Thyrotropin-Releasing Hormone Precursor Gene Knocking Down Impedes Melanocortin-Induced Hypertension in Rats

To the Editor:

Recently, da Silva et al reported that endogenous melanocortin may cause elevation of arterial blood pressure (ABP) in spontaneously hypertensive rats. We invite authors to consider that the hypothalamic thyrotropin-releasing hormone (TRH) system may be involved, because spontaneously hypertensive rats show an hyperactivity of this system, and intracerebroventricular (ICV) injections of a prepro-TRH antisense oligonucleotide (AS) decreases both elevated TRH content and ABP independent of thyroid status.

Leptin effects include increases in sympathetic activity and inhibition of the starvation-suppressed inhibition of thyroid hormones apparently by upregulating prepro-TRH gene expression. Then, leptin can increase the MC4R ligand (α-melanocyte-stimulating hormone) production to regulate TRH expression. Furthermore, we have shown that ICV leptin injections induce a pressor effect that is avoided by prepro-TRH AS pretreatment.

Hence, we proposed that melanocortin activity may raise ABP through TRH activation, and we report here that, in Wistar rats, the MCR4 agonist (α-melanocortin-stimulating hormone agonist [MTII])–induced elevation of ABP can be blocked by 24-hour ICV pretreatment with prepro-TRH AS.

Wistar rats were implanted with a guided canula into the III ventricle for MTII, AS, or saline infusion (V) as described elsewhere. Carotid artery was cannulated for mean ABP measurements. We measured body weight and food consumption in basal condition and 24 hours after ICV injection in awake animals with (ICV 1) vehicle (V), AS (150 pmol), and oligonucleotide with the inverted AS sequence (150 μg) as a control. After another 24 hours we performed a second injection (ICV 2) with V or MTII (0.6 nmol). Animals were then euthanized and the hypothalamus was removed to measure TRH (radioimmunoassay).

As expected, MTII induces a decrease in food consumption and body weight. Melanocortin also produced increases of mean ABP and hypothalamic TRH in rats treated with MTII, whereas AS pretreatment prevented both increases. MTII action was not reversed by the AS inverted sequence (Table).

In conclusion, we show that the melanocortin 3 and 4 agonist induced hypertension only in the presence of an intact hypothalamic TRH system; thus, we propose that an activation of the axis leptin-melanocortin-TRH might explain increases of ABP in this genetic model of hypertension.

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Disclosures
None.

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| Table. Effect of TRH Gene Knocking Down on Melanocortin-Induced Hypertension |
|------------------|------------------|------------------|------------------|
| ICV 1 | ICV 2 | ABP, mm Hg | ABP, mm Hg | ABP, mm Hg | TRH, pg/mg of Protein |
| V | V | 109.7±3.3 | 107.3±6.3 | 109±3.6 | 1161.4±212 |
| V | MTII | 105.1±2.0 | 106.5±2.8 | 113.8±7.3† | 1926.8±454.3‡ |
| AS | MTII | 105.7±3.2 | 102.4±2.4 | 93.9±3.4† | 1098.6±253 |
| Inv | MTII | 106.7±4.0 | 102.0±8.5 | 109.8±3.9* | 1839.3±297‡ |

*P<0.05 vs 24 hours.
†P<0.05 vs basal.
‡P<0.05 vs vehicle and AS+MTII (n=4).
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