Molecular and Cell Biology of the Hypothalamic-Pituitary System: A Symposium Review

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This symposium opened with a presentation by Prof. Argente. He reviewed the roles of hypothalamic neuro-peptides – growth hormone-releasing hormone (GHRH), somatostatin (SS), pituitary adenylate cyclase activating peptide (PACAP), growth hormone-releasing peptides (GHRPs) – and the GHRH receptor and SS receptor. Prof. Argente went on to describe the developmental and regulatory effects of the pituitary transcription factors (Pit-1 and Pit-2) and the effects of the insulin-like growth factor binding proteins on insulin-like growth factor.

Dr. Steiner described his work using double-labelled in situ hybridization techniques to investigate the neuroendocrine control of GH secretion by GHRH, SS and neuro-peptide-Y (NPY) neurones. GH exerts rapid effects on several neurone cells, including those expressing galanin and NPY as well as those expressing GHRH and SS; it appears to act indirectly on GHRH neurones, with NPY neurones mediating this effect.

The role of glial cells in the hypothalamus and their effects on the endocrine system were presented by Prof. García-Segura. Gonadal steroids modulate the formation of synaptic connections in different brain areas by changing the astroglial morphology. These changes modulate the number of GHRH neurones in the arcuate nucleus in addition to the effect on GHRH secretion.

Dr. Ingraham focused on the role of the transcription factors Pit-1 and SF-1. The latter is an orphan nuclear receptor and, though it binds to the MIS (TGF β -like) promoter in the testes, its ligands remain unidentified. She went on to describe a new element, Pal-1, which may be critical in the corticotrope expression of the 5HT3R gene, a serotonin-gated ion channel expressed in the melano-tropes of the intermediate pituitary lobe.

Knowledge of the complex intracellular pathways involved in growth hormone signal transduction contributes to our understanding of how GH affects metabolism and growth; Dr. Argetsinger reviewed the roles of two kinases – JAK2 and MAP kinase. At the nuclear level, more than six STAT transcription factors are involved in the activation of GH-responsive genes. Regulation of the kinases and STAT factors in different tissues after GH binding is still poorly understood.

The clinical aspects of genetic GH-deficiency were reported by Dr. Pfäffle. Point mutations in the Pit-1 gene result in a non-active Pit-1 transcription factor; this breakdown in the pathway leads to a combined pituitary hormone deficiency of GH, prolactin and thyroid-stimulating hormone. A dominant negative effect on GH gene expression results from the autosomal dominant mutation (R271W); here the DNA-binding activity of the Pit-1 protein is, however, not

affected. These naturally occurring genetic variants will help us understand the mechanism of Pit-1 action at the molecular level.

In short, the cloning and analysis of genes controlling neuropeptides, hormones and their receptors have increased our insight into the basic mechanisms of the hypothalamic-pituitary system. The current knowledge of growth hormone regulation reviewed in this symposium points to exciting directions for future research in this area.

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