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EDITORIAL

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Advances in neurohypophysial hormones research

Oxytocin (OXT) and arginine vasopressin (AVP), also known as the neurohypophyseal hormones, are evolutionarily conserved neuropeptides from nematodes to humans.[1,2] These peptides are involved in the maintenance of homeostatic functions such as water, salt and energy balance, as well as reproductive physiology, stress and social and sexual behaviours. Their disruption in humans has been implicated in autism spectrum disorder.[3] For the last century, the investigation of these neuropeptides has been pivotal in laying the foundations for the field of neuroendocrinology.

This special issue of *Journal of Neuroendocrinology* is based on presentations given at the 13th World Congress on Neurohypophysial Hormones (WCNH2019) held in April 2019, in Israel (http://www.weizmann.ac.il/conferences/WCNH2019). The conference took place in Kibbutz Ein Gedi, which is situated on a cliff plateau within the Judean Desert, overlooking the Dead Sea, the lowest point on earth. This conference continued the tradition of the first meeting that took place in Japan in 1995 by gathering together researchers who are studying developmental, physiological and clinical aspects of the OXT and AVP systems. These include evolutionary, developmental, physiological and behavioural aspects related to OXT and AVP, as well as the potential applicability of these neuropeptides for the treatment of human mental and metabolic diseases.

The special issue comprises reviews and original research articles covering basic aspects of the OXT and AVP systems, including neuroanatomy, neuropeptide release, gene expression, and physiological and behavioural outputs. The issue opens with a review by Tasker and colleagues on past and recent advances in the neurophysiology of magnocellular neuroendocrine neurones, including selected studies that were presented at the symposium "Electrophysiology of Magnocellular Neurons" within WCNH2019.[4] A second review by Lawson and colleagues describes the physiological role of OXT in the regulation of energy balance.[5] The authors summarise the effects of exogenous administration of OXT on food intake and weight loss in animal models of obesity and describe the ongoing challenges of OXT-based therapeutics to treat obesity in humans.

Although the neuroanatomy of neurohypophysial hormones has been studied for nearly a century, we still lack information on their neuronal circuits. In the present issue, Zhang and colleagues show that different subsets of AVP-positive neurones are either glutamatergic or GABAergic, suggesting a functional segregation of AVP neuronal subsets.[6] They further reveal previously unknown glutamatergic AVP-ergic neurones in the central entorhinal cortex, which projects to the hippocampus, suggesting another layer of complexity to the way limbic AVP neurones modulate behaviour. A complementary study by Freeman and colleagues compares the distribution of central OXT and AVP receptors among different rodent species, in an effort to localise conserved sites of action of the neurohypophysial hormones in the brain.[7] To complete the set of neuroanatomical papers, Kogami and colleagues describe a new OXT-specific monoclonal antibody, thus adding an important reagent to OXT-related research.[8]

The role of OXT in the modulation of social behaviour is the focus of many laboratories. Mouse pups prenatally exposed to valproic acid display social deficits, including impaired ultrasonic vocalisation used to communicate with their mother. Exemplarily, Tsuji and colleagues demonstrate that changes in OXT-ergic signalling components are associated with this behavioural deficiency and identify a critical early postnatal developmental period, in which administration of OXT increases the call rate of valproic acid-treated pups.[9] Another study by Ribeiro and colleagues uses the zebrafish, an emerging animal model of social behaviour, to demonstrate that OXT signalling differentially regulates social modalities.[10] They find that mutant zebrafish lacking a functional OXT receptor display normal drive to approach conspecifics, whereas their ability to discriminate between novel and familiar fish is impaired. Interestingly, OXT receptor mutants also exhibit impaired familiar vs novel object discrimination, suggesting that OXT signalling regulates a more general memory recognition.

Two original studies in this issue report different aspects of OXT and AVP neurophysiology. OXT neurones are involved in the regulation of energy balance by means of both central and peripheral actions. Paiva and colleagues determine the role of central insulin receptors in the response of OXT neurones in the supraoptic nucleus to peripherally administered or endogenously released insulin. They show that the response of OXT cells to gavage of sweetened condensed milk is mediated by the central actions of insulin.[11] Depolarisation-induced neuropeptide secretion from presynaptic terminals of magnocellular neurones is often dependent on extracellular calcium influx. Nevertheless, Velazquez-Marrero and colleagues show that voltage-induced calcium release from ryanodine-sensitive intra-terminal calcium stores is an important contributor to neuropeptide secretion from nerve terminals even in the absence external calcium.[12]

Regulation of neuropeptide synthesis in response to homeostatic challenges is critical for re-establishing a homeostatic state. Greenwood and colleagues report that chronic dehydration of rats induces the expression of the transcription factor Creb3l1, and of Pcsk1, which encodes the proprotein convertase enzyme 1 that is

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crucial for processing of peptide hormones such as pro-opiomelanocortin, AVP and OXT.[13] They further demonstrate that Creb3l1 regulates the expression of Pcsk1, which suggests that the transcriptional activation of enzymes that process neuropeptides from their prohormone precursors is regulated by homeostatic challenges. Lastly, Harbachova and colleagues describe the activation of AVP expression following audiogenic kindling, a phenomenon of epileptic activity that overspreads from the brain stem to the forebrain, which is used as a model of limbic epilepsy.[14]

On behalf of WCNH2019 organising committee, we thank all of the authors who contributed to this special issue and extend our sincere gratitude to the editors and staff of *Journal of Neuroendocrinology* for their support. We welcome all readers of this issue to the next, 14th, World Congress on Neurohypophysial Hormones, which will be held in 2021 in Atlanta, USA.

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REFERENCES

1. Knobloch HS, Grinevich V. Evolution of oxytocin pathways in the brain of vertebrates. *Front Behav Neurosci*. 2014;8:31.
2. Wircer E, Ben-Dor S, Levkowitz G. Non-mammalian models for neurohypophysial peptides. In: Murphy D, Gainer H, eds. *Molecular Neuroendocrinology: From Genome to Physiology*. Chichester: John Wiley & Sons Ltd; 2016:301-328.
3. Harony H, Wagner S. The contribution of oxytocin and vasopressin to mammalian social behavior: potential role in autism spectrum disorder. *Neurosignals*. 2010;18:82-97.
4. Tasker JG, Prager-Khoutorsky M, Teruyama R, Lemos JR, Amstrong WE. Advances in the neurophysiology of magnocellular neuroendocrine cells. *J Neuroendocrinol*. 2020;18:e12826.
5. Lawson EA, Olszewski PK, Weller A, Blevins JE. The role of oxytocin in regulation of appetitive behaviour, body weight and glucose homeostasis. *J Neuroendocrinol*. 2019;18:e12805.
6. Zhang L, Hernández VS, Zetter MA, Eiden LE. VGLUT-VGAT expression delineates functionally specialised populations of vasopressin-containing neurones including a glutamatergic perforant path-projecting cell group to the hippocampus in rat and mouse brain. *J Neuroendocrinol*. 2020;18:e12831.
7. Freeman AR, Aulino EA, Caldwell HK, Ophir AG. Comparison of the distribution of oxytocin and vasopressin 1a receptors in rodents reveals conserved and derived patterns of nonapeptide evolution. *J Neuroendocrinol*. 2020;18:e12828.
8. Kogami Y, Tsuji T, Tsuji C, et al. A monoclonal antibody raised against a synthetic oxytocin peptide stains mouse hypothalamic neurones. *J Neuroendocrinol*. 2019;18:e12815.
9. Tsuji C, Fujisaku T, Tsuji T. Oxytocin ameliorates maternal separation-induced ultrasonic vocalization calls in mouse pups prenatally exposed to valproic acid. *J Neuroendocrinol*. 2020;32:e12850. https://doi.org/10.1111/jne.12850
10. Ribeiro D, Nunes AR, Gliksberg M, Anbalagan S, Levkowitz G, Oliveira RF. Oxytocin receptor signalling modulates novelty recognition but not social preference in zebrafish. *J Neuroendocrinol*. 2020;18:e12834. https://doi.org/10.1111/jne.12834
11. Paiva L, Leng G. Peripheral insulin administration enhances the electrical activity of oxytocin and vasopressin neurones in vivo. *J Neuroendocrinol*. 2020;18:e12841.
12. Velazquez-Marrero C, Custer E, Marrero H, Ortiz-Miranda S, Lemos JR. Voltage-induced Ca2+ release by ryanodine receptors causes neuropeptide secretion from nerve terminals. *J Neuroendocrinol*. 2020;32:e12840. https://doi.org/10.1111/jne.12840
13. Greenwood M, Peterson A, Rahman P, et al. Transcription factor Creb3l1 regulates the synthesis of prohormone convertase enzyme PC1 in endocrine cells. *J Neuroendocrinol*. 2020;32:e12851. https://doi.org/10.1111/jne.12851
14. Harbachova EL, Chernigovskaya EV, Glazova MV, Nikitina LS. Audiogenic kindling activates expression of vasopressin in the hypothalamus of Krushinsky-Molodkina rats genetically prone to reflex epilepsy. *J Neuroendocrinology*. 2020;32:e12846. https://doi.org/10.1111/jne.12846