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Editorial

Neuropeptide Hormones and Stress

This issue contains invited papers from the 5th International Workshop of the University of Occupational and Environmental Health (UOEH), Kitakyushu, Japan, organized by Prof. Yoichi Ueta and Prof. Makoto Otsuki, and held on 30th August, 2003. The theme of the 5th Workshop was "Stress, feeding, neuroendocrine function and occupation", extending the theme of the previous Workshop, in 1995, on "Emotion, stress and metabolism" (see Yamashita *et al.*, 1999). The UOEH is a most appropriate venue for stress-related Workshops, because the research focus of the UOEH on occupational health necessarily embraces stress in the workplace, together with the objective of understanding the biological processes that are involved in stressor processing and the organization of stress responses, and in adaptations to chronic stress. Distinguished researchers and young investigators from Canada, France, UK, USA and Japan got together to present and discuss their recent research.

The 2003 Workshop comprised four sessions, on "Neuronal activity, bioactive substances and neuroendocrine function", "Synaptic events, modulation and oxytocin", "Stress, feeding and neuroendocrine regulation" and "Gene expression and receptors" and a special lecture by Dr Kiyomi Koizumi (SUNY, USA) on the history of electrophysiological studies of neurosecretory neurones. The selection of papers in this issue are based on the talks at the Workshop, and are predominantly concerned with roles of the neurohypophysial peptides, oxytocin and vasopressin, in neuroendocrine stress response mechanisms.

These papers are preceded by a cognate review from Volpi *et al.* (2004; not presented at the UOEH Workshop) on the role of vasopressin in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Volpi *et al.* review the evidence for the role of vasopressin from parvocellular paraventricular nucleus (PVN) neurones in supporting, through its actions on V1b receptors on the corticotrophs, the regulation of corticotropin (ACTH) secretion by corticotropin releasing hormone (CRH). They emphasise that this function of vasopressin is by no means static: there are striking changes with chronic stress, in particular in the up-regulation of expression of the vasopressin gene by the parvocellular PVN neurones, and in increased expression of the V1b receptor in the corticotrophs. Intriguingly, V1b receptor regulation importantly involves control at the level of translation. Volpi *et al.* have made substantial progress in elucidating the mechanism of this translational control, and discuss evidence for tonic intrinsic inhibition, overcome by protein kinase C (PKC) activation of an internal ribosome entry site in an untranslated region of the mRNA. The findings are consistent with the view that in chronic stress, when CRH gene responses in the PVN are reduced, the up-regulation of vasopressin mechanisms is crucial in maintaining HPA axis responses.

In contrast to the role of vasopressin from parvocellular PVN neurones in the regulation of ACTH responses to stress, osmotic stimulation of vasopressin release from the axon terminals of magnocellular neurones seems not to be involved in the regulation of ACTH secretion (see Volpi *et al.*, 2004). Nonetheless, the circumstances in which vasopressin secretion from the axon terminals of magnocellular supraoptic and PVN neurones in the posterior pituitary is stimulated (blood loss or dehydration, involving life-threatening homeostatic disturbance) are by definition stressful. Vasopressin secreted from the posterior pituitary in response to these stimuli has a major role in maintaining blood volume and pressure, and extracellular fluid volume and osmolarity through its pressor and antidiuretic actions. The nature of the receptors that monitor blood pressure and volume, and extracellular fluid osmolarity, and the neural pathways that connect then to the magnocellular vasopressin neurones have been intensively studied. Sladek (2004) reviews the studies that have identified the neurotransmitters used by these stress circuits, focusing on studies on an *in vitro* hypothalamic explant preparation, and how this has permitted identification of glutamate mechanisms in conveying signals from rostral osmoreceptors to the vasopressin neurones, which are actually themselves also osmoreceptors. Sladek also reviews the evidence that multiple transmitters, including ATP, neuropeptide Y and substance P are used by the brainstem neurones that convey cardiovascular information to the vasopressin neurones, and that these transmitters have complex synergistic interactions.

While, in the rat, vasopressin secretion from the posterior pituitary is in general not released in response to emotional and physical stressors that activate the HPA axis (but do not threaten cardiovascular or osmotic homeostasis), oxytocin secretion is generally stimulated by such

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stressors. However, it is increasingly evident that the dendrites of oxytocin and vasopressin neurones store and secrete oxytocin or vasopressin, and that peptide release from the dendrites is regulated independently of release from the axon terminals in the posterior pituitary. Such dendritic release of neuropeptide is important in auto-regulation of the neurones, but also provides a source of these neuropeptides within the brain, which can diffuse to act on other types of neurone (if they have appropriate receptors). These issues are reviewed and illustrated by Engelmann and Ludwig (2004). They used forced swimming and social defeat as stressors, and microdialysis to measure neuropeptide release (from dendrites) in the supraoptic nucleus with simultaneous blood-sampling. They showed that social defeat did not increase secretion of oxytocin or vasopressin into blood, but selectively increased dendritic release of oxytocin, and not vasopressin. In contrast, forced swimming increased oxytocin, but not vasopressin, secretion into blood, but increased dendritic release of both oxytocin and vasopressin. Clearly important issues are: what are the central roles of dendritically released oxytocin and vasopressin? and, how is dendritic release regulated independently from axonal terminal release? A further issue concerns the role of oxytocin released into the circulation in response to stress, for which presently there is not a clear answer. Previous studies indicate actions of dendritically released oxytocin or vasopressin on behaviours, and in the modulation of HPA axis responses, as well as actions on the magnocellular neurones themselves. In the present paper Engelmann and Ludwig address the issue of regulation of dendritic release, and provide evidence for important roles of locally released taurine and GABA.

The dendritic release of neuropeptide is likely to be a general property of peptide neurones, including CRH neurones regulating the HPA axis. The report by Yokota *et al.* (2004) shows convincing evidence that the central administration of neuromedin U activates CRH neurones in the parvocellular PVN, confirming that the stimulation of ACTH and corticosterone secretion after neuromedin U treatment does indeed involve CRH neurone activation. However, while the combination of Fos and CRH immunocytochemistry reveals activation of CRH neurones, it does not alone show whether this leads to CRH release from the dendrites (as discussed above for oxytocin and vasopressin neurones) or the axon terminals in the median eminence. Caution is needed in the absence of direct measurement of CRH release from the dendrites or axon terminals, in view of a recent study which shows that for oxytocin neurones Fos activation can be associated with stimulation of dendritic oxytocin release, without release from the axon terminals (Sabatier *et al.*, 2003).

The importance of auto-excitatory actions of oxytocin released by dendrites is exemplified during the extreme excitation of these neurones that occurs during precipitated withdrawal in morphine-dependent rats (Brown and Russell, 2004). Here, dendritic release of oxytocin is increased during withdrawal, and the central administration of an oxytocin antagonist reduces, but does not prevent, the excitation. Acute withdrawal from opiate, precipitated by naloxone, in dependency is stressful, but the excitation of oxytocin neurones in this state is (as discussed by Brown and Russell), a consequence of these neurones developing cellular dependence during chronic morphine exposure. This phenomenon provides a robust model to probe the cellular mechanisms that underlie withdrawal excitation, and hence dependence. Brown and Russell review their analysis, with electrophysiological techniques, of the changes in the properties of oxytocin neurones in morphine dependence that lead to withdrawal excitation.

Together, these different studies, mainly on neurones producing oxytocin and vasopressin, emphasise recent understanding of adaptive mechanisms that modulate the neuroendocrine networks in which they function, the complexity of neurotransmitter interactions in homoestatic regulation of their activity, and the separation (in terms of regulation and function) between the dendritic and axonal secretory compartments. These features need to be incorporated into the consideration of how other types of neuropeptide neurone involved in the regulation of stress responses perform their functions.

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