Editorial: Insulin-Like Growth Factor I—A Prototypic Peripheral-Paracrine Hormone?

Early endocrine physiologic principles were derived by observations of altered hormonal and metabolic homeostasis occurring after target gland ablation and subsequent hormonal replacement in animals and in human subjects. In these early studies, concepts of feedback regulation emerged as overriding mechanisms for maintaining harmonious hormonal balance.

Insights into classical physiologic regulation of the endocrine system were based upon several feedback principles. Multiple levels of feedback regulation involve endocrine target tissues, target glands, pituitary, and the hypothalamus. Primarily, negative feedback regulation of a pituitary trophic hormone by its respective target hormone enables a powerful control mechanism for pituitary function. Thus, ablation or disease of a target organ (gonad, thyroid, or adrenal gland) is associated with abundant hypersecretion of gonadotrophins, TSH, or ACTH. Conversely, target hormone hypersecretion, as encountered in patients with Grave's hyperthyroidism, or steroid-secreting adrenal tumors, is associated with blunted or undetectable TSH or ACTH secretion. Although insulin-like growth factor IGF-I was identified as a target hormone mediating GH action, the ubiquitous sites of its production did not provide a readily recognizable target organ failure syndrome (1, 2). However, several lines of clinical and physiologic evidence point to a controlled inverse interrelationship between GH and IGF-I. For example, intracerebral IGF-I infusions to animals (3). For example, injections to human subjects resulted in attenuated GH secretion (4, 5). It is also recognized that metabolic perturbations such as prolonged fasting or malnutrition resulting in lowered IGF-I levels are associated with inappropriately elevated GH levels (1).

Both central and pituitary sites are targets for IGF-I impacting on the GH axis. IGF-I acts at the level of the hypothalamus, where it stimulates hypothalamic SRIF synthesis, thus providing a centrally derived attenuation of GH (6). IGF-I may also secondarily deplete hypothalamic GHRH (7).

In addition to hypothalamic influences, the molecular mechanism for pituitary hormone negative feedback regulation appears to involve direct attenuation of trophic hormone transcription. Thus, glucocorticoids, sex steroids, thyroid hormone, and IGF-I all suppress intrapituitary transcription of their respective trophic hormones. For IGF-I, however, the paradigm is somewhat more complex inasmuch as only a portion of pituitary IGF-I is in fact derived from true endocrine (mainly hepatic) sources. Pituitary endothelial and other nonpituitary cells are a source of paracrine IGF-I, which in turn inhibits neighbouring somatotroph transcription (8). In addition, intrapituitary IGF-I also appears to regulate somatotroph function by an autocrine or possibly an intracrine mechanism, as IGF-I is coexpressed with GH in somatotroph cells. As pituitary IGF-I gene expression is regulated in a GH-dependent manner, a closed autocrine loop may also be operative in the mutual feedback regulation of these two anabolic polypeptide hormones (9).

Structure-function studies of the pituitary IGF-I receptor have revealed that the major determinant of somatotroph sensitivity to circulating or intrapituitary IGF-I is the relative abundance of somatotroph IGF receptors (8). Furthermore, mutation of key signaling motifs (10) of the somatotroph IGF-I receptor abrogates IGF-I-mediated GH suppression (11, 12). Thus, IGF-I receptor integrity may determine the well-known physiologic GH responses to malnutrition, pregnancy, and refeeding (10).

In this issue of the journal, Stefaneanu and colleagues (13) have employed a transgenic mouse model with disrupted IGF-I gene expression to further elucidate the role of IGF-I in determining somatotroph function. In homozygous IGF-I female knockout mice, somatotroph GH mRNA signals were enhanced, and the pituitary gland exhibited ultrastructural features of somatotroph stimulation, despite unchanged absolute numbers of somatotrophs. Replacement of IGF-I to the homozygote animals decreased pituitary GH mRNA levels as assessed by in situ hybridization signals. This latter finding strongly supports the role of endocrine-derived IGF-I in suppressing pituitary GH synthesis. Although the dwarf IGF-I knockout animals were not sufficiently large enough to provide multiple samplings for meaningful assays of GH secretion, previous workers had shown that circulating GH levels were indeed elevated in another model of IGF-I deficiency. Thus, using novel techniques, this work shows that deprivation of IGF-I leads to compensatory somatotroph hyperfunction. It will be interesting to determine the relative influence of potentially attenuated hypothalamic SRIF in these animals to further elucidate the respective roles of the hypothalamus and pituitary in mediating these responses.

An unexpected finding in this work was the pronounced effect of IGF-I disruption on PRL synthesis and secretion. It had been recognized from earlier in vitro models that insulin and IGF-I both induce PRL gene transcription and secretion (14). Surprisingly, although PRL levels were elevated in homozygous IGF-I knockouts, pituitary PRL mRNA levels were significantly lowered. Curiously, IGF-I treatment only increased pituitary PRL mRNA in WT but not in knockout animals. Clearly, further work is required to elucidate the impact of IGF-I on in vivo PRL synthesis and secretion.

Thus, Stefaneanu and colleagues, by using transgenic tech-
nology, now confirm the role of endocrine-derived IGF-I in regulating both somatotroph function as well as size. Based upon these new findings, and previous data, it is clear that negative feedback regulation of pituitary function involves integration of complex endocrine, paracrine, and autocrine IGF-I-mediated signals, all of which converge on the somatotroph and account for the ultimate secretory pattern of GH (15).

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References