

# Neuronal Synchronization in an Enzymatic Model of the Growth Hormone-Releasing Hormone Oscillator

Models of growth hormone (GH) rhythmicogenesis suggest that the GH pulses in the circulation are generated by a GH-releasing hormone (GHRH) oscillator with a periodicity of 1 hour. We have raised the possibility that this is an intrinsic neuronal rhythm resulting purely from enzymatic reactions occurring in the axon terminals. A Basalator reaction sequence can generate an hourly chemical burst of a primer, presumably a low molecular weight peptide, regulating Ca-triggered exocytosis of GHRH-loaded vesicles.

Our previous study was based on simulations of a single GHRH-releasing neuron. It is self-evident that a high degree of synchronization between the packed terminals of these neurons at the median eminence is a sine qua non for physiological significance in generating the highly ordered *in vivo* pulses of GH release. In the case of an oscillating chemical reaction, the gap junctions provide the necessary means of inter-terminal communication.

We proposed that the priming species is largely immobilized by binding within the terminal. The free primer is presumed able to diffuse and is alternately phosphorylated and dephosphorylated by a kinase and a phosphatase (or undergoes a similar pair of complementary reactions). Under appropriate conditions the model shows that the level of the primer peaks sharply at hourly intervals.

We have now examined the possibility that the unbound species, both unphosphorylated and phosphorylated, diffuse through gap junctions. Simulations of two adjacent neurons were performed to assess whether and when synchrony occurs. Initially their gap junctions were closed. Under these conditions the neurons were set to be 180° out of phase, i.e. in one case the burst is seen on the hour, in the other on the half-hour. Assuming the rates of exchange through the gap junctions to be comparable to the rate of exchange with bound peptide, opening the gap junctions results in rapid total synchronization (within about 3 minutes). The two oscillatory systems undergo mutual entrainment and both peaks now appear simultaneously at

an intermediate hourly interval. This result is independent of whether the mode of chemical feedback is positive or negative.

These initial findings have been extended to a linear array of four adjacent neurons (each off-set by 15 min) and support the view that clusters of neurons may behave as "hyper-neurons" in the coordination of pulsatile GH secretion.

## Selected Publications

Wagner, C., Caplan, S.R. and Tannenbaum, G.S. Genesis of the ultradian rhythm of growth hormone secretion: a new model unifying experimental observations in rats. *The American Journal of Physiology: Endocrinology and Metabolism* 275: E1046-E1054, 1998.

Caplan, S.R., Johnstone, R.M, and Tannenbaum, G.S. Modeling the growth hormone-releasing hormone oscillator. Program of the 88th Annual Meeting of the Endocrine Society, 2006, Abstract P3-179.

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