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Review

Cardiovascular effects of melanocortins ☆

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ABSTRACT

Melanocortins (MSH's) are three structurally related peptides derived from proopiomelanocortin. They regulate several physiologic functions including energy metabolism, appetite, and inflammation. Recent work in rodents has also identified important effects of MSH's, particularly γ-MSH, on sodium metabolism and blood pressure regulation. Normal rats and mice respond to a high sodium diet with an increase in the plasma concentration of γ-MSH, and remain normotensive, while those with genetic or pharmacologic γ-MSH deficiency become hypertensive on a high sodium diet. This hypertension is corrected by exogenous administration of the peptide. Mice lacking the γ-MSH receptor (the melanocortin 3 receptor, *Mc3r*) also become hypertensive on a high sodium diet but remain so when administered γ-MSH, and infusions of physiologic levels of the peptide stimulate urinary sodium excretion in normal rats and mice, but not in mice with deletion of *Mc3r*. The salt-sensitive hypertension in rodents with impaired γ-MSH signaling appears due to stimulation of noradrenergic activity, since plasma noradrenaline is increased and the hypertension is rapidly corrected with infusion of the α-adrenoceptor antagonist phentolamine. In contrast to the antihypertensive property of physiologic levels of γ-MSH, intravenous or intracerebroventricular injections of high levels of the peptide *raise* blood pressure. This occurs in mice lacking *Mc3r*, indicating an interaction with some other central receptor. Finally, the salt-sensitive hypertension in rodents with disruption of γ-MSH signaling is accompanied by insulin resistance, an observation which offers a new window into the study of the association of salt-sensitive hypertension with insulin resistance and type II diabetes.

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1. Introduction

Melanocortins (melanocyte stimulating hormones, MSH's) are peptides derived from proopiomelanocortin by proteolytic processing. There are three MSH peptides which share a common core heptapeptide sequence but differ in overall size and in C-terminal amidation. α- and β-MSH were initially identified by their actions on dispersion of melanin in skin of reptiles and amphibians. When the complementary DNA for proopiomelanocortin became available, Nakanishi and colleagues deduced a peptide sequence in the N-terminal region which shared some homology with α- and β-MSH and which was flanked with dibasic amino acid cleavage sites. They named this sequence γ-MSH with the expectation that it would be a secreted peptide with melanin dispersing properties (Nakanishi et al., 1979). Although subsequent work indicated little effect of γ-MSH on pigmentation, the peptide has been shown to possess a number of other important qualities. This review will summarize current information on the cardiovascular effects of the melanocortins, with particular emphasis on γ-MSH.

2. Properties of γ-MSH

2.1. Natriuresis

Initial interest in γ-MSH as a peptide with important renal and cardiovascular actions stemmed from the observations of Gruber and Callahan (1989). They were able to demonstrate that γ-MSH was natriuretic when injected in intravenous boluses into hydrated, anesthetized rats in low doses (<64 pmol) (Lymangrover et al., 1985) but was hypertensive when given in higher amounts (Callahan et al., 1984). The physiologic significance of the natriuretic property of the peptide became clear in 1987 when it was shown that a γ-MSH-like peptide mediated the reflex natriuresis which occurs after acute unilateral nephrectomy (Lin et al., 1987; Ni et al., 1998). These studies indicated that γ-MSH played a role in this specific situation of natriuresis, and opened up the possibility that it could have a broader role as a component in the maintenance of overall sodium metabolism by participating in the reflex regulation of sodium excretion.

The survival value from an evolutionary standpoint of the postnephrectomy natriuresis would on the face of it seem to be small, so it became of interest to see if γ-MSH could have a role in longer term adjustments accompanying changes in dietary sodium intake. Measurement of immunoreactive γ-MSH concentration in plasma of rats fed a high sodium diet (8% NaCl) vs a low sodium diet (0.07%) for ≥1 week showed that peptide levels were twice as high in rats fed the high sodium diet compared to those on the low sodium diet (Mayan et al., 1996). No change occurred in plasma adrenocorticotrophic hormone (ACTH) concentration, the major circulating peptide derived from processing of proopiomelanocortin in the anterior lobe of the pituitary. This increase in plasma γ-MSH concentration during ingestion of the high sodium diet was accompanied by an increase in γ-MSH content of the pituitary neurointermediate lobe but not of the anterior lobe. Whole pituitary proopiomelanocortin mRNA abundance increased progressively with duration of the high sodium diet, and *in situ* hybridization showed that this increase was almost exclusively confined to the neurointermediate lobe (Mayan et al., 1996). These observations, coupled with the natriuretic properties of the peptide (Chen et al., 1997b; Lin et al., 1987; Lymangrover et al., 1985; Ni et al., 1998), indicated that the γ-MSH system could be part of the coordinated response to circumstances of dietary sodium excess, thereby greatly strengthening the argument that it played an important physiological role.

2.2. Renal receptors for γ-MSH

MSH peptides interact with a family of five receptors, melanocortin MC_1 receptor through melanocortin MC_5 receptor. These are G-protein-coupled receptors with seven membrane-spanning units (Humphreys, 2004; Schioth, 2001; Wikberg et al., 2000). The melanocortin MC_1 receptor is expressed on skin melanocytes and mediates pigment dispersion by α-MSH, whereas the melanocortin MC_2 receptor is the ACTH receptor expressed in adrenal cortex and responsible for stimulation of glucocorticoid synthesis and secretion. The melanocortin MC_3 and MC_4 receptors are expressed in brain and other tissues, and information on their function has been gleaned from knockout mouse models lacking one of the receptors. The *Mc3r* knockout mouse has an alteration in energy metabolism with an increase in body fat content and decrease in muscle mass with no overall change in weight (Butler et al., 2000; Chen et al., 2000), and a role for γ-MSH acting through the melanocortin MC_3 receptor has been suggested in experimental arthritis (Getting et al., 2006). The *Mc4r* knockout mouse develops marked obesity and overeating (Huszar et al., 1997), and has been a useful approach to the molecular understanding of appetite control and the determinants of obesity (Ellacott and Cone, 2006). The melanocortin MC_5 receptor is expressed in a number of tissues including exocrine glands, and deletion of this gene in mice results in a picture of exocrine dysfunction (Chen et al., 1997a). Of these five receptors, γ-MSH has affinity at physiologic concentrations only for the melanocortin MC_3 receptor, and it has been viewed as the probable endogenous ligand for this receptor. No expression of melanocortin MC_1 or MC_2 receptor mRNA was found in renal cortex or medulla, but mRNA for the three other receptors could be detected in both regions of the kidney, with roughly similar signal abundance. However, signal intensity of the melanocortin MC_3, but not MC_4 or MC_5 receptor, increased dramatically in rats fed the high sodium diet; this increase was confined to the medulla. These changes in melanocortin MC_3 receptor mRNA abundance induced by the HSD were paralleled by an increase in melanocortin MC_3 receptor protein in inner medullary collecting duct cells isolated from rats ingesting the high sodium diet (Ni et al., 2006a), and in whole kidney homogenates from Dahl salt-resistant, but not salt-sensitive, rats (Chandramohan et al., 2009). This increase in melanocortin MC_3 receptor expression caused by the high sodium diet had functional significance, since γ-MSH-dependent cAMP production was much greater by collecting duct cells isolated from kidneys of rats ingesting the high sodium diet than from those eating the low salt diet, and intrarenal infusion of γ-MSH to rats fed the high sodium diet led to brisk increases in sodium and cAMP excretion that were not observed when the peptide was infused into kidneys of rats fed the low sodium diet. These results suggest that the γ-MSH system could be an important element in the renal response to high dietary sodium intake: both the plasma concentration of the peptide, reflecting increased synthesis and secretion from the pituitary, and the abundance of its receptor in the kidney, are increased during the ingestion of the high sodium diet.

3. Consequences of interruption of γ-MSH signaling

3.1. Genetic approaches

In view of the evidence just summarized that the γ-MSH system is responsive to dietary sodium intake, it became of interest to examine the consequences of disruption of this system. As mentioned earlier, γ-MSH is derived from pituitary proopiomelanocortin. Processing of proopiomelanocortin into its component peptides is driven by two