Modulation of blood pressure by central melanocortinergic pathways*

Tanja Maier and Joachim Hoyer

Department of Nephrology, Philipps-Universität Marburg, Marburg, Germany

Correspondence and offprint requests to: Joachim Hoyer; Email: hoyer@med.uni-marburg.de


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Introduction

Obesity is strongly associated with hypertension. However, the underlying molecular or pathophysiological mechanisms of obesity-induced hypertension are poorly understood.

In this context, the central melanocortin system is of interest for two reasons:

(a) Melanocortinergic signaling is a key regulator in the control of food intake and body weight,
(b) Centrally expressed melanocortin receptor (MCR) subtype MC4R not only conveys hypothalamic signals suppressing food intake and increasing energy expenditure but is also involved in blood pressure control.

In a recent study by Greenfield and coworkers in patients with a genetic form of obesity, a direct impact of neuronal melanocortins on the development of hypertension was hypothesized. Pharmacological treatment with an MCR agonist supported the observation of a blood pressure-regulating effect of the melanocortin system in humans [1].

The discovery of the melanocortin system has been enthusiastically well received in the last two decades. A large number of significant scientific reports demonstrated a large array of physiological functions and molecular mechanisms of this system. The characterization of MCRs and the ensuing synthesis of selective ligands with agonist and antagonist activity are generating a most promising source of innovative drugs for widespread pathological conditions, i.e. nutritional disturbances, myocardial infarction, rheumatoid arthritis, inflammatory bowel disease, diabetic neuropathy, sexual impotence and probably neurodegenerative diseases (for review, see references [2–12]).

Melanocortins [melanocyte-stimulating hormones (MSHs)] derive from the precursor proopiomelanocortin (POMC) in the nucleus arcuatus and their expression is strongly connected to leptin as part of the same loop of regulation of food intake and weight control (Figure 1) [13–17,19,20]. The actions of melanocortins are mediated by a family of five G protein-coupled receptors known as MCRs. MC3R and MC4R are largely distributed in the brain and the CNS (mainly the paraventricular, dorsomedial and lateral nuclei in the hypothalamus). The other MCRs are expressed in tissues apart from the nervous system and mediate the non-neuronal effects of MSH like pigmentation and ACTH-induced steroid synthesis [3–5,12].

The genetic deficiency of MC4R is the most common form of monogenic obesity and is a direct proof for the critical role of the melanocortin system in obesity [18,25]. In addition to hormonal effects and some bizarre effects on behaviour (i.e. excessive yawning, crisis of stretching or spontaneous penile erection), melanocortins have been reported to have a variety of important effects on cerebral function [10,11]. Melanocortins also have a direct effect on cardiovascular function [21–24,28]. Central administration of alpha-MSH increases the mean arterial pressure and heart rate, and animal data propagate that these effects are mediated via interference with autonomic outflow [22,23,29]. Numerous studies suggest that hyperinsulinaemia is involved in obesity-induced hypertension through effects on the activity of the sympathetic nervous system [26,27].

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In the study of Greenfield and coworkers, blood pressure, function of autonomic nerve system and metabolic data of subjects with obesity due to a loss-of-function mutation in the melanocortin 4 receptor coding gene (n=46) were compared to equally overweight controls (n=30, BMI 25–30 kg/m²) with a normal MC4R genetic sequence (observational study).

Furthermore, the pharmacologic effects of a synthetic peptide agonist (LY2112688), highly selective for MC4R, were studied in healthy overweight men and women (n=28, BMI 25–30 kg/m²; double-blind, dose-escalating, placebo-controlled crossover study design).
Summary of results

Blood pressure

The prevalence of hypertension (defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >85 mmHg or treatment with antihypertensive medication) was significantly lower in the MC4R-deficient group than in the control group even if only small groups were compared in this study. Also, mean blood pressure values were significantly lower in the MC4R group compared to the control group when subjects taking antihypertensive drugs were excluded from the analysis (four and seven subjects, respectively).

Autonomic nervous system activity

In order to test the autonomic nervous system, heart rate and its variability were examined with or without stimulation by insulin. No difference in sleeping heart rate between the two study groups was observed. However, the increase of heart rate on waking as a measure of sympathetic nerve activity was significantly attenuated in the MC4R group ($p=0.007$). Also, the high-frequency component of heart rate variability, predominantly a measure of parasympathetic activity, was attenuated during the early morning waking period in MC4R-deficient subjects.

By use of a hyperinsulinaemic–euglycaemic clamp procedure, the effect of insulin on heart rate was tested since i.v. insulin increases heart rate. During insulin clamping, MC4R-deficient subjects maintain significantly lower heart rates than control subjects ($p\leq0.001$). Also, during insulin clamping, the high-frequency component remained higher in MC4R-deficient subjects ($p=0.02$), consistent with greater parasympathetic activity and relatively lower sympathetic activity compared to the control group.

Furthermore, MC4R-deficient subjects had lower 24-h norepinephrine excretion compared to control subjects.

Other phenotypic and metabolic signatures

MC4R-deficient subjects had similar measures of total body fat and fat-free mass, intra-abdominal tissue area, subcutaneous abdominal adipose tissue and liver fat as the matched control group.

Throughout the insulin clamp procedure, both groups had similar mean steady-state levels of blood glucose and plasma insulin, no significant difference in insulin-mediated glucose uptake, with similar rates of insulin-stimulated oxidative and non-oxidative glucose disposal.

In principle, reduced activity of the sympathetic nervous system would be expected to result in an increased insulin secretion in the MC4R-deficient subjects. However, there was only a trend in insulin secretion levels during the intravenous glucose tolerance test without reaching statistical significance.

Effects of MC4R agonist (LY2112688)

Intravenous infusion of this agonist resulted in symptoms known to be mediated by melanocortin pathways like yawning, muscular stiffness and penile erection. There was a dose-dependent increase of blood pressure in overweight or obese adults compared with placebo.

At a fixed dose in 1.0 mg LY2112688 per 24 h, the average difference of systolic blood pressure at 24 h was 9.3±
1.9 mmHg (p ≤ 0.001). The average difference of diastolic blood pressure at 24 h was 6.6 ± 1.1 mmHg (p ≤ 0.001). Also, corresponding blood pressure changes were sustained at all doses after a 7-day infusion of LY2112688.

A significant increase in heart rate (3 bpm), but no increase in levels of urinary norepinephrine, plasma insulin and glucose, was observed after administration of the agonist LY2112688.

Discussion

The study by Greenfield and coworkers in patients with genetic deficiency of the melanocortin 4 receptor demonstrate that increases as well as decreases in central melanocortin signaling influence blood pressure in humans. Long-standing decreases in melanocortinergic tone are associated with reduced activity in the sympathetic nervous system; these effects are not explained by changes in insulin levels or insulin sensitivity.

MC4R haploinsufficient patients have a significantly lower prevalence of hypertension and decreased systolic as well as diastolic blood pressure. Correspondingly, a pharmacological stimulation of melanocortin signalling with a MC4R agonist increased systolic and diastolic blood pressure in obese volunteers.

The study is important with respect to two different aspects:

(A) The melanocortin system is involved in blood pressure regulation in obese patients and, apparently, obese patients with genetic MC4R deficiency are protected from the development of hypertension. Further studies are needed to test the melanocortin system as a new and independent regulator of blood pressure in normal or hypertensive subjects with or without obesity.

(B) The blood pressure-increasing effect of the specific agonist along with other side effects possibly limits its applicability as a weight control drug in obese patients.

The study cannot elucidate the particularly interesting effects of melanocortin pathways on hypertension in nutritional obesity or in any other form of obesity.

Furthermore, the study has some specific limitations due to the characteristics of the study population and the tests used to measure the activity of the autonomic nervous system. Therefore, general conclusions have to be derived with appropriate caution. The study population is constrained to patients with a specific genetic type of obesity. It will need further investigations to test the applicability of effects to other forms of obesity, especially to nutritional obesity. Furthermore, it should be noted that the subjects in the MC4R group were recruited from the Genetics of Obesity Study. Some of these patients were related to each other. Thus, additional genetic factors contributing to an altered regulation of blood pressure cannot be excluded. Unfortunately, the control group was not matched with respect to sex and had an opposite gender distribution compared to the MC4R group.

The use of urinary norepinephrine has to be considered not sufficient for the evaluation of the autonomic nerve system, and more precise measures like electrophysiological assessment of sympathetic tone will be warranted in further studies.

MC4R deficiency both in rodents and in children was shown to be associated with hyperinsulinaemia at a rate that is disproportionate to the degree of obesity, and several studies have implicated hyperinsulinaemia as a link between obesity and hypertension [26,27]. Greenfield and coworkers could not support this link because they found an association between MC4R deficiency and lower, but not higher, blood pressure.

The intervention study with the MC4R agonist in obese volunteers does not reveal any expected details about weight changes, but probably the time of intervention was too short. Further interventional studies over a longer time period in a much larger population with nutritional obesity together with a continuous blood pressure monitoring are needed.

Conclusion

In conclusion, the study by Greenfield and coworkers confirms the hypothesis that the melanocortin system is an independent regulator of systemic blood pressure in humans. It also proposes an interesting mechanistic link between a genetic form of obesity and hypertension. However, the role of the melanocortin system in non-obese patients and patients with nutritional obesity warrants further investigations. Also, the development of new treatment options targeting the MC4R might be hampered by various side effects.

Conflict of interest statement. None declared.

References

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