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4

Endocrine rhythms of growth hormone release: Insights from animal studies

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Growth hormone (GH) secretory patterns emerge following birth, and changes in patterning occur throughout life. These secretory patterns are coupled to growth, reproduction and metabolism. Comparing human and animal studies, this review will highlight ultradian patterning of GH release and the mechanisms that contribute to this. Discussions will focus on the emergence in variations in the number and frequency of GH secretory events, and the amounts of GH released (peak and basal). Animal studies have contributed significantly to our understanding of the processes that regulate GH release. However, translation of knowledge from animal models to benefit our understanding of human physiology is sometimes limited. To overcome these limitations, it is critical that we reconcile the cause and consequences of differences in GH release between humans and model organisms. In doing so, we can embrace emerging technologies that will rapidly advance our knowledge of endogenous process that control GH release.

Ultradian versus infradian patterns of GH secretion

The release of GH is a dynamic process, characterised by highly ordered secretory events dispersed by periods of low or undetectable levels of GH during basal secretory periods (inter-pulse intervals).

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The amplitude, frequency, regularity of GH secretory events, and basal levels of GH secretion vary considerably between individuals, sexes and relative to physiological needs.

Evidence from human studies show that GH pulses are ordered relative to the sleep-wake cycle, where secretory events reaching maximal GH release are observed following the onset of slow-wave sleep [1]. This association between sleep and the onset of GH pulses is highly robust. In healthy individuals, delays in sleep onset results in a delay in the onset of nocturnal GH secretory events [2–4]. In patients with sleep disorders, high amplitude pulses in GH release still precede the onset of periods of slow-wave sleep, however, the amplitude of GH secretory bursts are considerably reduced or absent [5,6]. Similarly, sleep deprivation in otherwise healthy individuals can result in the suppression of nocturnal GH pulses. In these instances, compensation for reduced GH release might occur through increases in peak GH secretion during the day [7], or following the resumption of the sleep cycle [8]. Whether the onset of GH secretory events contributes to sleep, or whether sleep regulates GH release remains somewhat unclear. Indeed, nocturnal GH secretory events might precede the onset of slow-wave sleep, and slow-wave sleep episodes are not always associated with the onset of GH secretion events [9].

Associations between sleep and GH secretion events are not robustly seen in species where sleep patterns are defined by multiple and sporadic sleep/wake cycles over a 24-h period. While initial studies found no link between GH release and sleep in the rat [10], it was later observed that diurnal variations in GH secretion profiles occurred in female rats [11]. In juvenile rats, an association between sleep and the onset of GH secretory events is observed [12], however this association is difficult to confirm in male adult rats [13]. In this species, sleep-wake patterns are complex and contain a mix of circadian and ultradian rhythms [14]. Given discrepancies between human and rodent studies, the remainder of this review will focus on ultradian patterns of GH release. Sleep deprivation in the rat results in reductions in high-amplitude GH secretory events [15]. Thus, the roles of sleep in regulating GH release in other species, including the rat, are not discounted. Rather, when compared to infradian patterns of GH release, ultradian patterns of GH release are generally conserved. Therefore, we will limit our discussion to the essential components involved in the generation of ultradian GH secretory patterns, and changes to GH patterning observed during periods of increased growth, during sex-differentiation and in response to increased or decreased energy provision. For detailed discussions on mechanics of peak GH generation, modelling of GH secretory output, and feedback of second-order regulators of GH release, the reader is encouraged to consult comprehensive reviews [1,16,17].

Regulation of ultradian GH secretory events

GH feedback and pulse generation

The ultradian pattern of GH release is generally organised by three cell types; somatotrophs located within the anterior pituitary gland and hypothalamic neurons that release somatostatin and growth hormone releasing hormone (GHRH). Growth hormone release is initiated through stimulatory GHRH neurons in the arcuate nucleus (ARC) and terminated by inhibitory somatostatin neurons in the periventricular nucleus (PeVN) of the hypothalamus.

The discovery of processes that contribute to the patterned release of GH relied on studies conducted on animal models, with hallmark observations in the 1970's and 80's [18,19] first demonstrating interactions between somatostatin, GHRH and GH. Studies from the rat showed that GHRH failed to stimulate GH release during periods of elevated somatostatin release, or in the presence of antibodies that bind and activate somatostatin receptor subtypes [20]. Building on these observations, it was soon found that somatostatin and GHRH are released during alternating intervals [21]. More recently, it was shown that somatostatin inhibits electrical activity within GHRH neurons, and thus oscillations in activity of GHRH neuronal populations [22]. Bridging decades of research, these and other observations have increased our understanding of the interactions between somatostatin and GHRH with respect to GH release, resulting in the development of the theory wherein peripheral and centrally mediated mechanisms modulate the pulsatile release of GH.

During periods of prevailing low levels of circulating GH, promotion of the activity of somatostatin expressing neurons in the PeVN is reduced. The resulting reductions in somatostatin release and somatostatin neuron activity results in the withdrawal of inhibition of GHRH neuronal activity in the ARC as

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