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Correspondence

Letter by Landa et al Regarding Article, "Protein Tyrosine Phosphatase 1B, a Major Regulator of Leptin-Mediated Control of Cardiovascular Function"

To the Editor:

Recently, Belin de Chantemele et al[1] reported that protein tyrosine phosphatase 1B may be a major player in the leptin-mediated control of arterial blood pressure (ABP) in mice. We invite the authors to consider that the hypothalamic thyrotropin-releasing hormone (TRH) system may be involved in this pathway. Leptin effects include increases in sympathetic activity and inhibition of the starvation-induced suppression of thyroid hormones by upregulating preproTRH gene expression. Furthermore, we showed that intracerebroventricular leptin injections induce a pressor effect that is avoided by preproTRH antisense oligonucleotide pretreatment.[2] In addition, we showed that diencephalic TRH levels were correlated with ABP and leptin levels in 2 genetic models of obesity, the hyperleptinemic and moderately hypertensive agouti yellow mouse and the Ob/Ob mouse, which lacks leptin and is hypotensive.[3]

Another important aspect is that leptin can regulate TRH expression through an increase in the production of the melanocortin receptor type 4 endogenous ligand (αMSH). Hence, we hypothesized that melanocortin activity may raise ABP through TRH activation, and we recently reported that in Wistar rats, the melanocortin receptor type 4 agonist (MTII)–induced elevation of ABP can be blocked by 24 hours of intracerebroventricular pretreatment with a preproTRH antisense oligonucleotide.[4] Then, we showed that the melanocortin receptor type 4 agonist induced hypertension only in the presence of an intact hypothalamic TRH system, and we proposed that an activation of the leptin-melanocortin-TRH axis might explain increases in ABP in a genetic model of hypertension, the spontaneously hypertensive rat. This is particularly important because it was recently shown that the activation of melanocortinergic pathways by synthetic melanocortin receptor type 4 agonists may increase ABP in patients bearing mutations in the melanocortin receptor type 4, who are genetically obese but with basal low ABP levels.[5] This point is crucial to the development of antiobesity drugs. We absolutely agree with the clever comment by Dr Mark in the companion editorial on the work of Belin de Chantemele et al[1] about the necessity to raise a yellow flag in the race to safe pharmacotherapy for obesity owing to the cardiovascular side effects of antiobesity drugs. To conclude, it is tempting to propose that TRH may participate in the mechanism by which leptin, through protein tyrosine phosphatase 1B, modulates ABP and may be a target for dissociating the effects of therapeutic interventions on body weight and ABP if it were possible.

Disclosures

None.

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