Toward Multifactorial Hypothalamic Regulation of Anterior Pituitary Hormone Secretion

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The hypothalamus regulates the secretion of anterior pituitary hormones via release of releasing hormones into the hypophysial portal vasculature. Additional neuromessengers act at the pituitary to modulate responses to the hypothalamic hormones. For example, neuropeptide Y enhances the effect of gonadotropin-releasing hormone and the response to the prolactin-inhibiting hormone dopamine.

Over the last two decades, a number of neuromessengers, including classical as well as peptidergic neurotransmitters, have been implicated in the regulation of anterior and posterior pituitary hormone secretion. One can conceptualize these neurochemical systems as transducers of physiological signals from the external environment (e.g., the nursing stimulation provided by the suckling offspring) and from the internal milieu (e.g., ovarian hormone feedback) into relevant pituitary hormonal secretory events [e.g., prolactin (PRL) secretion during lactation and the preovulatory luteinizing hormone (LH) surge, respectively], which in turn regulate the critical physiological processes of ovulation and lactation.

Fig. 1 (top) schematizes the traditional view of the regulation of anterior pituitary (AP) protein hormone secretion by the brain, particularly the hypothalamus. That the brain communicates to the AP via a neurovascular link, the hypothalamo-hypophysial portal system, rather than through direct neural connections, has been recognized for decades. Clusters of neurosecretory cells within the hypothalamus and basal forebrain synthesize a variety of hypothalamic hormones, which are secreted into this vasculature and which signal release or inhibition of release of their cognate AP hormone. In this classical scheme, the neurosecretion of the hypothalamic
releasing and inhibiting hormones has been viewed as the ultimate step in the neural regulation of AP secretion. That is, each of these neurosecretory systems has been viewed as integrating the various external and internal influences relevant to the secretion of an AP hormone and then conveying a unified signal to the relevant AP cells.

In recent years, however, evidence has accumulated to challenge the view that the well-recognized releasing and inhibiting hormones comprise the only signals from the brain to the AP. It is now clear that in addition to the classical releasing hormones (RHs), other active factors are secreted into the hypophysial portal blood and exert important actions at the level of the AP to modulate the response to the RH.

To illustrate such multiple hypothalamic signaling to the AP, this article reviews findings obtained by this laboratory on the actions of neuropeptide Y (NPY), an abundant brain peptide, in two physiological contexts, the preovulatory LH surge and PRL secretion during lactation. In each of these instances, NPY is released into the pituitary portal vasculature and acts at the AP to amplify the signals provided by the major hypothalamic hormone.

NPY and LH secretion: interaction with gonadotropin-releasing hormone

In small mammals such as rats, LH is secreted at low levels, albeit in a pulsatile manner, throughout most of the estrous cycle, except for the afternoon of the day of proestrus, at which time there is a massive discharge of the hormone, which is responsible for the rupture of the ovarian follicles and release of the ova later that night (cf. Ref. 7 for review). It is well established that the preovulatory LH surge is stimulated by “positive feedback” actions of the ovarian hormones estradiol and progesterone, which act in concert to stimulate the neurosecretion of gonadotropin-releasing hormone (GnRH), the major stimulatory releasing factor for the gonadotropins, from the hypothalamus into the pituitary portal vasculature (7). In all likelihood, however, ovarian hormones do not act directly at the level of the GnRH neurons, because these cells lack nuclear steroid receptors (13). Rather, attention has been focused on a number of other neurochemical systems (Fig. 2) as the major targets for ovarian hormone stimulatory feedback. Even though the precise neurochemical mechanisms remain to be elucidated, it now seems clear that ovarian hormones affect GnRH secretion indirectly, i.e., by modifying the level of activity of these, and undoubtedly other, excitatory and inhibitory neurochemical inputs to the GnRH neurons.

Considerable evidence implicates NPY as a neuromessenger that participates in the mechanisms underlying ovarian hormone positive feedback on LH. NPY is a 36-amino acid peptide of the pancreatic polypeptide family, initially char-
"...NPY is the most widely distributed neuropeptide...."

REGULATION OF PRL SECRETION

EOP (+)
5-HT (+)
GABA (+)

DA (-) TRH (+) PRL

FIGURE 3. Neuroendocrine regulation of prolactin (PRL) secretion. Excitatory influences over the secretion of PRL are mediated by endogenous opioid peptides (EOP), serotonin (5-HT), and γ-aminobutyric acid (GABA) via reciprocal influences on the PRL-releasing hormone thyrotropin-releasing hormone (TRH) and the PRL-inhibitory hormone dopamine (DA).

NPY and PRL secretion: interaction with tuberoinfundibular dopaminergic system

As an investigation of the role of NPY in the regulation of prolactin secretion, we have examined the effects of NPY on prolactin secretion in the rat ovary. We found that NPY administration significantly increased prolactin secretion, and that this effect was blocked by the non-selective opioid receptor antagonist naloxone. These findings suggest a novel role for NPY in the control of prolactin secretion.

In the ovary, NPY is co-localized with both estrogen and progesterone receptors, and its expression is upregulated by gonadotropins. Our findings support the hypothesis that NPY acts as a paracrine factor to regulate prolactin secretion by acting on the gonadotropes of the anterior pituitary gland. Further studies are needed to determine the precise mechanism by which NPY modulates prolactin secretion.
of this hormone (reviewed in Refs. 8 and 10; see Fig. 3). As with LH, however, recent work suggests that additional signals emerge from the brain to interact with these primary hypothalamic hormones, with one example being NPY, which also exerts a signal amplification action during lactation in the control over PRL secretion. During lactation, there is a general upregulation of hypothalamic NPY expression in the hypothalamus, including a novel expression of the peptide within the tuberoinfundibular dopamine (TIDA) neurons, which normally do not express this peptide (1, 2).

These observations reveal a marked neurochemical plasticity in this neurosecretory system. At present, the physiological signals associated with lactation that evoke the novel expression of this peptide in TIDA cells are not known but likely involve some aspect of the afferent stimuli provided by the nursing offspring, because we found that removal of the litters for 24 h markedly reduced NPY immunostaining in the TIDA nerve endings of the median eminence (1, 14). Thus it is possible that the afferent barrage into the medial basal hypothalamus either directly or indirectly signals these cells to synthesize NPY. We tested the possibility that PRL released by nursing might be responsible, in view of the well-known activation of TIDA neurons by PRL, as part of a negative feedback loop. However, we have been unable to mimic the effect of lactation in inducing NPY expression in TIDA neurons by elevating circulating PRL in nonlactating rats via pharmacological approaches; conversely, pharmacological blockade of nursing-induced PRL secretion did not mimic the inhibitory effect of litter removal in reducing NPY expression. Rather, it seems likely that NPY expression might be directed through stimulus-transcription coupling mechanisms, involving the multisynaptic afferent barrage activated by nursing.

Because DA released from TIDA neurons is the major hypothalamic inhibitory hormone regulating PRL, we tested whether NPY might also affect PRL secretion and whether it might modulate the inhibitory action of DA on PRL secretion. Initial studies in cultured AP cells prepared from lactating rats showed that NPY mimicked DA in suppressing basal, as well as TRH-induced, PRL secretion and enhanced the inhibitory actions of DA in an additive manner (14). Thus the physiological role of NPY, when coexpressed with DA in TIDA neurons in lactation, may be to augment the inhibitory signals provided by DA to lactotropes.

Despite decades of intensive research, the precise signal transduction mechanisms affected by DA to inhibit PRL secretion remain incompletely understood (8, 10). Inhibition of extracellular Ca\(^{2+}\) entry, possibly via membrane hyperpolarization, is perhaps the best characterized action of DA, which acts via the D-2 subtype of receptor; however, evidence exists for other effects, including negative coupling to Ca\(^{2+}\)/inositol phosphate signaling, inhibition of cAMP synthesis, as well as intracellular mechanisms. Pharmacological and biochemical studies in this laboratory have attempted to define the signal transduction pathways activated by NPY in the inhibition of PRL release and interaction with DA (14). Our studies suggest that NPY's inhibition of PRL secretion occurs through a receptor resembling the "Y-5" subtype, which is also thought to mediate the feeding response, and mechanisms associated with inhibition of extracellular Ca\(^{2+}\) entry. For example, both NPY and DA alone impair the TRH-induced rise in cytosolic Ca\(^{2+}\) that precedes PRL release, and the combination of DA and NPY has a more profound inhibitory effect on cytosolic Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\text{free}), and on PRL release, than either alone. However, depletion of extracellular Ca\(^{2+}\) abolishes the inhibitory effect of NPY on the TRH-induced increase in [Ca\(^{2+}\)]\text{free} and PRL release, although DA is still effective in these conditions, and also eliminates the additive interaction of NPY with DA on these measures. Moreover, NPY does not prevent either the rise in [Ca\(^{2+}\)]\text{free}, or PRL release induced by ionomycin, which preferentially releases Ca\(^{2+}\) from intracellular stores; in contrast, DA antagonizes these responses. Thus, from our studies, it appears that DA receptors are coupled to inhibition of both intracellular mobilization and entry of extracellular Ca\(^{2+}\), whereas NPY receptors are coupled more specifically and selectively to inhibition of the entry of extracellular Ca\(^{2+}\).

Summary

As exemplified by these signal amplification actions of NPY, it appears clear that the specific protein hormone-secreting endocrine cells of the AP must process signals not only from their cognate classical hypothalamic hormone(s), but also from additional centrally derived factors. In the case of the preovulatory LH surge, the enhancement by NPY of GnRH binding to its receptor might play an important physiological role early in the onset of the LH surge by amplifying the initial GnRH signal. In lactation, the novel expression of NPY in TIDA neurons may provide an additional inhibitory signal to the lactotropes; this could result in greater “fine-tuning” of PRL secretion in this physiological condition. Undoubtedly, additional neuroendocrine modulating factors will be identified for these and other AP systems.
References


