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Editorial

# Growth Hormone And Prolactin- So Much Still To Learn.

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The existence and importance of prolactin and growth hormone (GH) has been known for close to a century[1,2] and key aspects of their regulation and actions are well understood. This may have led to the assumption by many that there is little still to learn about the regulation, production and actions of these hormones, a view hotly contested by those of us involved in their study. The articles in this special issue, based on research presented at the 2019 FASEB meeting on Growth Hormone/Prolactin Family in Health and Disease, are testament to this. Presentations at the meeting ranged from understanding hypothalamic regulation of these two hormones, their production and secretion from both the pituitary and placenta, the wide range of their physiological functions in a range of tissues, including the brain, and the mechanism and consequences of dysregulation. One thing is for certain – it is no longer appropriate to be thinking about these hormones as having the one-dimensional function implied by their names: "growth" or "lactation". Rather, these pleiotropic hormones have evolved to contribute to multiple adaptive functions, ranging from metabolism, immune function, reproduction and aging (to only mention a few). The common ancestral origin of the two hormones, as well as their receptors and downstream signal transduction pathways, makes a meeting considering similarities and differences in their regulation and function highly informative. and this is highlighted in the collection of reviews and research articles in this special issue that focuses on some of the neuroendocrine topics covered within the meeting.

The hypothalamic regulation of prolactin by tuberoinfundibular dopamine (TIDA) neurons is well established[3] but the regulation of these neurons themselves less clear, as is how this is altered to reduce short-loop feedback of prolactin and ensure high levels of hormone to support lactation. Further understanding of TIDA neuron regulation is described here by Amamri and Broberger , who postulated that γ-aminobutyric acid (GABA) produced by a subset of TIDA neurons may act through GABAB receptors in the arcuate nucleus, with GABAB acting as an autoreceptor[4]. Their results demonstrate a role for GABAB receptors in both pre- and post-synaptic regulation of TIDA neurons, suggesting a key role for GABA in the regulation of prolactin by dopamine.

Recent studies have shown that TIDA neurons remain responsive to prolactin during lactation, discounting a mechanism where a loss of short-loop feedback supports the high level of hormone at this time[5]. Two studies reported here provide insights into the plasticity of TIDA neurons that may underlie their altered function during lactation. Yip et al[6] elegantly demonstrate a change in somatic spine density that would be expected to result in increased TIDA neuron

excitatory output; it is possible that this supports release of a TIDA neuron neuropeptide, such as met-enkephalin that has been shown to be produced in these neurons in lactation[7], that would stimulate prolactin release in a feed-forward loop. This possibility is supported by the study of Silva et al.[8] in this issue who show that reduced dopamine alone does not account for suckling induced rises in prolactin, indicative of a role for a prolactin releasing factor, such as met-enkephalin.

In addition to hypothalamic regulation, peripheral signals also regulate GH and prolactin production and release but the mechanism of many of these are poorly understood. Cell-specific manipulation of receptor expression can provide insights into this, as is demonstrated in the study of Allensworth-James et al[9] who have shown that the decreased GH secretion following loss of leptin receptors specifically in GH-secreting somatotrophs is mediated by alterations in both gene transcription and translation. Key mediators in the regulation of prolactin have also been identified in fish, where prolactin has an osmoregulatory role[10]. Despite the altered role for prolactin, regulatory mechanisms are likely conserved across phyla and the review of Seale et al[11] identifies regulators of prolactin gene expression likely to have similar roles in mammals. It is also important to remember that members of the prolactin and GH family are also produced in the placenta, with dramatic effects on physiology in pregnancy; Cattini, et al.[12] review studies of the mechanism linking obesity with reduced placental lactogen production in pregnant women, which may increase the risk of peripartum depression.

An additional feature of both prolactin and GH are their pleiotropic actions, an excellent example of which is the description of the role of prolactin in vascularisation of the retina[13]. This adds to the multiple roles of prolactin, which have recently focused on its importance for regulation of metabolism, which are reviewed here by Lopez-Vichi, et al.[14]. Of course, GH has a major role in metabolic regulation and two papers from the Berryman/Kopchick group highlight the effects of GH on adipose tissue in mouse models with either a loss[15] or increase[16] in GH actions on this tissue, which differs between fat depots. A deeper understanding of the intracellular pathways mediating GH and prolactin actions may provide insights into tissue specific effects and the importance of temporal aspects of hormone action. Two papers describing actions of prolactin over differing timescales highlight the necessity of considering the canonical pathways activated by GH and prolactin through Stat5 activation[17] and potential novel pathways mediating rapid action[18].

The diversity of papers presented in this special issue and the novelty of many findings illustrates that study of the prolactin and GH systems is not merely a matter of refining understanding of a well-described system. Exciting advances in all aspects of both hormones are currently being made and will continue for the foreseeable future, from regulation by the brain and periphery, to temporal and differential effects on tissues that are only beginning to be understood.

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