COMMENTARY ON: **Monosodium l-glutamate-obesity onset is associated with disruption of central control of the hypothalamic-pituitary-adrenal axis and autonomic nervous system. TORREZAN R, MALTA A, DE SOUZA RODRIGUES WDN, DOS SANTOS AAA, MIRANDA RA, MOURA EG, LISBOA PC, DE FREITAS MATHIAS PC. *J NEUROENDOCRINOL* 2019 6: 1–10.**

Tanisse C M Teale, Gareth M Rurak, and Melissa J Chee
Department of Neuroscience, Carleton University, Ottawa ON Canada

Obesity has become a pervasive worldwide epidemic[1]. In North America alone, nearly two in three adults are either overweight or obese[2–4]. Obesity increases the risk of developing several debilitating, and sometimes fatal diseases, including Type 2 diabetes, cardiovascular disease, and even some forms of cancer[1]. Furthermore, obesity-related complications result in nearly 3 million deaths each year[1]. It is classically diagnosed by increased body weight and adiposity, often as a result of dysfunction in energy homeostasis and metabolism[5]. However, the development of obesity can be multifactorial, and stress, which plays a critical role in maintaining energy homeostasis, is also correlated with weight gain[6,7].

The stress response engages both the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis[8]. Specifically, the ANS aims to provide a rapid neuronal response following an acute stressor[8]. This response allows for preparation to cope with the stressor through actions in the cardiovascular and respiratory systems, as well as the release of catecholamines[8]. The HPA axis maintains homeostasis through slower, long-lasting adaptive hormonal responses that involve the release of corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) in response to acute or chronic stressors[8,9]. ACTH acts by stimulating the adrenal cortex to secrete the glucocorticoid hormone, cortisol (i.e., corticosterone in rodents), which directly and indirectly affects metabolic pathways, such as carbohydrate, lipid, and protein metabolism[10]. These downstream effects of cortisol can result in either anabolic or catabolic events, ultimately affecting energy expenditure and food intake[11]. Likewise, the HPA axis also regulates the ANS during a stress response through negative feedback[12]. However, in both the HPA axis and ANS, if chronically stimulated, these adaptive responses may lead to maladaptive consequences[9]. Previous studies have related elevated levels of cortisol or corticosterone and over-responsive HPA axis activity to the onset and maintenance of obesity[13–15]. In this study, Torrezan et al. demonstrated that in a lean animal, central glucocorticoid infusion influences the HPA axis altering metabolic homeostasis through ANS activity and glucose homeostasis[12]. By contrast, obese animals exhibit dysregulation of the HPA axis and consequently, a decrease or cessation of ANS activity and metabolism in the presence of central CRH or synthetic glucocorticoids[12].

Torrezan et al. treated neonatal rats with monosodium L-glutamate (MSG) to induce adult obesity and determined whether MSG-mediated obesity disrupted ANS activity and metabolism[16]. MSG is added to food as a flavor enhancer, but its use has been linked with diabetes and obesity[17–19]. MSG-treated rats are known to have increased parasympathetic nervous activity and share similar biochemical and physiological measures and outcomes to obesity observed in humans[10,12,15,16]. For example, MSG-treated rats gain more weight and

adiposity, have higher circulating leptin, glucose, and insulin levels, and are glucose intolerant and insulin resistant[5].

With regards to the HPA axis, Torrezan and colleagues found that MSG-treated rats have elevated corticosterone levels relative to saline-treated littermates[5]. Activation of the HPA axis stimulates hypothalamic CRH release, which then stimulates the anterior pituitary to produce ACTH and drive the production of corticosterone by the adrenal glands[8]. In turn, corticosterone normally provides negative feedback to the hypothalamus and pituitary to inhibit CRH or ACTH release, respectively, thereby suppressing further corticosterone production[8]. In this study, Torrezan and colleagues showed that although MSG-treated rats remained sensitive to the anorexigenic effects of CRH, the synthetic glucocorticoid dexamethasone (DEXA) was unable to suppress circulating levels of corticosterone[12].

The CRH and DEXA model employed has been replicated in previous studies confirming that CRH delivered by intracerebroventricular administration decreases food intake without changes in plasma glucose, insulin, or glucocorticoids[22]. Given that both lean and MSG-treated rats remained responsive to the anorexigenic effects of CRH, Torrezan et al. suggest that MSG-treated rats remain sensitive to output from the HPA axis[5,12]. To determine whether the HPA axis may be insensitive to negative feedback from corticosterone, they measured corticosterone levels following central DEXA administration[12]. DEXA decreased corticosterone levels in saline- but not MSG-treated rats, thus suggesting that the HPA axis in MSG-treated rats became insensitive to negative feedback[12]. This implicated that MSG-induced obesity may stem from insensitivity within the negative feedback loop from corticosterone to protect against the hyperstimulation of the HPA axis.

To analyze the sensitivity of the HPA axis, Torrezan et al. determined the effects of centrally administered CRH or DEXA on hyperglycemia and hyperinsulinemia in saline- and MSG-treated rats[12]. CRH may offer relief from obesogenic symptoms like hyperglycemia and hyperinsulinemia, while DEXA treatment promoted positive energy balance. DEXA treatment produced similar outcomes on blood glucose, serum insulin levels, and ANS activity in saline- and MSG-treated rats[12]. During stress, chronic activation of the HPA axis increases corticosterone production and may result in increased food intake and elevated glucose and insulin levels, thus rendering the organism glucose intolerant or insulin resistant[23]. When challenged with a glucose load via an intravenous glucose tolerance test, CRH did not affect blood glucose but suppressed insulin release[12]. DEXA administration produced glucose intolerance and hyperinsulinemia in control rats, however, this condition was not augmented in MSG-treated rats[12]. DEXA administration also ubiquitously facilitates insulin resistance, and Torrezan et al. suggest that insulin resistance may arise due to a developed sensitivity to corticosterone in the HPA axis, which may interact with the ANS response[12].

Given that the stress response also engages the ANS, Torrezan et al. directly measured parasympathetic nerve activity through electrical recording of the left superior vagus nerve from the superior cervical ganglion, and they measured sympathetic nerve activity by directly recording from the vagus nerve[12]. These novel methods for isolating and recording from the vagus nerve *in vivo* are effective and direct techniques for understanding ANS physiology and are unique assets to this study. ANS activity contributes to the development of obesity[24], and

Torrezan and colleagues showed that MSG-treated rats have reduced sympathetic nerve activity and elevated parasympathetic nerve activity[12]. In control rats, CRH expectedly stimulated sympathetic nerve activity and has no significant effect on parasympathetic nerve activity; meanwhile, DEXA suppressed sympathetic activity and elevated parasympathetic activity[12]. By contrast, both the sympathetic and parasympathetic nerve activity in MSG-treated rats were insensitive to either CRH or DEXA[12]. The suppressed and elevated sympathetic and parasympathetic nerve activity, respectively, may reflect a ceiling effect produced by elevated corticosterone levels in MSG-treated rats.

In aggregate, these findings highlight the differential contribution of glucocorticoids to the HPA axis and ANS activity under metabolic stress from MSG-induced obesity. Torrezan et al. highlight the relevance of the MSG-induced obesity model for representing the metabolic and physiological changes that occur in the HPA axis as a result of obesity. Injections of central CRH and DEXA demonstrate impairments to the negative feedback loop within the HPA axis that may result in dysfunction within the ANS. DEXA may work in opposition to CRH to promote positive energy balance, and this study suggests that elevated corticosterone levels promote MSG-induced obesity[12]. In conclusion, Torrezan et al. presents an effective study supporting the role of the HPA axis and the ANS in the onset and maintenance of obesity[12]. This article provides a greater mechanistic understanding of stress-related pathways in the etiology of obesity.

References:

1. Levesque RJR. Obesity and Overweight. In: *Encyclopedia of Adolescence*, pp. 1913–1915.
2. Statistics Canada. Overweight and obese adults (self-reported), 2014, https://www150.statcan.gc.ca/n1/pub/82-625-x/2015001/article/14185-eng.htm.
3. Centers for Disease Control and Prevention. Overweight & Obesity, https://www.cdc.gov/obesity/data/prevalence-maps.html#overall.
4. Rtveladze K, Marsh T, Barquera S, et al. Obesity prevalence in Mexico: impact on health and economic burden. *Public Health Nutr*. 2014;**17**:233–239.
5. Newburgh LH. Obesity: I. Energy metabolism. *Physiol Rev*. 1944;**24**:18–30.
6. Bose M, Oliván B, Laferrère B. Stress and obesity: The role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Curr Opin Endocrinol Diabetes Obes*. 2009;**16**:340–346.
7. van der Valk ES, Savas M, van Rossum EFC. Stress and obesity: Are there more susceptible individuals? *Curr Obes Rep*. 2018;**7**:193–203.
8. Laurent HK, Powers SI, Granger DA. Refining the multisystem view of the stress response: Coordination among cortisol, alpha-amylase, and subjective stress in response to relationship conflict. *Physiol Behav*. 2013;**119**:52–60.
9. Kyrou I, Tsigos C. Stress hormones: physiological stress and regulation of metabolism. *Curr Opin Pharmacol*. 2009;**9**:787–793.
10. Christiansen JJ, Djurhuus CB, Gravholt CH, et al. Effects of Cortisol on Carbohydrate, Lipid, and Protein Metabolism: Studies of Acute Cortisol Withdrawal in Adrenocortical Failure. *J Clin Endocrinol Metab*. 2007;**92**:3553–3559.
11. Asensio C, Muzzin P, Rohner-Jeanrenaud F. Role of glucocorticoids in the physiopathology of excessive fat deposition and insulin resistance. *Int J Obes*. 2004;**28**:S45–S52.
12. Torrezan R, Malta A, de Souza Rodrigues W do N, et al. Monosodium l-glutamate-obesity onset is associated with disruption of central control of the hypothalamic-pituitary-adrenal axis and autonomic nervous system. *J Neuroendocrinol*. 2019;**31**:1–10.

13. Rosmond R, Dallman MF, Björntorp P. Stress-Related Cortisol Secretion in Men: Relationships with Abdominal Obesity and Endocrine, Metabolic and Hemodynamic Abnormalities. *J Clin Endocrinol Metab*. 1998;**83**:1853–1859.
14. Vrabcova M, Mikuska L, Zeman M, et al. Exaggerated activity of HPA axis in obese rats fed normocaloric liquid nutrition. *Acta Biol Hung*. 2014;**65**:285–293.
15. Mattsson C, Lai M, Noble J, et al. Obese Zucker Rats Have Reduced Mineralocorticoid Receptor and 11β-Hydroxysteroid Dehydrogenase Type 1 Expression in Hippocampus—Implications for Dysregulation of the Hypothalamic-Pituitary-Adrenal Axis in Obesity. *Endocrinology*. 2003;**144**:2997–3003.
16. da Silva Franco CC, Previate C, de Barros Machado KG, et al. Chronic Glibenclamide Treatment Attenuates Walker-256 Tumour Growth in Prediabetic Obese Rats. *Cell Physiol Biochem*. 2017;**42**:81–90.
17. Nagata M, Suzuki W, Iizuka S, et al. Type 2 diabetes mellitus in obese mouse model induced by monosodium glutamate. *Exp Anim*. 2009;**31**:35–42.
18. Sasaki Y, Suzuki W, Shimada T, et al. Dose dependent development of diabetes mellitus and non-alcoholic steatohepatitis in monosodium glutamate-induced obese mice. *Life Sci*. 2009;**85**:490–498.
19. Boonnate P, Waraasawapati S, Hipkaeo W, et al. Monosodium glutamate dietary consumption decreases pancreatic β-cell mass in adult Wistar rats. *PLoS One*. 2015;**10**:e0131595.
20. Gobatto CA, Mello MAR, Souza CT, et al. The monosodium glutamate (MSG) obese rat as a model for the study of exercise in obesity. *Res Commun Mol Pathol Pharmacol*. 2002;**111**:89–101.
21. Hirata AE, Andrade IS, Vaskevicius P, et al. Monosodium glutamate (MSG)-obese rats develop glucose intolerance and insulin resistance to peripheral glucose uptake. *Braz J Med Biol Res*. 1997;**30**:671–674.
22. Jeanrenaud B. Central nervous system and peripheral abnormalities: clues to the understanding of obesity and NIDDM. *Diabetologia*. 1994;**37**:S170–S178.
23. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: Focus on adipose tissue function and lipid metabolism. *Endocrinol Metab Clin North Am*. 2014;**43**:75–102.
24. Bray GA. Obesity, a disorder of nutrient partitioning: The MONA LISA hypothesis. *J Nutr*. 1991;**121**:1146–1162.