Suppression of γ-Melanocyte–Stimulating Hormone Secretion Is Accompanied by Salt-Sensitive Hypertension in the Rat

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Abstract—γ-Melanocyte–stimulating hormone (γ-MSH) is a natriuretic peptide derived from proopiomelanocortin (POMC) in the pituitary neurointermediate lobe (NIL); its plasma concentration in rats doubles after ingestion of a high (HSD; 8% NaCl) compared with a low sodium diet (LSD; 0.07%). Because NIL function is regulated through dopaminergic pathways, we asked whether dopaminergic stimulation with bromocriptine (5 mg/kg IP daily for 1 week) or inhibition with haloperidol (5 mg/kg IP for 1 week) alters the γ-MSH response to a HSD. In vehicle-treated rats, plasma γ-MSH and NIL γ-MSH content on the HSD were both markedly elevated over values in rats on the LSD (P<0.001); no difference in mean arterial pressure (MAP) occurred. In haloperidol-treated rats on the LSD, both plasma γ-MSH and NIL γ-MSH content were greater than in vehicle-treated rats (P<0.05) and did not increase further on the HSD; MAP was also no different. In bromocriptine-treated rats, neither plasma γ-MSH nor NIL γ-MSH content increased on the HSD versus LSD, and MAP was markedly elevated on the HSD (132±3 versus 106±3 mm Hg, P<0.001). Intravenous infusion of γ-MSH (0.4 pmol/min) to bromocriptine-treated rats on the HSD restored plasma γ-MSH concentration to a level appropriate for the HSD and lowered MAP from 131±6 to 108±5 mm Hg (P<0.01). These results demonstrate that the increases in NIL content and plasma concentration of γ-MSH normally occurring during ingestion of the HSD are prevented by dopaminergic suppression of NIL function. This results in deficiency of γ-MSH on the HSD and is accompanied by elevated blood pressure, which is corrected by infusion of the peptide. γ-MSH may be an important component in the normal response to a HSD; interruption of this response leads to salt-sensitive hypertension. (Hypertension. 2003;42:962-967.)

Key Words: natriuretic peptides • pituitary • hypertension, sodium-dependent • dopamine

Melanocyte-stimulating hormones (MSHs) are peptides of α, β, and γ primary structure, which are derived from the ACTH/β-endorphin precursor proopiomelanocortin (POMC). Identified initially from the property of α- and β-MSH to induce melanin dispersion in melanocytes of fish and amphibians, they are highly conserved in mammalian species, where their pigmentary function is minor. This has suggested that they may serve other important biological functions, and roles in inflammation, temperature regulation, satiety, and cardiovascular control have all been indicated.1–4 Each of the MSH peptides is also natriuretic,5–8 and the plasma concentration and pituitary content of γ-MSH immunoreactivity increase in rats fed a high sodium diet (HSD).9,10 Additional support for a role in sodium homeostasis comes from the observations that an HSD increases the mRNA abundance of POMC and of the prohormone convertase enzymes PC1 and PC2 involved in its processing into γ-MSH in the neurointermediate (NIL) of rat pituitary but not the anterior lobe (AL).9,10 We have recently observed that genetic deficiency of circulating γ-MSH caused by disruption of the PC2 gene is accompanied by marked salt-sensitive hypertension,11 further suggesting an important role of this peptide in sodium metabolism and blood pressure control.

POMC synthesis and processing in the NIL are under tonic dopaminergic suppression through the dopamine D2 receptor12,13; the dopamine agonist bromocriptine suppresses the synthesis of POMC and the processing enzymes PC1 and PC2, whereas the dopamine receptor antagonist haloperidol does the opposite.14,15 We asked if dopaminergic manipulation modified in any way the action of a diet high in sodium content to stimulate the abundance of NIL γ-MSH content and the plasma concentration of γ-MSH, and, if so, what effect this would have on blood pressure and sodium excretion (UNaV). We used systemic injections of bromocriptine, a
dopaminergic agonist, and haloperidol, a dopamine receptor antagonist, to do this. We found that bromocriptine treatment of rats fed the HSD prevented the increases in plasma concentration and NIL content of γ-MSH and led to a marked increase in blood pressure, indicating that these rats had salt-sensitive hypertension.

**Methods**

We studied male Sprague-Dawley rats weighing 210 to 280 g; they were obtained from Harlan Laboratories, Ltd (Jerusalem, Israel) and Charles River Laboratories (Hollister, Calif). The protocols were reviewed and approved by the Committees on Animal Research of UCSF and of Chaim Sheba Medical Center at Sacker School of Medicine.

**Experimental Groups and Drug Treatment**

Rats were divided into groups (10 to 20 per group) and placed on a low sodium diet (LSD; 0.07% NaCl, Purina Mills Purified Diet 5755, Catalog No. 46843). After a week, half of each group was changed to a diet high in sodium content (8% NaCl, Purina Mills, Catalog No. 32892), the other half remaining on the LSD. At this time, all rats underwent daily intraperitoneal injections of bromocriptine (Sigma) (5 mg/kg dissolved in methanolic sulfonic acid methyl ester), haloperidol (5 mg/kg dissolved in 1% lactic acid), or vehicle. Half of the vehicle-treated rats received methanesulfonic acid methyl ester and haloperidol; the other half received 1% lactic acid; results were pooled for analysis. These daily injections were maintained for 1 week. Six animals from each group were placed in metabolic cages after 1 week of the diets for 24-hour urine collection to determine U\textsubscript{NaV} on the LSD and HSD with the different treatments. Urine sodium concentration was determined by flame photometry (model 940, Instrumentation Laboratory).

**Pituitary γ-MSH Content**

Rats (6 per group) undergoing the above-described dietary and drug treatments were killed by decapitation, and the whole pituitary gland was removed and divided into the AL and NIL under a dissecting microscope. The lobes were placed in 100 μL 1N HCl, homogenized with a Dounce homogenizer, centrifuged, and aliquots of the supernatant taken for radioimmunoassay of γ-MSH (see below) and for measurement of protein by the dye-binding method of Bradford (Bio-Rad Laboratories).

**Measurement of Arterial Blood Pressure**

Rats treated with the diets and drugs listed above were surgically prepared as described.\(^8\),\(^16\) After 10 to 20 minutes for stabilization from surgery, blood pressure was recorded for 5 minutes, a large blood sample was withdrawn, and the animals were killed. This protocol was followed in 10 vehicle-treated and 10 bromocriptine-treated rats each on the LSD and HSD and 5 haloperidol-treated rats on each diet. In 11 additional bromocriptine-treated rats on the HSD, vehicle (normal saline containing 2 g glucose and 2.5 g bovine serum albumin per 100 mL) was infused intravenously at 10 μL/min. After 10 minutes of recording mean arterial pressure (MAP), the infusion was changed to vehicle containing α-MSH to deliver 0.4 pmol/min (n=6) or 20 pmol/min (n=5). MAP was recorded for 30 minutes, at which point the vehicle was changed again to one containing γ-MSH to infuse at the same rates. After an additional 30-minute period, a large blood sample was obtained and the rats were killed.

**Radioimmunoassays**

Blood was drawn into Vacutainer tubes (Becton-Dickinson) containing EDTA and 500 KIU aprotinin. These were centrifuged at 4°C for 10 minutes, and the plasma was decanted into conical tubes for storage at −70°C until assay. For the assays of γ-MSH and atrial natriuretic peptide (ANP), samples were extracted as previously described.\(^9\),\(^10\),\(^16\) Eluates were lyophilized and stored at −70°C until assayed. Pituitary extracts were assayed directly without extraction.

| Twenty-Four Hour Urine Volume and Sodium Excretion in Rats on the Low Sodium or High Sodium Diets |
|---------------------------------|-----------|-----------|-----------|
| Treatment                      | LSD       | HSD       | LSD       | HSD       |
| Vehicle                        | 15.8±1.3  | 33.7±1.3† | 0.04±0.01 | 14.6±0.84* |
| Bromocriptine                  | 15.3±1.0  | 42.0±1.9* | 0.05±0.02 | 12.6±0.33* |
| Haloperidol                    | 14.5±1.4  | 43.0±1.8* | 0.01±0.04 | 17.1±0.57‡ |

Data are mean±SEM of values from 6 rats in each group. LSD indicates low sodium diet; HSD, high sodium diet; and U\textsubscript{NaV}, sodium excretion volume.

*Significantly greater than LSD value, P<0.001.
†Significantly less than bromocriptine or haloperidol values, P<0.01.
‡Significantly greater than bromocriptine value, P=0.019.

The assay for γ-MSH was performed with the use of a commercial kit (Peninsula Laboratories), following the manufacturer’s instructions. The characteristics of the assay have been described.\(^10\),\(^16\) The assay for ANP also was performed with the use of a commercial kit (Peninsula Laboratories) and was carried out according to instructions with the kit. This assay measures rat α-ANP, Plasma renin activity (PRA) was assayed in unextracted samples with the use of a kit from DiaSorin.

**Statistical Analysis**

Values for each group are expressed as mean±SEM. Analysis was carried out with the use of GraphPad Instat software (GraphPad Software Inc). Comparisons between and among groups were carried out with the use of the paired or unpaired t test with only 2 groups and 1-way ANOVA when more than 2 groups were compared; when significant differences were detected, the Bonferroni post hoc test was used. Data from groups with unequal standard deviations were log-transformed before carrying out the comparisons. A probability value of <0.05 was used to indicate a significant difference.

**Results**

**Sodium Excretion**

The weight of the rats increased comparably during the study period regardless of diet or drug treatment. The HSD produced the expected high rate of U\textsubscript{NaV} in vehicle-treated rats, accompanied by a large urine volume (Table). Urine volume on the LSD was one third to one half as much as on the HSD, and U\textsubscript{NaV} was vanishingly low. Treatment with bromocriptine or haloperidol did not markedly alter the results compared with vehicle-treated rats except that U\textsubscript{NaV} in haloperidol-treated rats exceeded that in bromocriptine-treated rats on the HSD (P=0.0186). Also, urine flow during ingestion of the HSD was greater in both bromocriptine- and haloperidol-treated groups than in rats receiving the vehicle (P=0.01).

**Plasma γ-MSH Concentration**

Plasma γ-MSH concentration in vehicle-treated rats after 1 week of the HSD was more than double the value observed in rats on the LSD (75.9±8.3 versus 34.6±4.9 fmol/mL, P<0.001) (Figure 1). These results are comparable to those reported earlier by us.\(^9\),\(^10\) Dopaminergic stimulation with bromocriptine in rats on the LSD led to a comparable plasma concentration of γ-MSH (29.7±6.4 fmol/mL) as in vehicle-treated rats on LSD but markedly blunted the increase seen on the HSD (40.6±5.6 fmol/mL, P<0.01 versus vehicle-treated rats on the HSD). Indeed, the plasma concentration of γ-MSH in bromocriptine-treated rats on the HSD was not statistically different from that in bromocriptine-treated rats on the LSD.
During ingestion of the LSD, plasma γ-MSH concentration (67.2 ± 6.3 fmol/mL) was greater than that in either vehicle- or bromocriptine-treated rats (P < 0.05 for both) (Figure 1). Ingestion of the HSD caused no further increase (66.7 ± 8.2 fmol/mL), and this value was not statistically different from vehicle-treated rats on the HSD. Dopaminergic blockade with haloperidol thus stimulated plasma γ-MSH concentration in rats on the LSD to levels appropriate for a HSD, and on the HSD, the plasma concentration rose no further.

**Pituitary γ-MSH Content**

Immunoreactive γ-MSH content in pituitary NIL paralleled the results just described for plasma γ-MSH concentration. γ-MSH content was low in vehicle-treated rats on the LSD (0.14 ± 0.02 pmol/μg protein) but increased markedly in rats on the HSD (1.26 ± 0.09 pmol/μg protein, P < 0.001) (Figure 2). Bromocriptine treatment to rats on the LSD did not significantly alter NIL γ-MSH content compared with vehicle-treated rats (0.08 ± 0.03 pmol/μg), but bromocriptine treatment completely prevented the increase in NIL content of the peptide during ingestion of the HSD (0.11 ± 0.03 pmol/μg protein, P < 0.001 versus vehicle). As was true with plasma γ-MSH concentration, haloperidol treatment produced results opposite to those of bromocriptine. During ingestion of the LSD, NIL γ-MSH content was elevated to a level similar to that seen in vehicle-treated rats on the HSD and significantly greater than levels in either vehicle- or bromocriptine-treated rats on the LSD (1.28 ± 0.25 pmol/μg protein, P < 0.005 for both). There was no further increase in NIL content of γ-MSH in haloperidol-treated rats on the HSD (1.34 ± 0.21 pmol/μg, Figure 2).

γ-MSH content in the AL was much less than in the NIL (only approximately one tenth to one fiftieth) and was minimally influenced by dietary sodium content. In vehicle-treated rats, values were 0.020 ± 0.001 pmol/μg on the LSD and 0.034 ± 0.003 pmol/μg on the HSD (P < 0.05). The drug treatments caused no significant changes in AL γ-MSH content. Bromocriptine-treated rats had values of 0.02 ± 0.002 and 0.02 ± 0.003 pmol/μg on the LSD and HSD, respectively (P = NS). Corresponding values for haloperidol-treated rats were 0.03 ± 0.007 and 0.05 ± 0.008 pmol/μg (P = NS).

**Mean Arterial Blood Pressure**

MAP in vehicle-treated rats on the LSD was 101 ± 3 mm Hg and was statistically unchanged at 106 ± 3 mm Hg during ingestion of the HSD (n = 10 for each group, P = NS) (Figure 3). MAP on the LSD was not affected by bromocriptine (100 ± 3 mm Hg) or haloperidol (100 ± 5 mm Hg) treatment, nor did MAP change significantly in haloperidol-treated rats ingesting the HSD (103 ± 6 mm Hg). However, bromocriptine-treated rats exhibited a large increase in MAP while on the HSD (132 ± 3 mm Hg, P < 0.001 versus all other values) (Figure 3). These results indicate that γ-MSH deficiency as a consequence of bromocriptine treatment is associated with marked salt-sensitive hypertension.

**Effect of MSH Infusion**

To evaluate the causative role of γ-MSH deficiency in this salt-sensitive hypertension, we infused MSH peptides intravenously at 2 different rates to anesthetized bromocriptine-treated rats that had ingested the HSD for 1 week. Six rats received infusions at 0.4 pmol/min; control MAP in these rats was 132 ± 5 mm Hg. Infusion of α-MSH for 30 minutes had no effect on MAP (134 ± 3 mm Hg, P = NS versus control). On the other hand, subsequent infusion of γ-MSH for 30 minutes reduced MAP to 108 ± 5 mm Hg (P < 0.01 versus control or α-MSH infusion), a value not significantly different from values observed in vehicle-injected rats on the HSD. Plasma γ-MSH concentration at the end of the infusion was 63.5 ± 6.7 fmol/mL, a level statistically indistinguishable from that seen in vehicle-treated rats on the HSD and significantly greater than levels in either vehicle- or bromocriptine-treated rats on the LSD (1.28 ± 0.25 pmol/μg protein, P < 0.005 for both). There was no further increase in NIL content of γ-MSH in haloperidol-treated rats on the HSD (1.34 ± 0.21 pmol/μg, Figure 2).

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from the 75.9±8.3 fmol/mL measured in vehicle-injected rats on the HSD. Thus, restoration of plasma γ-MSH to levels appropriate for the HSD was accompanied by rapid normalization of MAP. In 5 other similarly treated rats, a higher rate of peptide infusion (20 pmol/min) produced similar results: α-MSH had no effect on MAP (control, 138±3, α-MSH 138±2 mm Hg, P=NS), whereas γ-MSH infusion reduced MAP to 99±3 mm Hg (P<0.001), a value not significantly different from that observed with the lower rate of infusion. Plasma γ-MSH concentration at the end of these experiments was 4.5±0.8 pmol/mL.

**Plasma Renin Activity and Plasma ANP Concentration**

PRA in 5 vehicle-injected rats on the LSD was 5.0±1.3 ng AI/mL per hour and was reduced in 5 other rats on the HSD to 1.6±0.4 ng AI/mL per hour (P<0.05). In bromocriptine-injected rats, the corresponding results were 4.9±1.2 and 1.1±0.4 ng AI/mL per hour (n=5 for each group, P<0.05). Plasma ANP concentration in vehicle-injected rats was 14.7±3.9 and 52.6±12.4 pg/mL on the LSD and HSD, respectively (n=5 per group, P<0.05). In bromocriptine-treated rats, the corresponding values were 15.6±3.3 and 45.7±13.0 (n=5 per group, P=0.0547). Hormone measurements were not carried out in haloperidol-treated rats.

**Discussion**

Several observations point to a possible role of γ-MSH as a natriuretic peptide. First, physiological concentrations of the peptide are natriuretic when infused directly into a renal artery,8,17 indicating a direct action on the nephron to result in an increase in UNaV. Second, ingestion of an HSD leads to an increase in the NIL of POMC mRNA, immunoreactive γ-MSH content, and the mRNAs of PC1 and PC2,9,10 necessary for the cleavage of POMC into its smaller derived peptides such as γ-MSH. Third, these changes in NIL POMC metabolism result in an approximate doubling of plasma γ-MSH concentration, which presumably interacts with other natriuretic pathways to increase UNaV to match the level dictated by the amount of sodium ingested in the HSD.9,10 Fourth, in preliminary studies, we have demonstrated renal expression of MC3-R, the melanocortin receptor for which γ-MSH is the endogenous ligand6; the HSD increases the abundance of MC3-R mRNA and protein in the kidney.19 These observations all suggest that an HSD stimulates a coordinate upregulation of a natriuretic system composed of increased synthesis and secretion of γ-MSH in the NIL, an increase in its plasma concentration, and enhanced expression of its receptors in the kidney. Further support for the importance of this system in sodium metabolism comes from our recent observation that mice with targeted disruption of the PC2 gene, necessary for processing of POMC into its smaller component peptides including γ-MSH,20 leads to deficiency of this peptide and the development of salt-sensitive hypertension, which is rapidly corrected with infusion of γ-MSH.11 Although these data strongly incriminate an important mechanistic role for the γ-MSH deficiency in the hypertension observed on the HSD,11 other interpretations are possible, given the role of PC2 in the processing of numerous prohormones,20 including prodynorphin, proglucagon, progastrin, and prosomatostatin, in addition to POMC.20-24 If other vasoactive peptide hormones also required processing by PC2, the hypertension could result from such impaired processing in addition to γ-MSH deficiency. We sought therefore to manipulate the γ-MSH system in another way in an effort to extend understanding of the role of this system in sodium metabolism and the regulation of blood pressure.

POMC synthesis and processing is under dopaminergic regulation in the intermediate lobe through the dopamine D2 receptor.12-15 and the dopamine agonist bromocriptine is known to modify (suppress) NIL synthesis of POMC and its processing into smaller peptides.14,15 We consequently chose to use a pharmacological approach to probe the γ-MSH system by using this agent and the dopamine receptor antagonist haloperidol in rats ingesting the LSD and the HSD. It must be recognized that bromocriptine and haloperidol are nonselective agents and were given systemically, leading to the possibility of interaction with dopaminergic pathways throughout the body. In particular, dopamine receptors have been identified in the vasculature and in the kidney, where they have been shown to participate in the regulation of UNaV and renin release.25,26 The effects of bromocriptine treatment could thus be due to actions in the kidney or blood vessels rather than the pituitary intermediate lobe. Although our approach cannot definitively answer this question, several observations make it seem likely that the bromocriptine treatment led to salt-sensitive hypertension through its effect to alter POMC synthesis and processing in the NIL. First, there was no major difference in 24-hour UNaV; although haloperidol-treated rats had a higher rate of UNaV than bromocriptine-treated rats, the latter value did not differ significantly from that in vehicle-treated rats. Since we did not do rigorous balance studies, we cannot state whether the slightly reduced level of UNaV in bromocriptine-treated rats reflected altered excretion or reduced dietary intake. Nor did we evaluate the time course with which the different groups came into balance on the HSD; it may be possible that bromocriptine-treated rats retained more sodium, and this contributed to the development of hypertension. Second, despite these limitations with respect to sodium balance, it seems clear that our drug treatment produced the desired effects on POMC metabolism. Bromocriptine treatment clearly resulted in a large reduction in NIL immunoreactive γ-MSH content compared with vehicle-treated animals on the HSD, and this was accompanied by a failure of plasma γ-MSH concentration to increase. These changes are to be expected from dopaminergic suppression of NIL POMC, PC1, and PC2 expression.14,15 Third, the HSD led to equivalent suppression of PRA and stimulation of plasma ANP concentration in bromocriptine- and vehicle-treated rats, suggesting that the drug did not alter these consequences of the HSD and that the hypertension on the HSD was not a result of dysregulation of one of these important vasoactive systems. Fourth, the hypertension observed in bromocriptine-treated rats on the HSD was rapidly corrected by intravenous infusion of γ-MSH, which restored plasma levels of the peptide to those appropriate for the HSD; α-MSH was without effect. We therefore conclude that whatever other
dopaminergic pathways may have been activated by bromocriptine treatment, the salt-sensitive hypertension that developed in these rats appears to be specifically related to the deficiency of γ-MSH. Our earlier study showed that intravenous infusion of γ-MSH increased plasma ANP concentration, and one may ask if the reduction in blood pressure achieved as a result of the infusion was due to increased levels of ANP. Although we did not measure plasma ANP concentration at the end of the γ-MSH infusion, we think this possibility very unlikely. Our earlier study used a much higher rate of γ-MSH infusion, and elevation of plasma ANP concentration was observed at levels of γ-MSH that were much higher than the values measured in the present study at the end of the low-dose infusion. Moreover, we have shown in mice with γ-MSH deficiency that the correction of hypertension by the peptide occurs after cerebroventricular administration of a small dose that had no effect when given intravenously and that would not affect plasma ANP concentration.

These results thus complement and extend the findings of this recent report in which γ-MSH deficiency was observed in mice with targeted deletion of the PC2 gene. Hypertension developed in these mice while ingesting the HSD, and, as with the bromocriptine-treated rats in the present study, the hypertension was rapidly corrected with infusion of synthetic γ-MSH. Our data indicate that pharmacological interruption of NIL POMC metabolism during ingestion of the HSD also exposes the rats to salt-sensitive hypertension. It does not seem likely that our results reflect an artifact of the anesthesia used during the recording of blood pressure: the elevation in pressure in bromocriptine-treated rats on the HSD was 30 mm Hg, a magnitude too large to reflect such an artifact. In addition, we were able to show, in mice with hypertension caused by interruption of γ-MSH signaling, that blood pressure was not materially different in conscious versus anesthetized animals.

The observation that γ-MSH infusion lowers blood pressure in these hypertensive rats runs counter to numerous earlier reports on the cardiovascular actions of this peptide (reviewed in Wikberg et al, Schioth, and Gruber and Callahan) which have indicated that both central and intravenous injections of the peptide cause blood pressure to increase by stimulating sympathetic outflow. This action of γ-MSH is observed with injections that are orders of magnitude greater than those infused in the present experiments. One study reported a hypotensive and bradycardic action of the peptide when injected directly into the nucleus of the tractus solitarius (NTS). The NTS is shielded from circumventricular organs lying outside the blood-brain barrier, such as the area postrema immediately adjacent to the NTS, to exert its hypotensive action through pathways similar to or identical with those involved in the baroreflex. The relation of this action to the numerous observations reporting an effect of γ-MSH to increase blood pressure must await further study; as mentioned above, the threshold for this effect is at much higher doses than used in our study, and it has been suggested that this property of administered γ-MSH could reflect activation of a separate receptor different from the known melanocortin receptors.

The pathway(s) by which dietary sodium abundance leads to hypertension in these bromocriptine-treated rats is not known. Some data indicate that an HSD leads to a small but measurable increase in sodium concentration in the cerebrospinal fluid and perfusion of the cerebroventricular system with artificial CSF high in sodium concentration stimulates sympathetic nervous system outflow and raises blood pressure. Data from our recent report argue that the melanocortin-3 receptor (MC3-R) is required, since mice with this receptor knocked out also have salt-sensitive hypertension but without γ-MSH deficiency, and γ-MSH administration did not correct the hypertension. This blood pressure–lowering action of the peptide probably involves a central site of action, since it was able to lower blood pressure when administered into the lateral cerebral ventricle of hypertensive PC2 knockout mice in a dose that had no effect when given systemically. These observations in aggregate would suggest that in the integrated response to the HSD, γ-MSH must serve to act as a brake on sympathetic outflow in the central nervous system; in the face of deficiency of the peptide, whether from genetic or pharmacological disruption of POMC metabolism, this brake is removed during ingestion of the HSD, allowing increased sympathetic activity to cause hypertension. Although we did not measure UoV during peptide infusion in these studies, this action of γ-MSH would appear to be separate from its natriuretic action in view of the rapidity of the lowering of blood pressure and the effect of γ-MSH to lower MAP when given centrally. These 2 properties could interact in the long-term regulation of blood pressure. Much work will be required to substantiate such a proposed mechanism of action and to characterize the nature of the relation between the central and the renal actions of the peptide.

Our finding that γ-MSH deficiency leads to salt-sensitive hypertension raises the possibility that a similar mechanism may be involved in salt-sensitive hypertension in humans. Circulating γ-MSH is thought to derive from secretion from the NIL, which does not exist as a clearly defined pituitary lobe in humans. Nevertheless, cells with histochemical and immunocytochemical features of melanotrophs can be identified in the human pituitary, and immunoreactive γ-MSH-like material has been identified in human plasma. In addition, components of this system are found in a variety of extrapituitary tissues. The possibility that the peptide could cause some forms of idiopathic hyperaldosteronism was raised several years ago. However, there are no data in humans on the responsiveness of this hormone system to dietary sodium intake or the relation of this response, if present, to salt-sensitivity of blood pressure.

**Perspectives**

Salt sensitivity of blood pressure is a commonly observed but poorly understood phenomenon. Given the increasing prevalence of hypertension in Western societies and the consequences of this hypertension on cardiovascular and renal disease, greater understanding of the pathophysiological bases underlying it must be sought to develop more success-
ful strategies for prevention and treatment. Our data show that pharmacological interruption of the normal increase in NIL-γ-MSH content and plasma γ-MSH concentration that occur during ingestion of an HSD in the rat results in a marked increase in blood pressure. This result appears to be a specific consequence of altered POMC metabolism, since blood pressure is rapidly normalized by infusion of γ-MSH. These findings indicate that γ-MSH may be an important participant in the normal response to an HSD and raise the possibility that defects in this system may be involved in some forms of salt-sensitive hypertension in humans. If true, this would offer a potentially important target for therapeutic intervention.

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References

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