THE CENTRAL CONTROL OF GROWTH HORMONE RELEASE –
Electrophysiology and Functional Role of Neuroendocrine Somatostatin Neurons

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Background: Growth hormone (GH), and its down-stream mediator, insulin-like growth factor-I (IGF-I), exert powerful age-dependent effects on metabolism\(^1\). In childhood and adolescence, the GH axis orchestrates normal growth by actions on bone and muscle. In adulthood, GH has potent lipolytic actions\(^1\) and altered GH secretion disrupts glucose homeostasis\(^2\). The secretion of GH into the bloodstream occurs in discrete pulses, a pattern that is necessary for the hormone’s full actions on target organs\(^3\). The mechanisms underlying GH pulsatility remain obscure, however. - The GH-producing cells in the pituitary are under competing influences from two populations of neuroendocrine neurons in the hypothalamus: growth hormone-releasing hormone (GHRH) neurons, which stimulate GH release, and somatostatin (Som) neurons, which inhibit GH release\(^4\). Recent evidence suggests that intermittent relief of Som secretion, rather than pulsatile GHRH release underlies the plasma profile of GH\(^5\), but the neuronal interactions that produce normal GH secretion remain elusive. Thus, it is not known e.g. how Som neurons contribute to pulse generation; how Som neurons – and thus the control of GH release – are integrated within the broader CNS network that controls feeding and energy balance; and if neuroendocrine network interactions change in an age- and sex-dependent manner.

Hypothesis: Som cells possess electrophysiological characteristics that allow them to participate in the GH pulse generator. Modulation of these properties determines the functional state of the somatotrophic axis and, as a consequence, of whole-body metabolism.

Objectives: In the proposed project the postdoctoral candidate will
1) characterize the membrane properties and network behaviour of hypothalamic Som neurons;
2) identify how Som electrophysiology is modulated by feedback signals, glycaemic state and hormones (e.g. leptin), and signals from other metabolism-regulating CNS populations;
3) determine how experimental manipulation of Som neurons affects hormone status in the somatotropic axis and metabolism.

Work Plan incl. Methodology: These issues will be explored using transgenic mice where fluorescent reporter proteins and ion channels genetically engineered for control by light (optogenetically) or by exogenous ligands (DREADD methodology) are selectively expressed by Cre expression in Som neurons following stereotactic viral delivery, using AAV vectors. The electrical properties and network behaviour, as well as its modulation by hormones, neurotransmitters, glucose and lipids, will be determined by in vitro patch clamp recordings.
and Ca$^{2+}$ imaging (using transgenic expression of the indicator, GCaMP3). In vivo manipulation of Som electrophysiology will be investigated for effects on temporal patterns of hormonal status and a comprehensive repertoire of growth and metabolic parameters, e.g. feeding, glucose tolerance and fat metabolism. The experiments will initially be performed in prepubertal males, but once the basic properties of the system in this model have been determined, Som neurons and their actions will be recorded in male and female mice during early development, adolescence and in adulthood.

**Significance:** The GH/IGF-I system is a drug target in disorders ranging from gigantism, acromegaly and idiopathic short stature to age-related GH deficiency⁶, and regulates lipid metabolism¹. Moreover, GH therapy increases the risk for developing type 2 diabetes even in children⁷, highlighting its powerful counterregulatory actions on glucose homeostasis. The proposed project will provide conceptually new information for the understanding of these and other conditions that may be exploited for therapeutic strategies, as well as crucial insight into the fundamental endocrine question of how pulsatile hormone release is generated.

**The laboratory:** In the past few years, we have identified an oscillating population of neuroendocrine dopamine neurons whose behaviour may be part of the pulse generator for pituitary prolactin secretion⁸⁻¹⁰. Our group, within a department characterized by state-of-the-art neuroscience and an international atmosphere, uses electrophysiology, neuroanatomy and behavioural protocols to dissect neural networks in the hypothalamus that underlie basic survival functions such as metabolism, reproduction and aggression.

**Postdoc profile:** We particularly welcome candidates with training in electrophysiological recording techniques, but all candidates with experience from working with experimental animal models are encouraged to apply.

**References:**

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