New kids on the block: RF-amides and neuroendocrine control of reproduction

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The reproductive process is driven by the secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus, which stimulates the synthesis and secretion of gonadotropins from the pituitary gland. The reproductive neuroendocrine system is, in turn, regulated by classical feedback exerted by gonadal steroids but GnRH cells do not possess the appropriate receptors. Accordingly, other neuronal systems in the brain, that do express receptors for reproductive steroids, relay information to GnRH cells. In recent years, it has emerged that cells in the hypothalamus that produce kisspeptin are provide a major input to the GnRH cells. Kisspeptin belongs to a family of peptides with a common C-terminal RF-amide motif. In the sheep brain, kisspeptin cells are found in the arcuate nucleus predominantly and are upregulated immediately prior to the preovulatory surge in GnRH (Estrada *et al.*, 2006). The kisspeptin cells express estrogen and progesterone receptors and respond appropriately to castration and sex-steroid treatment (Smith *et al.*, 2007; Smith & Clark, 2007). The kisspeptin cells also produce neurokinin B and dynorphin, two other regulators of GnRH cells (Goodman *et al.*, 2007). Administration (i.v.) of kisspeptin to seasonally anestrous ewes causes ovulation, further indicating that the peptide is a key regulator of reproduction (Caraty *et al.*, 2007). These data and information from other species indicate that kisspeptin cells provide a major postitive input to GnRH cells.

More recently, another RF-amide peptide has emerged as a major regulator of the reproductive neuroendocrine system. This is gonadotropin inhibitory hormone (GnIH), which is produced in the paraventricular nucleus and the dorsomedial nucleus of the hypothalamus. Whereas the function of this peptide has been expounded in birds, data has been lacking for a function in mammals. In the ovine brain, cells producing GnIH project to the secretory zone of the median eminence, suggesting secretion into the hypophysial portal system to act on the pituitary gland. GnIH potently inhibits GnRH-stimulated gonadotropin secretion from gonadotropes *in vitro* and *in vivo*. The peptide blocks GnRH-stimulated elevation in intracellular free calcium. Recent work on the function of these RF-amide peptides prompts a revision of the neuroendocrine control of reproduction.

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