GH Controls Glycemia and Metabolic Adaptations to Starvation Via Neurons That Express the Leptin Receptor

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Authors

Jose Donato Jr. PhD (/tristar_endo17/speaker/9f6300891abea35983bbd25dff41b164)

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Jose Donato Jr.[*1], Isadora C Furigo[2], Gabriel Orefice[2], Angela M Ramos-Lobo[2], Carlos RJ Soares[3], Edward O List[4] and John J Kopchick[4]
[1]University of Sao Paulo, Sao Paulo - SP, Brazil, [2]University of Sao Paulo, Sao Paulo, Brazil, [3]IPEN-CNEN/SP, [4]Ohio University, Athens, OH

Growth hormone (GH) responsive neurons are extensively distributed in many hypothalamic nuclei that also have leptin receptor (LepR)-expressing cells (1). However, whether GH affects metabolic functions regulated by leptin remains unknown. In the present study, we initially performed a co-localization study and confirmed that a large percentage of LepR-expressing neurons are directly responsive to peripherally injected GH in different brain nuclei. Then, we generated mice lacking GH receptor (GHR) specifically in LepR-expressing cells (LepR GHR KO mice). Although LepR GHR KO mice exhibited a similar body weight, food intake, energy expenditure, glucose tolerance and leptin sensitivity compared to control mice, we observed a lower adiposity in mutant mice. LepR GHR KO mice also showed a lower capacity to recover from insulin-induced hypoglycemia and a blunted counterregulatory response evoked by 2-deoxyglucose (2DG) administration. Co-infusion of 2DG with sympathetic blockers, but not parasympathetic blockers, was able to abolish the differences observed between groups. Remarkably, while control mice adapted to a 60% food deprivation period by progressively saving energy, LepR GHR KO mice exhibited a blunted metabolic adaptation to starvation, which led to hypoglycemia and an increased lethality rate, energy expenditure and weight loss, compared to control animals. In order to identify the specific neuronal populations responsible for the observed responses, we generated mice lacking GHR in steroidogenic factor-1 (SF1) cells, which comprises the ventromedial nucleus of the hypothalamus (VMH). SF1 GHR KO mice exhibited a similar metabolic phenotype in the basal condition, compared to littermate controls. On the other hand, SF1 GHR KO mice also showed a lower capacity to recover from insulin-induced hypoglycemia and a blunted counterregulatory response evoked by 2DG. However, metabolic adaptations to starvation were not affected by SF1-specific GHR deletion, which suggests that VMH does not mediate these latter changes. In summary, GHR expression in the brain is required to properly regulate glycemia and energy balance, especially during situations in which GH is highly secreted (e.g., hypoglycemia and food restriction). In addition, our findings revealed a previously unrecognized role of GH to coordinate, together with leptin, the metabolic adaptations to starvation in order to ensure survival, via the same neurocircuitry.

Nothing to Disclose: JD Jr., ICF, GO, AMR, CRS, EOL, JJK

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