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Integrated insights into the role of alpha-melanocyte stimulatory hormone in the control of food intake and glycaemia

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ABSTRACT

Identifying peptide hormones with multipotent actions on both weight and glycaemia can have a significant impact on therapeutic options in the treatment of obesity and diabetes. This has been exemplified by recent advances involving pharmacological exploitation of glucagon-like peptide 1 biology. Herein, we summarise evidence supporting the potential candidacy in this light of alpha-melanocyte stimulatory hormone, an endogenous peptide hormone and a breakdown product of the neuropeptide pro-opiomelanocortin. We reference its well described central actions in the control of food intake and moreover highlight new data pointing to an important role for this peptide hormone in the periphery, in relation to glycaemic control.

1. Introduction

Numerous studies have documented the relationship between obesity and a number of comorbidities such as cardiovascular disease, dyslipidaemia, cancer, and most commonly type 2 diabetes mellitus (T2DM) [1,2]. This has contributed significantly to recent classification of obesity as a chronic medical disease by a number of global health organizations including the World Health Organization (WHO), Food and Drug Administration (FDA), the National Institutes of Health (NIH), the American Medical Association (AMA), and the Canadian Medical Association (CMA) [3,4].

Diabetes mellitus is recognized as the fastest growing chronic condition around the globe. In 2015, the International Diabetes Federation estimated that approximately 415 million adults have diabetes, with a rise to 642 million adults by 2040 projected [5]. T2DM accounts for at least 90% of all cases of diabetes mellitus. T2DM is characterised by fasting hyperglycaemia and exaggerated post-prandial glucose excursions arising from both β-cell dysfunction, resultant impairments in the temporal kinetics of insulin secretion, and insulin resistance in target tissues.

"Diabesity" is an increasingly used term which refers to the clinical phenotype of patients presenting with co-morbid T2DM and obesity [6]. Diabesity is a complex disorder involving disruption to the homeostatic regulation of food intake, energy metabolism, and glycaemia. Dysregulation of regulatory peptide hormone biology is implicated in the pathogenesis of diabesity. Understanding and correcting neuroendocrine deficits represents a central tenant of the current state of the art in the management of this disorder. This is attested to by the dual efficacy of targeting glucagon-like peptide-1 (GLP-1) as a means of optimizing weight and glycemic control in patients with diabesity phenotype. Identifying other peptide hormones with multipotent actions on weight and glycaemia could open a pathway to the development of new therapies for diabesity.

In the present review, we examine the evidence supporting the potential candidacy of alpha-melanocyte stimulatory hormone (α-MSH) in this regard. We address its well-recognised central actions in the control of food intake and highlight new data that point to an important role for peripheral α-MSH in glycaemic control.

2. α-MSH-structure, synthesis, signalling and target tissues

The 13-amino acid acetylated peptide hormone (Ac-SYSMEHFRWGKPV-NH2) is the active form of α-MSH [7]. The hormone was so named after its initial description as a regulator of melanin

Abbreviations: WHO, World Health Organization; FDA, Food and Drug Administration; NIH, The National Institutes of Health; AMA, The American Medical Association; CMA, The Canadian Medical Association; T2DM, Type 2 Diabetes Mellitus; α-MSHl, Alpha-melanocyte stimulatory hormone; POMC, Pro-opiomelanocortin; PC1-2, Prohormone convertase 1–2; ACTH, Adrenocorticotropic hormone; CPE, Carboxypeptidase E; PAM, Alpha-amidating monooxygenase; NAT, *N*-acetyltransferase; MC1R and MC3R-MC5R, Melanocortin receptors; ARC, Arcuate nucleus; CART, Cocaine- and amphetamine-related transcript; NPY, Neuropeptide Y; AgRP, Agouti-related protein; GULT, Glucose transporter proteins; MTII, Melanocyte receptor agonist; ATP, Adenosine triphosphate; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-alpha

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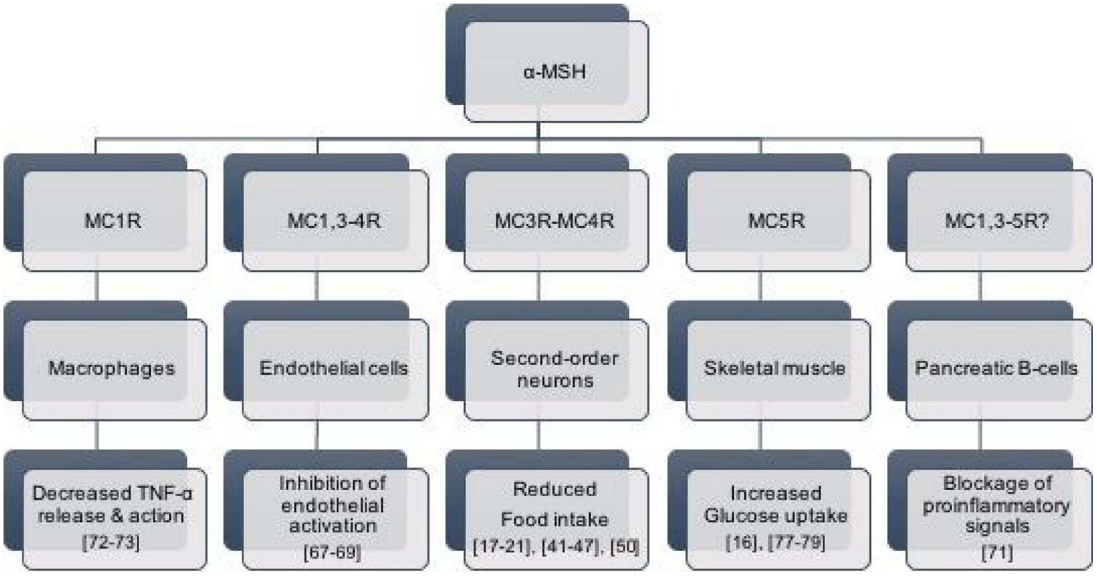

Fig. 1. The multidimensional effects of alpha-MSH relevant to the control of body weight and glycaemia.

synthesis [8] (Fig. 1). Alpha-MSH is a breakdown product of the neuropeptide pro-opiomelanocortin (POMC). During the first step of the breakdown process, POMC is cleaved by prohormone convertase 1 (PC1) to generate pro-adrenocorticotrophic hormone (ACTH) and β-lipotropin. PC1 further cleaves pro-ACTH to form $ACTH_{1\text{-}39}$. $ACTH_{1\text{-}39}$ is cleaved by prohormone convertase 2 (PC2) to create $ACTH_{1\text{-}14}$. A series of processes initiated by carboxypeptidase E (*CPE*), α-amidating monooxygenase (*PAM*), and *n*-acetyltransferase (*NAT*) take place to transform $ACTH_{1\text{-}14}$ to desacetyl $\alpha\text{-}MSH_{1–13}$, and then to acetyl-$\alpha\text{-}MSH_{1–13}$., respectively [9].

Natural alpha-MSH has a short half-life of just a few minutes due to its susceptibility to breakdown by proteases and thus development of a more stable analogue was an important breakthrough for studies seeking to exploit the physiological actions of this peptide [10]. The first analogue [Nle^4, d-Phe^7] α-MSH (melatonin receptor agonist-1 (MT-I)) was developed in 1980 by Sawyer TK *et al.* [11]. The replacement of Met^4 by Nle^4 prevented sulphur oxidation and the replacement of Phe7 by its synthetic version D-Phe^7 increased its stability. Hence the potency of the analogue was 26 times that of the natural peptide [11]. More work on the development of the analogue was carried out by Sawyer's groups [12], followed by the work of Al-Obeidi's group to develop to date the most potent alpha-MSH (melatonin receptor agonist-1 (MT-II)) analogue with a half-life of 2–3 days [13].

The hormone binds non-preferentially based on local receptor abundance to any one of four G-protein coupled melanocortin receptors designated MC1R, MC3R, MC4R and MC5R, resulting in multiple physiological functions for the peptide [14]. For decades, consideration of the function of α-MSH was limited to its role as a primary regulator of pigmentation through the MC1R receptor which is abundantly expressed in melanocytes and primed to respond to paracrine generation of α-MSH. In the skin α-MSH engagement of MC1R on melanocytes activates melanin synthesis regulating skin and hair colour.

More recently, elucidation of the central MC3R and MC4R dependent effects of POMC neuron derived α-MSH has constituted a seminal advance in understanding of the control of energy homeostasis [15]. Binding of α-MSH to MC5R was initially thought to be a negative regulator of exocrine secretion, but recent evidence indicates that elevated post-prandial levels of α-MSH in the periphery may be of mechanistic importance in glycaemic control via MC5R [16].

3. Central release of α-MSH and regulation of food intake

3.1. The effect of α-MSH on food intake

Alpha-MSH plays a role in the control of energy homeostasis. Central administration of alpha-MSH results in significant reduction in food intake in animal studies [17–21]. The central effect of α-MSH on food intake is primarily based on its binding with MC3R and MC4R in the hypothalamic nuclei, particularly the paraventricular nucleus, following liberation from projecting POMC neurons in the arcuate nucleus (ARC) [22]. Via engagement of specific melanocortin receptor subtypes on second-order neurones, α-MSH transduces an anorexigenic signal to various brain regions involving downstream mediators including brain-derived neurotrophic factor (BDNF) [23].

In mice, deletion of MC3R results in increased adiposity, reduced energy expenditure and fat oxidation, but does not alter food intake [24]. In humans, the phenotypic features of MC4R deficiency include hyperphagia, increased fat and lean mass and hyperinsulinemia. Congenital MC4R deficiency explains around 5% of non-syndromic cases of morbid obesity [25]. Specific mutations within the MC4R gene are found in approximately 1–7% of people with paediatric onset obesity and BMI above 40 kg/m^2, and collectively represent the commonest monogenic form of obesity in humans [26]. Interestingly, two polymorphisms of the MC4R gene (I251L and V103L) which they have a protective effect against obesity [27–29]. Those polymorphisms increase the function of MC4R and therefore reduce food intake and increase energy expenditure [30]. The discovery highlighted the vital role this receptor in body weight homeostasis [29].

Autoantibodies against MC4R have also been detected in 3.6% of obese study subjects but not in normal weight subjects [31]. Intracerebroventricular administration of anti-α-MSH immunoglobulin in rats results in increased food intake, suggesting a possible role for autoimmune, Type II hypersensitivity reactions in the pathogenesis of obesity in some individuals [31].

The engagement of MC3R-MC4R by α-MSH is subject to competitive inhibition by Agouti-related peptide AgRP [32]. Central administration of AgRP in rodents stimulates food intake and reduces energy expenditure [33,34]. Various polymorphisms in the gene encoding AgRP are associated with either predisposition to, or protection from obesity, as well as susceptibility to anorexia nervosa [35–37].

The expression of neuropeptide Y (NPY) in neurones is stimulated in states of negative energy balance and fat loss, for example in the