Tackling the Controversial Topics in Neuroendocrinology

Gonadotrophin-releasing hormone (GnRH) neurons are the final output neurons of the hypothalamic systems controlling reproduction, and as such, are essential to the survival of vertebrate species. Because of this critical role, there has been extensive investigation of the anatomy and physiology of these neurons, ever since they were first proposed to exist by Geoffrey Harris in the 1950s. As with many neurosecretory neurons, their distribution is somewhat scattered within the hypothalamus, making physiological studies extremely difficult. If one places electrodes into the rostral preoptic region, where the neurons are located in most species, there is a very low probability of recording from a GnRH neuron because there are just so few of them. Studies using post hoc labelling of neurons to identify their phenotype after electrical recordings went for years and only recorded from a few GnRH cells. It was extremely challenging work. To overcome these difficulties, investigators turned to cell culture models, but these too had complications, not least of which was the fact that cells derived from tumour cells (e.g. GT1-7 cells) had a number of characteristics not shared by native GnRH neurons. Moreover, these systems clearly lacked the intricate neuronal network controlling function of GnRH neurons in vivo. The advent of transgenic technologies provided a tool to facilitate investigation of these fascinating neuroendocrine neurons. By expressing green fluorescent protein under the control of the GnRH promoter, it was possible to visualise living GnRH neurons within a brain slice, meaning that it was also much more feasible to target these neurons for electrophysiological recordings. This approach has lead to significant advances in our understanding of the electrical properties of these neurons.

In this month’s issue of the Journal of Neuroendocrinology, we are privileged to publish a review on the electrophysiology of GnRH neurons, co-authored by Allan Herbison and Sue Moenter. As many readers will be aware, over the past decade or more these two investigators and their laboratories have been at the forefront of efforts to investigate the electrical activity of the GnRH neurons. They have each, independently, provided novel insights into the basic properties of these cells, and characterised the effects of numerous compounds on the firing of GnRH cells. To many interested observers, however, one particular question stands out as being quite controversial: is the amino acid neurotransmitter, GABA, inhibitory or stimulatory to the firing of adult GnRH neurons? Both laboratories have extensively investigated this question, but the results of these parallel studies have been somewhat confusing. In essence, the two laboratories seem to have been reporting opposite answers to this question.

In the present article, the first that they have authored together, these two excellent scientists have come together to directly tackle this controversy. They have provided a basic description of GABAergic neurotransmission, focussing on how this might impact on GnRH neurons. They have then taken a fresh look at the data from each laboratory, and attempted to determine why the data are so apparently dissimilar. In particular, they have highlighted the key methodological differences between the experiments undertaken by the two groups, and discussed how each method has its own particular strengths and limitations. A number of caveats to interpretation are provided. For example, an ongoing difficulty that becomes apparent is the lack of real knowledge about the anatomical location of the GABA neurons that project onto GnRH neurons. Without this knowledge, it is not possible to target these cells specifically, and hence, the only way to manipulate the system is to apply drugs to the slice as a whole. This approach might have unexpected or unintended consequences, by affecting other neurons in the slice that might then influence the GnRH neurons indirectly.

So, is the amino acid neurotransmitter, GABA, inhibitory or stimulatory to the firing of adult GnRH neurons? Perhaps not surprisingly, the answer is a bit of both! Each group has reported incidences of both inhibition and stimulation, under different experimental conditions. Clearly, it is difficult to resolve all experimental differences from a decade of intense research within a single review. Both authors will freely admit that there is much more to learn about this system. It seems likely that further technological developments, such as tracing afferent inputs from GnRH neurons, or developing the ability to record from these cells in vivo – possibly even in conscious animals, will enhance our understanding further. No doubt, both authors will be involved in providing further novel insights in future, and it also seems likely that they may disagree on aspects of this research, too. But as of right now, what the authors have achieved admirably is to provide a consensus view about their current understanding of the GABAergic inputs to GnRH neurons, to provide a basis for these ongoing investigations of the system. I think many of our readers will find this an interesting and useful discussion.

This review marks the start of what we (the Editors) hope will become an ongoing, occasional feature in the Journal of Neuroendocrinology. We aim to identify similar areas of con-
trovery in the field, and then to go straight to some of the major protagonists in that area and ask them to discuss the data in a collaborative way. This is not an easy thing to do. We all form strong opinions about our data, and build upon our own interpretation of the results. However, we hope that our colleagues will be prepared to take an honest and open-minded look at the data supporting both sides of an argument, coming to a point of consensus on the most likely interpretations – or even agreeing to disagree. It can only be good for the field to have a forum for openly discussing these points of controversy.