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Growth hormone (GH) is a well-known metabolic factor secreted by pituitary somatotropes. Transcription factors such as POU1F1 and NEUROD4 promote somatotrope differentiation, maturation, and function. The forkhead transcription factor, FOXO1, is necessary for the proper timing of somatotrope differentiation and function, but the underlying mechanisms behind it have yet to be unraveled. Pituitary gland development also depends on regulation by signaling factors and hormones. Glucocorticoids have mixed effects on growth hormone production. However, when the effects of glucocorticoid signaling on the hypothalamus and pituitary gland are uncoupled, the direct effects of glucocorticoid signaling on pituitary somatotropes are not only stimulatory, but necessary for initiation of somatotrope maturation and for maintenance of somatotrope function. We find that FOXO1 is necessary for glucocorticoid induction of important somatotrope genes. Activation of glucocorticoid signaling in the somatotrope-derived MtT/S cell line induces transient expression of the bZIP transcription factor, *Crebl2* within 2 hours. Interestingly, glucocorticoid induction of *Crebl2* as well as the somatotrope genes *Ghrhr* and *Gh1,* is impaired in the presence of the FOXO1 inhibitor (AS1842856). There are several possible mechanisms underlying the requirement of FOXO1 in glucocorticoid induction of somatotrope maturation. One possible mechanism is that glucocorticoid signaling upregulates expression of *Foxo1* and ultimately FOXO1 targets. Consistent with this possibility, *Foxo1* expression is induced 8 hours after activation of glucocorticoid signaling. This does not appear to be the only mechanism underlying the role for FOXO1 in mediating glucocorticoid-induced somatotrope maturation, however, because many FOXO1 target genes, such as *Neurod4* and *Fosl2* are not affected by glucocorticoid signaling. We are currently investigating whether cooperative binding between FOXO1 and the glucocorticoid receptor contributes to transcriptional regulation of common targets genes. Together these data demonstrate that FOXO1 is a key factor mediating glucocorticoid induction of somatotrope maturation.

Neuroendocrinology and Pituitary

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Role of Growth Hormone in Ghrelin's Metabolic Actions

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Objective: Ghrelin regulates eating, body weight, and blood glucose. Upon binding to its receptor (growth hormone secretagogue receptor; GHSR), administered ghrelin increases food intake, body weight, and blood glucose. In contrast, blocking ghrelin lowers body weight and food intake. Also, mice that lack ghrelin or GHSR develop life-threatening hypoglycemia when submitted to a prolonged caloric restriction protocol providing only 40% of usual daily calories. Although GHSR was first identified in the pituitary, ghrelin was first defined by its ability to stimulate GH secretion via GHSRs, GH replacement prevents hypoglycemia in ghrelin-KO mice undergoing prolonged caloric restriction, and GH is known to modulate body composition, relatively little attention has been devoted to the role of GH-secreting pituitary somatotrophs ("GH cells") in ghrelin action. The objective here was to determine the requirement for GHSR-expressing GH cells in mediating ghrelin's metabolic actions. **Methods:** Mice with GH cell-selective GHSR deletion were generated by crossing novel GH-IRES-Cre mice to novel floxed-GHSR mice. GH cell-selective GHSR knockout mice and three control littermate groups were studied. Plasma GH, food intake, and blood glucose were measured after ip or sc ghrelin administration. Blood glucose and plasma GH were measured over the course of a 15-d calorie restriction protocol providing only 40% of usual daily calories. **Results:** In mice with GH cell-selective GHSR deletion, ghrelin-induced GH secretion and food intake were attenuated (by 84.1% at 15 min and by 35.3% at 45 min, respectively) as compared to controls; ghrelin-induced blood glucose elevation was unchanged. Mice with GH cell-selective GHSR deletion exhibited an attenuated GH rise (by 76.8%) over the 15-d calorie restriction period, yet they nonetheless resisted life-threatening hypoglycemia which is observed in similarly-treated ghrelin-KO mice, GHSR-null mice, and mice with hepatocyte-selective GH receptor deletion. **Conclusions:** These results suggest that GH cell-expressed GHSRs are required for ghrelin's acute orexigenic and GH secretory actions but are dispensable for ghrelin's glucoregulatory actions, at least in the settings assessed here. Although GH cell-expressed GHSRs are required for the progressive GH elevations associated with prolonged calorie restriction, they are not required for ghrelin's overall protective effects to block prolonged calorie restriction-associated hypoglycemia.

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Somatostatin, as a Bridge Between the GH-Axis and the Gth-Axis

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Somatostatin (SST) is a 14-amino acid peptide produced in the hypothalamus of vertebrates, including fish. It regulates many physiological processes such as growth development and metabolic processes in the animal's body. Negative control of growth hormone in vivo and in vitro was characterized in several fish species such as salmon, goldfish, rainbow trout and tilapia. Although very important, the SST/SST-R system in Nile tilapia (*Oreochromis niloticus*) was not deeply characterized. The somatostatin system in tilapia possess two ligands (Somatostatin1b and Somatostatin 2), and five receptors (SST-R 1-5). Unlike mammals, in fish, FSH and LH are secreted from different cell populations in the pituitary. By performing cell specific