Neuro-endocrinology

48

BRIEFINGS

Navigating pituitary structure and function - defining a roadmap for hormone secretion

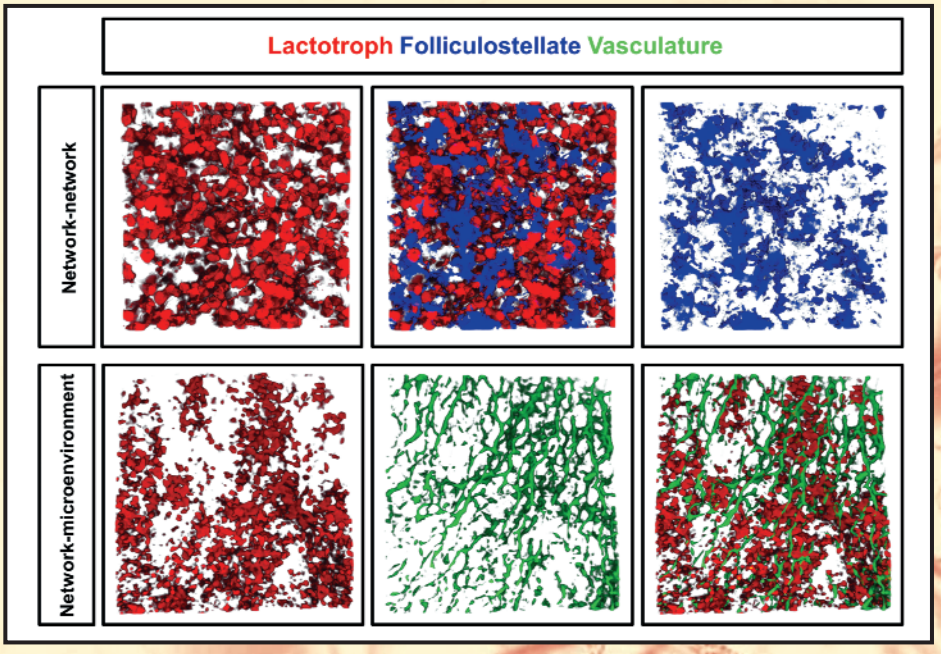
SUMMARY

The human pituitary gland may be the size of a pea, but it punches well above its weight due to secretion of hormones that regulate essential homeostatic processes ranging from growth to stress. Recent advances in imaging and genetics have allowed large-scale interrogation of pituitary structure and function, and in doing so, have revealed that output relies on its organisation into highly plastic networks.

The hypothalamo-pituitary axis regulates function of downstream tissues via the pulsatile secretion of hormone, and failure to generate the appropriate rhythm and/or quantity leads to hypopituitarism (hormone deficiency). The anterior pituitary has been assumed to represent a simple organ whose activity is sculpted by brain input. As such, scant attention has been paid to an intrinsic role for this endocrine gland in hormone release. In recent years, however, the advent of high-resolution imaging approaches has provided an unprecedented view of structure-function relationships. This has dramatically altered our perception of the pituitary, and we now consider it a complex tissue which plays a major role in orchestrating hormone secretory dynamics. The pituitary may therefore be an important target for insults which result in disorders of growth, metabolism, stress, fertility and lactation.

The pituitary is an oscillator

It is believed that the hypothalamus interprets external cues, like stress levels, before commanding hormone secretion from the pituitary "slave". This view remained unchallenged until early this century when a potent combination of imaging, animal genetics and mathematical analysis revealed that most pituitary cell types are organised in three-dimensions to form plastic populations which display remarkable levels of modularity and robustness, pre-requisites for their classification as biological networks (Figure 1). Thus: 1) corticotrophs (important in the stress response) form a scaffold which may underlie generation of daily rhythms of stress hormone release; 2) somatotrophs (important in growth and development) together amplify incoming signals to encode



Secretory lactotrophs (red), support cells (blue) and vasculature (green) form plastic 3D networks which influence and shape hormone secretion from the mammalian pituitary gland. Network-network and network-microenvironment interactions may add a further level of structural and functional regulation.

hormone patterns which drive certain sex differences; 3) lactotrophs (important in lactation) constitute interconnected ensembles which learn from previous experience to improve function in response to future lactational demands; 4) non-endocrine cells provide a long-distance route for coordinated propagation of signals between distant pituitary regions; and 5) progenitors, able to give rise to all pituitary endocrine cell types, form a network which may host stem cell niches. Consequently, a revised view of the hypothalamo-pituitary axis includes a dual oscillator model where the pituitary itself can dynamically adjust in response to various stimuli to directly influence hormone secretion and homeostasis.

The microenvironment

Endocrine cell networks are closely associated with highly vascularised capillary beds, hinting at an intimate functional relationship between hormone output and the pituitary microcirculation. To investigate this, newly developed imaging approaches have been applied to the ventral surface of the surgically exposed pituitary. Such studies have demonstrated that the pituitary vasculature not only compensates the substantial energy requirements associated with endocrine network activity, but also represents a rate-limiting step in secreted peptide, shaping the build-up of hormone pulses accordingly. Hence, the pituitary microenvironment encompasses a functional unit with endocrine networks, failure of which may further aggravate defective hormone output.

Current understanding of pituitary function

Gaps still remain in our knowledge concerning the impact of tissue organisation on pituitary output. Foremost: do endocrine cell networks similarly exist in higher mammals including humans? Can we improve performance of an under-functioning pituitary gland (hypopituitarism)? Are we able to modulate activity to maintain hormone secretion in the face of incorrect incoming signals? Is it possible to rebuild functional networks? Likewise, can we prevent formation of unwanted network properties (e.g. tumours which secrete excess hormone)? It is hoped that a better understanding of pituitary architecture and function may eventually allow hormone secretion to be restored by repairing the pituitary *in situ* in man. This is all the more pertinent considering that the pituitary gland has recently become the first multicellular organ to be reproduced in a petri dish.

A long journey ahead

The last 20 years have seen rapid innovations in light microscopy and animal trangenesis. By harnessing the power of these methods to image endocrine organs both *in situ* and *in vivo*, many novel facets of pituitary structural and functional regulation continue to be revealed.

"the pituitary is capable of displaying both short- and long-term plasticity in response to a range of stimuli and demands"

Indeed, it is evident from these studies that the pituitary is a complex organ which, akin to its neuronal counterparts, is capable of displaying both short- and long-term plasticity in response to a range of stimuli and demands. Insults which impact network activity are therefore likely to result in impaired secretion by dampening output of the pituitary oscillator. Future investigations should pay particular attention to the interactions which harmonize hypothalamic and pituitary rhythms, the role of the pituitary microenvironment in gatekeeping hormone release, and the contribution of network dysfunction to endocrine dysfunction.

Authors:
David J. Hodson
Department of Medicine, Division of Diabetes Endocrinology and Metabolism, Imperial College London, UK

Patrice Mollard
Institut de Génomique Fonctionnelle, CNRS UMR-5203, INSERM U661, Universités de Montpellier 1 & 2, France

Editor:
Professor Mike Ludwig
Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK
mike.ludwig@ed.ac.uk

The full Briefings series can be viewed at website http://www.neuroendo.org.uk