

The First International Meeting of the Growth Hormone Research Society

June 1 - 4, 1994; Aarhus, Denmark

A Meeting Review by Paul Saenger, MD, Professor of Pediatrics, Department of Pediatrics, Montefiore Medical Center, Bronx, New York

Over 400 delegates attended this meeting, which was devoted to clinical and basic science aspects of growth hormone (GH) research. At the meeting, which had attracted a large number of adult endocrinologists, the importance of GH in adults with GH deficiency was examined. Particular emphasis was placed on further study of the regulation of GH secretion, diagnosis, and characteristics of adult GH deficiency, and the effects of GH replacement therapy in adults.

Professor Iain Robinson, London, England, spoke about peptidal and nonpeptidal GH-releasing substances and their interaction with the GH-releasing factor (GRF) neuron. The GRF neuron has to be

viewed as a clearinghouse for a wide variety of afferent neuronal information. He stressed that, in his view, the GH-releasing action of GRF is not its primary function.

The pulsatile GH release is most likely regulated by somatostatin. Somatostatin optimizes the pulse frequency pattern, thus stimulating growth by setting a pulse pattern that is most economical for achieving the maximum growth of peripheral tissues. He could show elegantly that 9 GH pulses per day give more bone growth in the rat than 1 large pulse of GH with a similar area under the curve. The GRF/somatostatin interplay has been studied not only in physiologic settings but also in disease, such as in patients with ectopic GRF production where, even under constant GRF exposure, GH release remains pulsatile.

Professor Robinson reported preliminary data on

12-hour GH sampling in premature infants. In collaboration with Dr. David Dunger, Oxford, England, he was able to show that in 34-week gestation premature infants, GH is already secreted in bursts. The striking difference compared with older children was that their GH level never declined to zero. Peaks of GH were superimposed over a baseline level of 5 to 10 ng/mL of GH. Dr. Robinson indicated that the high GH levels in premature infants suggest that GH probably has important metabolic functions in utero.

Professor Robinson stressed it is far from true that all GRF pulses are associated with a subsequent GH release. It is only due to pulsatile somatostatin that we achieve a GH release after GRF at all.

The major function of GRF, according to Professor Robinson, is to build up GH stores in the pituitary. Indeed, it has been shown that GRF does induce increased GH gene transcription. He cited the *little* mouse, which does not respond to GRF, as an intriguing animal model to study the physiology of GRF action. A single point mutation in the extracellular domain of the GRF receptor renders the *little* mouse resistant to GRF. This then leads to a total failure of postnatal GH cell proliferation in the pituitary and the pituitary GH cell population is near zero. GRF, therefore, exerts a trophic function for growth hormone secreting cells as well.

Professor Robinson stressed further that the pituitary has to be viewed as a plastic organ that can change the number of GH-producing cells in responses to afferent input, GRF being among them. Physiologic GRF production is then enmeshed in a feedback loop where GH release exercises a negative feedback. Furthermore, central GH receptors are equally responsive to circulating peripheral GH. There are several afferent inputs for the GRF neuron. These inputs come from GH itself, somatostatin, synthetic GH-releasing peptides (GHRPs), neurotransmitters, and possibly also IGF-1.

Professor Robinson concluded his talk by reviewing the current knowledge of GHRPs. Simply just the fact that GHRPs have an effect in man suggests that there may be endogenous, still elusive, GHRPs produced in the brain. Since synthetic GHRPs are effective, one has to postulate that there are receptors in the brain for these synthetic GHRPs. Whether they are identical to GHRP receptors for endogenous GHRP is not clear. GHRPs work through their own receptors, not through GRF receptors. Furthermore, GHRPs also have a hypothalamic target in addition to a pituitary target. GHRPs act in synergism with GRF and regularize the response to GRF. Elegant studies utilizing anti-GRF show that GRF-Abs interfere with GHRP action. A functioning hypothalamus is required for full GHRP action. Additional effects of GHRP may also influence the firing rate of the arcuate nucleus. In studies using

the pregnant ewe as a model, investigators could show that GHRP stimulates GRF and GH release as well as somatostatin by measuring efferent products in the effluent of portal blood of the pregnant ewe. Little is known yet about the effects of these compounds in chronic use.

Dr. C. Eschen, Copenhagen, Denmark, showed that the administration of GHRP-6, originally synthesized by Dr. Cyril Y. Bowers, to rats for 14 to 90 days had little effect on weight gain or IGF-1 levels. Several new GH secretagogues have been synthesized recently. These GHRP analogues were discussed by Professor Robinson, and were also the topic of several poster presentations at the meeting.

One of the analogues, hexarelin, was described as a potent GH releaser in children and laboratory animals such as dogs. Its usefulness in the more refined diagnosis of GH deficiency was proposed. It should be noted that only 0.3% of GHRP is absorbed via the oral route, thus limiting its potency considerably. This does not seem to be the case for newer nonpeptidic oral secretagogues such as L-692,429 and L-692,585, which have a manifold higher potency and also better absorption.

Dr. S.L. Dickson, Cambridge University, England, showed that GHRP L-692,585 was inducing *fos* protein in the arcuate nucleus. Elegant neurocytochemistry documented the induction of this key protein in the wall of the third ventricle.

The GRF neuron can best be characterized as a clearinghouse for the multiple afferent neurons. The pituitary has to be viewed as an organ with considerable plasticity. The primary function of the hypothalamus, according to Professor Robinson, is to regulate pituitary size and thus enable specific pituitary hormonal responses. In conclusion, GHRPs, which were thought to act directly on GH secretion cells in the pituitary, are now believed to produce many of their effects by interacting with somatostatin and by stimulation of GRF neurons in the hypothalamus.

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