Commentary

MOLECULAR METABOLISM

Unforeseen role for glucocorticoids in combinatorial anti-obesity pharmacology

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In this issue of Molecular Metabolism, Lee et al. report that pharmacological suppression of the hypothalamic-pituitary-adrenal (HPA) — axis, enhances anti-obesity properties of glucagon-like peptide-1 (GLP-1) receptor agonism in obese rats [1]. Whereas previous investigations of the crosstalk between GLP-1 and HPA-axis have illustrated that both central and peripheral administration of GLP-1 analogues promote release of stress-axis hormones, such as ACTH and corticosterone [2,3], the therapeutic potential of this interaction is uncharted. To this end, Lee and colleagues now provide evidence for a novel functional interaction between central incretin action and the endogenous HPA axis in obese rodents.

The authors exploit the ability of the synthetic glucocorticoid agent dexamethasone to suppress corticosterone production. They show that blunting endogenous corticosteroid activity by dexamethasone enhances the efficacy of the GLP-1R agonist exendin-4 (Ex-4) to reduce food intake and to lower body weight. Thus, a major conclusion from this article is that the stress-axis may counterbalance the pharmacological benefits of GLP-1 mimetics on energy metabolism. This observation implies potential therapeutic value for treating obesity by inhibiting the stress axis. Indeed, although GLP-1R agonists exert potent gluco-metabolic effects in patients with type-2 diabetes [4], the anti-obesity efficacy of this class of compounds is still dwarfed by the efficacy of the metabolic surgeries [5]. Therefore, identification of pharmacological strategies that can potentiate the metabolic virtues of GLP-1R agonism is a promising undertaking [6].

Frequently reported side effects of dexamethasone and analogous steroid-based glucocorticoids include adiposity and worsened glycemic control [7]. Thus, the use of a glucocorticoid receptor (GR) agonist as a relevant pharmacological partner of GLP-1 mimetics in an anti-obesity strategy is somewhat counterintuitive. Irrespective, the report from Lee et al. clearly shows that chronic co-treatment with Ex-4 and dexamethasone synergistically lowers body weight in obese rats [1]. The authors link this finding to the relative low-dose of dexamethasone used, which is believed to scarcely enter the brain, but to exhibit potent endocrine negative feedback at the pituitary to suppress endogenous HPA-activity. Whether this is an accurate explanation for the central sensitization of the metabolic effects of Ex-4 is not completely mapped out in the present study. Nonetheless, GLP-1R activity seems to be appropriately dosed to counteract conceivable negative consequences of dexamethasone on glycemic control — not unlike what is observed with dual GLP-1 and glucagon action [8]. Thus, the work of Lee et al. suggests that dexamethasone, at certain doses, might be a promising adjunct therapy to GLP-1R-agonism — an observation that may pave the way for translational studies investigating the metabolic benefits of this combination approach in obese human subjects.

The authors further probed the underlying neuronal circuitry implicated in the crosstalk between the GLP-1R system and HPA-axis control. Ex-4 treatment stimulates catecholamine-expressing neurons located in the hindbrain. These neurons project to hypothalamic nuclei driving HPA-activity and thus increased corticosterone release from adrenals glands. Intriguingly, by using a neurotoxin-based approach to selectively ablate this sympatho-adrenal axis, the authors observe an increased ability of Ex-4 to reduce food intake — supporting their pharmacological studies. Therefore, the work of Lee et al. highlights the critical role played by a novel neuronal circuit by which Ex-4 controls the HPA-axis, and further suggest that, blocking specific components of this circuit, or downstream effects of this axis, such as corticosterone release, might represent a novel strategy to potentiate the metabolic benefits of GLP-1R agonists (Figure 1).

Although this work is fascinating, multiple questions remain to be answered. First, whether alterations in central GR activity play a causal role for the Ex-4-induced metabolic responses has yet to be uncovered. Second, the HPA axis has an impact on several peripheral tissues involved in regulation of energy balance; therefore the analysis of the relative contribution of peripheral versus central glucocorticoid signaling to the metabolic effects achieved with GLP-1 agonism requires further investigations. Furthermore, investigating the physiological relevance of the crosstalk between GLP-1 and the HPA-axis in humans is of paramount importance. Indeed, although an interaction between GLP-1 and corticosterone regulation has been reported in a small human study [3], intervention studies with increased sample size are necessary to pursue these observations. Intriguingly, it may be speculated that, based on the findings by Lee et al., subjects with pathologically elevated glucocorticoid levels exhibit a blunted response to the metabolic benefits of GLP-1R agonists. Finally, emerging data

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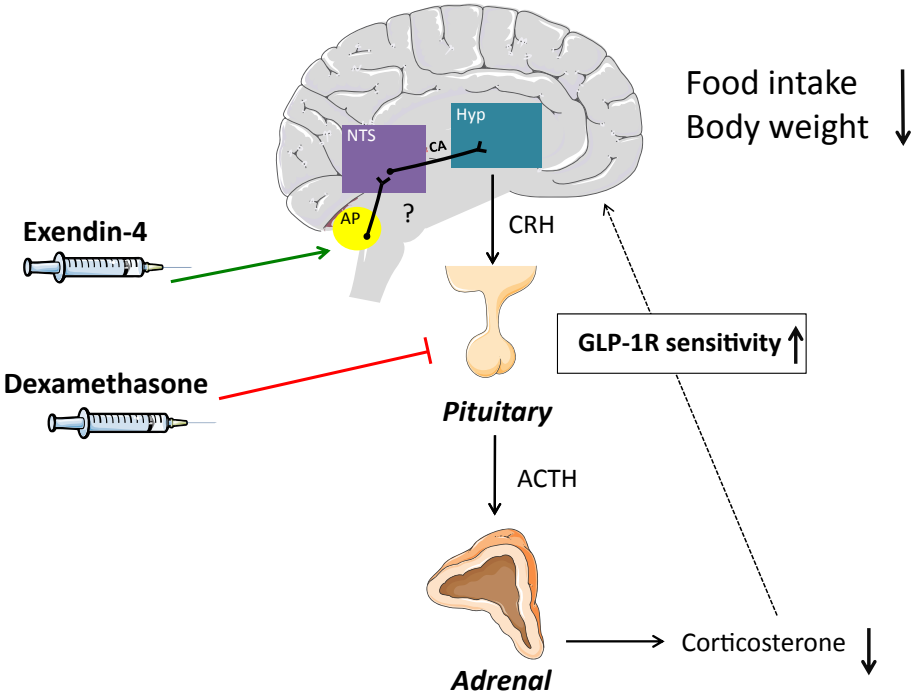

Figure 1: Cartoon overview of exendin-4 and dexamethasone co-administration.

support that dietary excess of saturated fat not only promotes a low-grade chronic inflammatory state in peripheral tissues, but also in the hypothalamus. As a matter of fact, recent reports have suggested that inflammatory-like processes in the hypothalamus might represent a key-contributing factor to the obesity pathogenesis [9]. Relevantly, it was reported that Ex-4 reverses diet-induced hypothalamic microgliosis in a body weight independent manner [10]. However, given the fact the GLP-1 elicits glucocorticoid secretion, dampening endogenous HPA-activity with dexamethasone might hamper the GLP-1-linked benefits on hypothalamic inflammation. This idea should be carefully probed in future studies.

In conclusion, the work from Lee et al. illustrates synergistic anti-obesity effects of Ex-4 and dexamethasone co-administration. Although this is not the first report to exemplify interactions between the incretin hormone GLP-1 and the HPA-axis, it may facilitate renewed interest in dexamethasone as an adjunct agent for metabolic complications. Granted, reversing obesity is a critical challenge — but a parallel appropriate control of glucose handling, insulin sensitivity, and lipid homeostasis is equally important for translational value. Therefore, it will be exciting to see if follow up investigations support efficacy as well as safety of dexamethasone and Ex-4 co-administration. Finally, understanding the neuronal circuitry and molecular details involved in amplifying GLP-1R activity might hold promise to facilitate the development of more efficacious incretin-based anti-obesity pharmacotherapies.

When injected peripherally, exendin-4 activates central nervous system (CNS) feeding circuits including the area postrema (AP). Here, neuronal signals directed to the nucleus of the solitary tract (NTS) lead to activation of catecholamine (CA) expressing neurons projecting to the hypothalamus (Hyp). This NTS-Hyp circuitry stimulates the HPA axis to secrete corticosterone, which mitigates the effect of exendin-4 on eating. Conversely, administration of low-dose dexamethasone suppresses HPA-activity, which has a sensitizing effect on central exendin-4 to reduce food intake and ameliorate obesity.

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