to respond to a high-salt diet by increasing γ-MSH level. Thus, γ-MSH–deficient Pc2-null mice are rendered significantly hypertensive after just a week of a high-salt diet, in contrast to wild-type littermates, which remain normotensive. This hypertension can be readily reversed by γ-MSH but not by α-MSH.

Despite these data, much contention remains about γ-MSH, not least of which is the determination of the predominant form in the circulation, with at least 4 different species recognized (γ1-, γ2-, γ3-, and lys-γ3 MSH). Furthermore, much of the work relating to the cardiovascular role of γ-MSH has focused on rodent models, which, unlike humans, have a clearly discernible pituitary intermediate lobe from which circulating forms of this peptide are thought to arise. Thus, uncertainty remains as to whether data from these rodent models can be extrapolated to human physiology, with scant data on the role of γ-MSH in human cardiovascular physiology.

**Antiinflammatory Actions of Melanocortins**

The immunological milieu following tissue damage is complex, with a cascade of interacting mediators influencing the pathophysiological response. Although by no means as well defined as the evidence base supporting the role of melanocortin signaling in energy homeostasis, data now indicate that melanocortins can inhibit peripheral production of the chemical mediators of inflammation and, by doing so, potentially modify inflammatory cell migration. Interestingly, just as peripheral signals of energy balance are integrated within the brain, so do central melanocortinergic systems also appear to have an important role in modulating the inflammatory response to peripheral stress.

Melanocortins have long been known to have potent antipyretic properties, quite distinct from any role in normal thermoregulation and via a mechanism that does not involve the adrenal gland. Both α-MSH and ACTH administered centrally can significantly ameliorate the fever brought on by peripheral administration of endogenous pyrogens even in adrenalectomized animals.
The ability of melanocortins to substantially ameliorate the deleterious effects of severe tissue hypoxia in animal models led Bazzani et al.\textsuperscript{55} to study whether they may also have a beneficial effect on the tissue damage induced by coronary occlusion. Using ligation of the left anterior descending coronary artery in rats as the model, this group showed that intravenous administration of ACTH 1-24 caused a significant dose-dependent reduction in the incidence of arrhythmia and death and effectively doubled the volume of healthy cardiac muscle remaining compared with sham-treated animals (Figure 5). Furthermore, in animals subject to temporary occlusion followed by reperfusion, ACTH treatment almost completely prevented the ischemia/reperfusion-induced increase in circulating free radical levels. However, the authors present no data to exclude that this effect is partially or wholly mediated by ACTH-stimulated corticosterone production.

Once again, the central action of melanocortins appears to be critical in bringing about this protective effect,\textsuperscript{56} with the effector arm of the circuit being efferent vagal fibers (Figure 6).\textsuperscript{57} Interestingly, this particular protective loop may, at least in part, preferentially involve MC3-R.\textsuperscript{58,59} Indeed, MC3-R may also be the critical receptor in affecting melanocortin-derived ischemic protection in the mesenteric microcirculation. Leoni et al.\textsuperscript{60} have recently shown not only that Mc3r-null mice display a more exuberant inflammatory response to mesenteric artery ischemia/reperfusion than do wild-type mice but also that pharmacological treatment with a selective MC3-R agonist that attenuates inflammatory damage in wild-type mice fails to do so in Mc3r-null littermates.

**Brain**

The synthetic melanocortin analog NDP-MSH has recently been shown to have a neuroprotective role. Giuliani et al.\textsuperscript{61} induced transient global cerebral ischemia by bilateral occlusion of common carotids in gerbils. This resulted in active inflammation and neuronal damage within the hippocampus, with peripheral administration of NDP-MSH inhibiting cytokine expression and reducing histological damage within this brain region. Further pharmacological exploration of this pathway indicated that MC4-R but not MC3-R activation was responsible. Similar results have been seen in other species,\textsuperscript{62} and as in hypovolemic and septic shock, it now appears that the vagus nerve is important in mediating the protective effects of the melanocortins against cerebral ischemia. Ottani et al.\textsuperscript{63} showed that focal cerebral ischemia in rats induces a cerebral and hepatic inflammatory cascade that can be suppressed by melanocortins.

**Therapeutic Perspectives**

A plethora of data has accrued over the last 15 years on the structure and function of melanocortin receptors, particularly with respect to their role in energy homeostasis. With the
prevalence of obesity continuing to rise worldwide, the ability to modulate the activity of a surface receptor like MC4-R becomes a tantalizing pharmacological goal. However, getting a “clean hit” with a drug that tackles obesity by acting on central receptors is no mean feat. Consider the cannabinoid system, which, just like the melanocortin system, has a central action in the regulation of food intake and is widely expressed in the central nervous system. The early clinical promise of rimonabant, an antagonist at the cannabinoid 1 receptor, was dashed when unwanted off-target actions led to problems that resulted in the withdrawal of the drug. So it may be for drugs that act as melanocortin agonists.

Long before the melanocortin receptor system was characterized, central administration of a melanocortin agonist was reported to evoke a bizarre systemic syndrome of stretching yawning. Move forward 50 years, and melanocortin agonists designed primarily as an agent to reduce food intake and decrease body weight are, perhaps unsurprisingly, reported to cause similar systemic effects. Such findings will, at the very least, inject a note of caution into the active pursuit of these agents as effective and safe weight loss agents. However, a drug effect is only an adverse effect if it is unwanted, either in its direction or in its magnitude. A drug that causes an increase in blood pressure is going to be hard to let pass as a long-term treatment in a patient population likely to be burdened with other cardiovascular risk factors, but in an acute life-threatening emergency, this rapid-onset pressor effect may be far more helpful. Indeed, the history of melanocortin pharmacology has already gone through a similar cycle of serendipity whereby an “unwanted side effect” of penile erection after melanocortin agonist administration led to this class of drugs being developed as a treatment for erectile dysfunction.

There is still pharmaceutical industry interest in designing drugs to perturb melanocortin signaling, with high-throughput screening of compounds, in silico modeling, and the development of novel, nonpeptide, low-molecular-weight organic compounds all ongoing (see review by Wikberg and...
Mutulis. However, there is still much to do before melanocortin-derived agents, whether modified peptides or chemically distinct small molecules, make it into the clinical arena. There may be a need to design an agent that goes beyond simple receptor specificity and that also has tissue, or in the case of the brain, region specificity.

It is also clear that the roles of melanocortins in pathways controlling energy balance have been demarcated more clearly than those relating to cardiovascular disease. The data on melanocortins and ischemic damage are derived almost entirely from experimental animal models, and there are no substantive data linking melanocortins with the pathogenesis of atherosclerosis. However, we suggest that the recent proof-of-concept studies highlighting the beneficial effects of melanocortin on limiting tissue damage in cases of ischemia and inflammation merit further attention. We look forward to following the evolving story of how perturbations in melanocortin signaling, whether from congenital deficiency or following the evolving story of how perturbations in melano-cortin signaling, whether from congenital deficiency or pharmacological manipulation, influence cardiovascular pathophysiology.

Summary

The diverse roles of the melanocortin system can be viewed as crucial components of the body’s defense mechanisms, whether by limiting ultraviolet light damage to the skin, fueling the drive to eat when energy stores are low, or fine-tuning the inflammatory response to physical trauma to minimize tissue damage. Our knowledge of melanocortin biology continues to evolve and develop. The importance of key parts of the system in the control of energy homeostasis remains unchallenged, with, for example, common variants near MC4-R now being implicated in influencing fat mass, weight, and obesity risk at the population level. Furthermore, although not discussed in this review, there is an increasing body of work highlighting the role that increased melanocortin activity has in the pathogenesis of cachexia (see review by Marks et al).

With this ongoing expansion of knowledge, it is surely only a matter of time before pharmaceutical agents derived from these simple peptides come of age. However, whichever niche these drugs eventually occupy, clinicians need to remain mindful of this evolving sphere of influence and remain attuned to potential effects, good and bad, in tissue and organs distant from the primary target.

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Disclosures

None.

References


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