INVITED COMMENTARY

Somatostatin infusion withdrawal and growth hormone release in dogs and man

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The hypothalamic neuropeptides growth hormone-releasing hormone (GHRH) and somatostatin (SS), respectively, stimulate and inhibit the release of growth hormone (GH) from the anterior pituitary gland in both man and other animals. Even before the discovery of GHRH (in 1982) a series of small peptides, derived from met-enkephalin, had been developed and shown to specifically release GH *in vitro* (1). These GH-releasing peptides (GHRPs) along with a number of non-peptide analogues (collectively termed GH secretagogues; GHS) are now known to act on a specific GH secretagogue receptor (GHS-R), present in the hypothalamus and pituitary (2). Recently, a peptide isolated from rat stomach (and called ghrelin) was identified as an endogenous ligand for the GHS-R and suggests another pathway in the regulation of GH secretion (3).

In this issue of the *European Journal of Endocrinology*, Rigamonti *et al.* (4) investigate functional interactions between GHRH and a GHRP on the GH response that occurs at the end of a peripheral infusion of SS. The rebound GH response to SS withdrawal is well documented in both humans and other animals and appears to be mediated by increased hypothalamic GHRH release. The mechanism of action of synthetic GHSs is complex. Although *in vitro* studies have shown a direct pituitary action of GHSs, the GH response is attenuated in humans and other animals with hypothalamic–pituitary disconnection or following blockade of endogenous GHRH, suggesting that activation of hypothalamic GHRH neurones is an important mechanism of action of these compounds *in vivo* (5). Numerous studies have reported the effects of SS withdrawal, GHRH administration and GHS administration on GH release in both man and other animals. Here, Rigamonti *et al.* (4) have tried to probe the interaction between endogenously released GHRH following SS withdrawal and exogenously administered GHRP in dogs since they are a good model for GH regulation in humans. Whereas administration of GHRH at the end of SS infusion had a slight additive effect on GH secretion compared with the response seen during saline infusion, a marked enhancement of the GH response was seen following administration of GHRP at the termination of SS infusion compared with saline infusion. This is in agreement with the findings of a similar study performed in man using

SS, GHRH and the synthetic GHS, hexarelin (6). It is possible that this reflects a synergistic interaction between endogenous GHRH (following SS withdrawal) with the administered GHRP. However, this hypothesis has not been tested directly and it is important to note that while the acute GH response to SS withdrawal can be blocked by GHRH antiserum in rats, a GHRH antagonist failed to prevent the GH rise to SS withdrawal in humans (7), highlighting potential species differences in the generation of GH pulses. This is an important point, since it reminds us that we must remain cautious in the extrapolation of animal data to human physiology. Furthermore, if the GH response to SS withdrawal is not due to increased GHRH then what other mechanisms could be responsible (ghrelin perhaps)? The answer to this question may give us more insight into interactions between SS, GHRH and GHSs involved in the regulation of GH secretion.

Based on their results Rigamonti *et al.* (4) suggest that the combined application of SS withdrawal and GHRP administration might be a useful test for the diagnosis of GH deficiency (GHD), perhaps even discriminating GHD of pituitary origin from hypothalamic impairment. The diagnosis of GHD in both children and adults is far from simple and in both instances requires the use of provocative tests of GH secretion. For children, a number of tests can be used which makes standardization difficult, while in adults the ‘gold standard’ test recommended by the Growth Hormone Research Society (insulin-tolerance test) has a number of contraindications and suffers from poor reproducibility. There is clearly a need for a simple, reliable alternative. Would SS withdrawal combined with administration of a GHRP fit the bill?

In adults, an initial cycle of SS withdrawal does not always lead to rebound GH secretion although subsequent cycles of SS withdrawal do seem to elicit GH release (7, 8). This procedure alone could therefore lead to a high number of false positive results although it has been used successfully to discriminate normal control from GHD children (9). Administration of GHRP at the termination of SS infusion does appear to be a robust stimulus for GH secretion both in dogs (4) and humans (6) although it seems that this is no more effective than the combined administration of GHRH plus GHRP during saline infusion (4). This latter

combination has also recently been proposed as a test for GHD (10, 11) and would seem to offer advantages of reproducibility as well as simplicity and rapidity over SS withdrawal since it does not require a 1-h long infusion period before injecting the secretagogue.

Perhaps SS withdrawal plus GHRP could be used in the differential diagnosis of GHD resulting from hypothalamic (GH neurosecretory dysfunction, GHND) versus pituitary impairment? The GHND is thought to reflect an abnormality and/or a neuro-regulatory alteration of hypothalamic GHRH function. Interestingly, SS withdrawal alone was unable to distinguish GHD of pituitary origin from GHND in children, with neither GHND nor pituitary GHD children exhibiting GH responses to SS withdrawal, although GHND children exhibited a small GH response to clonidine, another stimulus thought to activate endogenous GHRH (9). Earlier studies have assessed the ability of GHRP-6 and hexarelin to distinguish normal controls from GHD children (12, 13) with limited success. Overall, GH responses in GHD children are lower than normal controls although, on an individual basis, there can be a considerable degree of overlap between patients with idiopathic GHD and controls. It is feasible that a number of GHD patients who show a GH response to synthetic GHSs may have a residual vascular component of the pituitary stalk (13). Thus it is possible that there would be a sub-population of pituitary GHD children who would exhibit GH responses to SS withdrawal plus GHRP if carried out in a large number of children. It is difficult to predict the response to SS withdrawal plus GHRP in GHND children. Synthetic GHSs seem to require the presence of endogenous GHRH for their full *in vivo* effect on GH release so it seems plausible that a moderate response to SS withdrawal plus GHRP would be observed in GHND as suggested (4).

The data presented by Rigamonti *et al.* (4) indicate that SS withdrawal plus GHRP administration is a potent stimulus for GH secretion in healthy dogs and on their own do not immediately suggest that this may be a useful test for GHD in humans. Obviously, basic scientific and medical research must be driven by the generation and testing of hypotheses, although the point merits reinforcement that we should be wary of over-interpretation of animal data and its direct application to human health and disease.

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