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EXPERT REVIEWS

Translational neuroendocrinology

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The 7th International Congress of Neuroendocrinology (ICN2010)

11–15 July 2010, Rouen, France

Neuroendocrinology has moved far beyond its initial focus on the regulation of pituitary hormone secretion. It now embraces not only the actions on the brain of a diverse range of 'new' hormones, such as leptin and ghrelin, but also the expanding roles of peptides as hormone-like messengers within the brain, controlling many fundamental behaviors and physiological processes. A recent International Congress of Neuroendocrinology highlighted the translational importance of some of these new insights.

In July 2010, the 7th International Congress of Neuroendocrinology was organised by Hubert Vaudry and his colleagues at the University of Rouen (France) on behalf of the International Neuroendocrine Federation – an umbrella organization representing national and regional societies of neuroendocrinology – and attracted more than 800 delegates from approximately 30 countries. This Congress is held every 4 years (the next one will be in Sydney, Australia, in 2014), and this was the largest to date. The scientific program included nine plenary lectures and 64 'State-of-the-Art' lectures, together with volunteer oral communications and several hundred posters. The program had four parallel strands on reproductive neuroendocrinology; the neuroendocrinology of stress; growth and metabolism; and neuropeptides.

Regulation of reproduction

The pinnacle of each Congress is the Geoffrey Harris lecture, commemorating the 'father of neuroendocrinology', and this year it was given by Ian Clarke of Monash University (Australia). Geoffrey Harris first established the principle that the hormones of the anterior pituitary gland are controlled by substances released from hypothalamic neurons into the portal vessels that perfuse the gland, most of which turned out to be peptides, and 30 years ago, Ian Clarke was the first to show directly (by measurements of peptide release into the portal blood in sheep) that the pulsatile secretion of luteinizing hormone is directly governed by pulsatile secretion of gonadotrophin-releasing hormone (GnRH) into the portal vasculature. Today neuroendocrinology has moved far beyond these early horizons, with the recognition that neurons in the brain make a vast diversity of peptides (more than 100 known to date), and the recognition that the brain also receives a vast diversity of peptide signals from the periphery – including leptin and other adipokines from adipose tissue [1] and ghrelin from the gastrointestinal tract [2,3]. In this lecture, Ian Clarke focussed on how two relatively new neuropeptides, gonadotrophin inhibitory hormone (GnIH) and kisspeptin, interact to regulate GnRH secretion, controlling not only the ovarian cycle but also the onset of puberty [4]. GnIH was first identified in birds (and initially neglected); an illustration of some of the important insights that can be realised from comparative approaches, which featured strongly in the programme [5].

Gut–brain communication

Today, neuroendocrinology is very much about information processing by peptides, and as peptides can be released from neurons independently of neurotransmitter release, from different cellular compartments, and with very different scope and style of action [6], insights from neuroendocrinology are changing our understanding of information processing in the brain. In addition, neuroendocrinology has gained a new translational importance as peptides are such important targets for new drug development. The Congress ended with a plenary lecture by Matthias Tschöp (University of Cincinnati, OH, USA) on 'Gut–brain

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communication as a therapeutic target for metabolic disease' that powerfully exemplified this. The ghrelin system is a key mechanism regulating energy balance and metabolism in mammals. A peculiarity of this hormone is its acylation, which confers its biological activity; this step is catalyzed by the enzyme ghrelin *O*-acyltransferase (GOAT), which is emerging as a novel target to regulate the biological actions of ghrelin, with several therapeutic possibilities for the treatment of the metabolic syndrome [7]. Other important new developments include the recognition that the hypothalamus may directly control cholesterol metabolism by the liver. Elevated blood concentrations of low-density lipoprotein cholesterol are a risk factor for metabolic and cardiovascular disorders, whereas high-density lipoprotein cholesterol in the blood is thought to be beneficial. Circulating cholesterol is the balance among dietary cholesterol absorption, hepatic synthesis and secretion, and the metabolism of lipoproteins by various tissues. Importantly, inhibiting the brain's melanocortin system by pharmacological, genetic or endocrine interventions increases circulating high-density lipoprotein cholesterol by reducing its uptake by the liver [8].

Hyponatremia: a major problem in critical care

While we have mentioned a few of the many 'new' peptides, some 'old' peptides continue to spring surprises; for example, vasopressin turns out to be expressed not only in the hypothalamus but also in the rodent olfactory system, where it plays a key role in social recognition [9]. But even some of the 'old' roles of 'old hormones' have acquired a fresh translational significance, as exemplified in a plenary lecture from Joe Verbalis of Georgetown University (DC, USA).

Vasopressin plays a key role in body fluid homeostasis, and dysregulation of the vasopressin system causes water retention, often leading to dilutional hypo-osmolality. The brain is particularly vulnerable to this – one serious complication is brain edema during hypo-osmolar states, caused by water movement into the brain along osmotic gradients. The compensatory mechanisms involved with brain adaptation to osmotic stresses involve transient changes in water content and sustained changes in electrolyte and organic osmolyte contents – including a loss of up to 30% of brain glutamate content. This compensatory mechanism comes with risks: the decreases in brain glutamate level are associated, perhaps causally, with neurocognitive disturbances and gait instability, and these are associated in turn with an increased incidence of falls in hyponatremic patients [10,11]. In addition, the activation of osteoclasts, to recover the sodium entrapped in bone matrix, leads to bone loss and osteoporosis, potentially further increasing the risk of fractures in hyponatremic patients. Now this is far from a marginal problem – disorders of sodium and water homeostasis are among the most commonly encountered disturbances in the critical care setting, because many disease states cause defects in the complex mechanisms that control the intake and output of water and solute. A new class of vasopressin receptor antagonists induces aquaresis (free water diuresis without natriuresis or kaliuresis), and many clinical trials have shown that these are effective in patients with hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion or edema-forming states, such as congestive heart failure and cirrhosis. Further studies are needed to assess their potential benefit for correction of symptomatic hyponatremia and for long-term treatment of minimally symptomatic hyponatremia to reduce the risks of neurocognitive dysfunction and gait instability.

Integrative insights & new technological developments

Conferences in neuroendocrinology bring together an extraordinary spectrum of understanding and expertise; neuroendocrine systems control all aspects of reproduction: gonadal regulation, sexual behavior, pregnancy, parturition, maternal behavior and lactation; they control growth, appetite and metabolism, our responses to stress, the immune system, and myriad other physiological systems that impact powerfully on our health and happiness. They also provide some of the most powerful model systems in contemporary neuroscience. Most importantly, these model systems offer a 'window on the brain' that allows neuronal behavior to be directly associated with physiological function, and hence remarkable translational opportunities. Conferences in neuroendocrinology play a critically important role because of this breadth of expertise; again and again in this conference came the lesson that these physiological regulatory systems are not tightly compartmentalized – for example, reproduction and food intake are reciprocally regulated, and these reciprocal control systems are deeply embedded and highly conserved through evolution. Leptin is a hormone that controls not only appetite but also puberty, and a similar duality is echoed across many systems. Thus, neuroendocrinologists have much to learn from each other even when their apparent focuses of interest seem far apart. Meetings are exciting when you learn things that you did not think you needed to know, but that turn out to hold essential insights.

The control of the activity of types of neurons *in vivo* and *in vitro* using optogenetics is an exciting new direction; for example, it is now possible to develop transgenic mice in which light-activated channel proteins have been introduced into specific neuronal populations enabling their activity to be directly regulated by light of a specific wavelength. Akihiro Yamanaka (Okazaki Institute for Integrative Bioscience, Okazaki, Japan) demonstrated how the activity of orexin neurons in such transgenic mice can reveal how the activity of these neurons controls particular behaviors [12]. However, mice are small, and rats remain the preferred model for many functional studies. Yoichi Ueta (University of Occupational and Environmental Health, Kitakyusha, Japan) has recently developed two new transgenic rat models in which fluorescent reporter proteins are expressed in vasopressin neurons and oxytocin neurons, respectively. At the conference in Rouen, he presented another new transgenic rat model, in which monomeric red fluorescent protein is expressed under the control of the regulatory sequences in the immediate early gene c-*fos* [13]. *c-fos* is expressed transiently in neurons following activation, so these models offer important new opportunities for studying function in neuroendocrine systems.

The exciting opportunities afforded by such models are well illustrated by the remarkable work of Patrice Mollard (Institute of Functional Genomics, Montpellier, France). He and his colleagues have developed optical imaging methods that allow them to identify single hypothalamic neurons *in situ* in living mice and record their activity electrophysiologically [14], and to monitor directly *in vivo* the relationship between the blood vasculature and pituitary cell types in mice [15].

The invited contributors have submitted review manuscripts for special issues of the journals *Stress*, *Neuroendocrinology,* the *Annals of the New York Academy of Science* and the *Journal of Neuroendocrinology* (which has already published its special issue; Volume 22, number 7, 2010). Some of the plenary lecturers will publish their reviews in *Frontiers in Neuroendocrinology.*

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