International Neuroendocrine Federation: Year 2020 in Review

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The year 2020 can only be classified as an *annus horribilis* by any modern standards, with successive waves of Covid-19 bringing the world to a virtual standstill. The member societies of the International Neuroendocrine Federation, which encompasses national, regional and thematic societies from around 30 countries, were by no means spared. Nevertheless, many remarkable breakthroughs have come to light, testifying to the dedication of our researchers and providing a ray of optimism as we head towards the 10th International Congress of Neuroendocrinology (ICN) to be held in Glasgow, hopefully in person, in August 2022. In this "Year in Review", we highlight a few major achievements selected from the work of 10 member societies. This cross-section of studies, covering a wide spectrum of topics and species, serves as a reminder of the critical role of neuroendocrine systems with regard to our survival and long-term health, and thus their vulnerability, in a world that still has the potential to surprise us.

First off the bat, four rather complementary behavioral studies shed light on the nitty gritty of the neuroendocrine mechanisms underlying these behaviors. Contributed by the International Regulatory Peptide Society, Tang et al. (1) provide an elegant demonstration that non-nociceptive "social touch" in virgin female rats triggers the activation of the small population of parvocellular oxytocin (OT) neurons in the paraventricular nucleus of the hypothalamus. Interestingly, these neurons, which receive afferents that are at least partly distinct from those of the much larger population of magnocellular OT neurons, stimulate the latter to release OT that then acts on relevant forebrain regions controlling social behavior, with implications for a variety of neuropsychiatric disorders. On the flip side of the coin, Liu et al. (2) of the Chinese Neuroendocrine Group show that, in a mouse model of depression and anxiety, chronic restraint stress (CRS) also selectively affects only one of two closely related neuronal populations. Thus, while CRS, through increased presynaptic glutamate release, tips dorsomedial prefrontal cortex (dmPFC) neurons that unilaterally project to the basolateral amygdala (BLA) towards increased excitation, it does not affect dmPFC projection neurons that are reciprocally connected with the BLA. Together with unchanged inhibitory inputs, this relieves amygdala suppression by the PFC and aggravates anxiety-like behaviors, a phenomenon reversed by low-frequency optogenetic stimulation of the unidirectional projection neurons. In the third such study, and one moreover that pinpoints the fact that neuroendocrinology encompasses more than just the hypothalamus, Berland et al. (3) of the French Société de Neuroendocrinologie explore how mesocorticolimbic dopaminergic reward pathways regulating food intake are altered by triglycerides (TGs) from lipid-rich foods. Here

too, the lipoprotein-lipase-gated entry of dietary TGs into medium spiny neurons modifies their activity and dopamine-dependent reward behavior through the dopamine receptor DRD2 but not DRD1, in a cell-type and region-specific manner, providing a basis for the dysregulation observed in compulsive overeating. Strikingly, fMRI studies in human participants carrying a copy of the TaqIA-A1 polymorphism, associated with deficient striatal DRD2, show heightened responses to food cues in the ventromedial prefrontal cortex in the presence of dietary TGs. Finally, in a very different example of a dopamine-dependent behavior mediated by the hypothalamus, submitted by Hypothalamic Neuroscience and Neuroendocrinology Australasia, Stagkourakis et al. (4) reveal a gain control system in which differential electrical oscillation frequencies of tuberoinfundibular dopamine neurons lead to species-specific differences in paternal care of pups. Specifically, in sexually-experienced males, serum prolactin, whose levels are inversely correlated with dopamine release into the pituitary, itself inversely regulated by the neuronal oscillation frequency, enters the brain to act on prolactin-receptor-expressing galanin neurons of the medial preoptic area to influence parental care.

Further exploring the function, regulation and development of hypothalamic-pituitary neuroendocrine systems, Matsumoto et al. (5) from the Japan Neuroendocrine Society use cells from a patient with congenital pituitary hypoplasia associated with a variant of the transcription factor orthodenticle 2 (OTX2) to generate induced pluripotent stem cells (iPSC) and 3D organoids. Using this tool and elegant CRISPR/Cas9-mediated mutation repair and knockout experiments, they show that the survival and differentiation of pituitary progenitors depends on a hypothalamic OTX2/hypothalamic FGF10/oral ectoderm LHX3 pathway.

Several member societies have also focused on the thyrotropic and gonadotropic axes. Regarding the former, Wood et al. (6) of the British Society for Neuroendocrinology elucidate an epigenetic circadian clock mechanism underlying photoperiodism in sheep, based on a coincidence timer regulated by a flip-flop switch consisting of the transcriptional activator BMAL2 and its repressor DEC1. Together, under the influence of photoperiod-specific pineal melatonin secretion, these increase or decrease thyrotropin expression in the *pars tuberalis* of the pituitary under the influence of the transcriptional co-activator EYA3. Also with regard to the thyrotropic axis, Farkas et al. (7) of the Hungarian Neuroendocrine Section demonstrate that the release of thyrotropin releasing hormone (TRH) into the pituitary portal circulation at neuroendocrine terminals in the external zone of the hypothalamic median eminence is controlled by a reciprocal neuron-tanycyte interaction. In short, tanycytic end-feet take up

glutamate released by TRH neuronal terminals through AMPA/kainite receptors and glutamate transporters, and in return, surprisingly synthesize endocannabinoids, a typical neuronal signal, to repress TRH neuronal activity through the CB1 receptor.

Moving on to the gonadotropic axis, Kotarba et al. (8), of the Polish Society for Neuroendocrinology, have shown that pulsatile administration of a copper-gonadotropin-releasing hormone complex (Cu-GnRH) increases the transcription of GnRH target genes in the pituitary and luteinizing hormone release through both IP3/PKC and cAMP/PKA-dependant pathways, providing a valuable analog with which to study this axis. Furthermore, Chaube et al. (9) of the Indian Neuroendocrine Group infer that the conserved kiss2-type Kisspeptin transcripts that they identify in a catfish species are indeed estrogen-responsive and could play a role in the brain-pituitary-gonadal axis across species. Finally, Abreu et al. (10) of the Pan American Neuroendocrine Society present a detailed and convincing report implicating makorin ring finger protein 3 (MKRN3) in GnRH secretion and the onset of puberty. Specifically, drawing from patients with central precocious puberty (CPP) linked to MKRN3 variants and rodent and non-human primate models, they show that MKRN3 acts as a gonadal-steroid-independent tonic brake on Kisspeptin and Neurokinin B expression in hypothalamic arcuate neurons that is relieved in the run-up to puberty. Moreover, this transcriptional repression, linked to the MKRN3 RING domain, could be related to its ubiquitinase activity.

To conclude, the studies reviewed above not only advance existing knowledge of how the brain uses conserved or divergent endocrine pathways to control critical physiological functions, and their deregulation in a wide spectrum of disorders, they also provide new insights into previously unsuspected mechanisms with wider implications than have been discussed here. In addition, the innovative nature of the investigations also create several experimental and therapeutic avenues to be further investigated. Additionally, emerging evidence from the Covid-19 pandemic is providing our first glimpses of the neuroendocrine consequences of brain viral invasion. We look forward to exploring these established and novel facets of neuroendocrinology at ICN2022 (http://icn2022.org/).

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