Commentary

MOLECULAR METABOLISM

Brain insulin receptors link stress and metabolism*

Stephen C. Woods*, James P. Herman

In this issue of Molecular Metabolism, Chong et al. [1] observed altered functioning of the hypothalamic—pituitary—adrenal (HPA) axis in mice lacking insulin receptors (IR) in selected regions of the brain. The rationale was to push beyond the original report of altered HPA activity in mice lacking IR in all brain neurons (NIRKO mice) [2] by assessing animals lacking IR in more targeted neuronal types. Specifically, male mice lacking IR broadly in forebrain areas, including most of the hypothalamus ($IR^{Nkx2.1}$ KO mice), had enhanced anxiety-like behavior on several tasks as well as elevated basal plasma arginine vasopressin (AVP) and increased secretion of corticosterone (CORT) in response to physical restraint. To determine the impact of IR knockout in specific populations of hypothalamic neurons, HPA axis function was also assessed in IR^{Sim1} KO and IR^{Agrp} KO male mice. In IR^{Sim1} KO, the IR should be absent in the paraventricular and supraoptic nuclei (as well as a few extrahypothalamic areas) [3]. These mice manifested no changes of HPA activity or related behavior, implying that neurons located within the PVN (and/or SON) that express IR are unlikely to be the source of the stress phenotypes observed in $IR^{Nkx2.1}$ KO mice. There was a phenotype involving the HPA axis in male IR^{Agrp} KO mice that appeared superficially to be somewhat opposite to that observed in $IR^{Nkx2.1}$ KO mice, including reduced basal AVP and reduced CORT in response to restraint. From these data, Chong et al. concluded that signaling through IR on AgRP-expressing neurons increases responsivity of the HPA and AVP systems.

As Chong et al. review, close associations between influences over metabolic homeostasis and behaviors related to HPA activity have been well-documented, and it is generally accepted that a state characterized by excess energy storage and hyperinsulinemia predisposes to anxiety and related behavioral disorders while at the same time anxiety and depression are risk factors for obesity. Thus, observing specific alterations related to the stress axis in animals lacking IR in one or another neuronal type is not surprising; i.e., the results represent a small but potentially important step toward unraveling the complex calculus linking influences over energy homeostasis and the HPA axis. Since the original reports that insulin exerts a major catabolic action within the brain [4], identifying the underlying mechanisms and their clinical potential [5], and more recently the ability of the brain to work in parallel with systemic insulin to control glycemia [6], has come a long way. At the same time, insulin, acting on brain IR, has been found to influence multiple systems in addition to the HPA axis, including the sympathetic nervous system [7] thermoregulation [8] and reproduction [9] among others.

The Chong et al. report presents an interesting entry point for further dissection of the link between metabolic signals, neuroendocrine stress responses and metabolism. Nonetheless, a number of questions remain to be answered. For example, with regard to the $N^{kx2.1}$ KO mice, it is important to remember that Nkx2.1 is broadly expressed in forebrain [10], including the hippocampus, which is replete with insulin receptors [11]. As the hippocampus can modulate both behavior and HPA axis function [12], it is plausible that the effects observed in this study may be extrahypothalamic in origin. In addition, there are very pronounced sex differences in HPA axis stress reactivity and behavioral phenotypes; indeed, the NIRKO phenotype is more exaggerated in females [2]. Consequently, study of sex differences should be a natural extension of these studies. With regard to the observation of altered basal AVP, assessment of water intake, urination or plasma osmolality would have been informative, especially since it was recently reported that AVP-expressing neurons in the supraoptic nucleus function as glucose sensors [13]. Finally, contrary to the conclusions of the authors, true negative feedback regulation of the HPA axis was not robustly tested. The observed HPA phenotype was limited to small changes at a single time point; there were no measures of ACTH to complement the CORT endpoints; and, importantly, there were no direct tests of central feedback. Thus while the phenotype is provocative and potentially important, additional steps need to be taken to ascertain the true nature of the HPA axis phenotype.

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Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA

*Corresponding author. Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, 2170 East Galbraith Road, Cincinnati, OH 45237, USA. E-mail: Steve.woods@uc.edu (S.C. Woods).

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