Noradrenergic regulation of cyclic GnRH secretion

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The GnRH cells represent the final output neurones of an integrated neuronal network used by the brain to generate pulsatile LH secretion from the pituitary gland. Changes in LH secretion profile throughout the ovarian cycle, including the preovulatory LH surge, result principally from alterations in the output of this GnRH network and it has been a key goal of many neurobiologists to elucidate the components and nature of this network. This review documents recent progress in understanding the role of noradrenaline within the GnRH network and highlights and explains its ‘enabling’ or permissive characteristics. Network behaviour analysis suggests that noradrenaline should be considered as a permissive agent promoting high output states of the GnRH network. On the basis of recent molecular and neuroanatomical data, it is proposed that oestrogen influences brainstem noradrenergic neurones specifically within the nucleus tractus solitarius to facilitate synaptic transmission within the GnRH network. In this manner, noradrenaline is likely to play a role in bringing about the increased GnRH messenger RNA expression and secretion necessary for ovulation.

The pulsatile pattern of luteinizing hormone (LH) secretion from the pituitary gland is dictated by the GnRH neurones residing within the hypothalamus and preoptic area of the brain. The frequency and amplitude of LH pulses varies substantially over the course of the ovarian cycle and culminates in mid-cycle with a massive surge of LH secretion which is directly responsible for initiating ovulation. Our understanding of the pulsatile nature of LH release and the preovulatory LH surge itself requires, therefore, a clear understanding of mechanisms controlling GnRH neurone activity. Despite enormous interest and the attention of many neuroendocrinologists, the technical difficulties inherent in gathering information from identified GnRH neurones has made this goal difficult to achieve. Nevertheless, through essentially indirect means, progress has been made in determining the neural and humoral factors involved in regulating the biosynthetic and electrical activity of GnRH neurones. Quite clearly, the GnRH neurones do not operate in isolation within the brain and can be visualized most simply as the ‘final output’ neurones of an interconnected neural circuit responsible for co-ordinating and determining the functioning of the gonadal axis. Collectively, this relatively ill-defined group of neurones is termed the ‘GnRH network’.

The first evidence that noradrenergic neurones may form a component of the GnRH network was provided by Sawyer and colleagues (1947) who showed that ovulation in rabbits was blocked by the administration of an alpha adrenergic receptor antagonist. Subsequent studies in a number of laboratories went on to establish the ability of noradrenaline (NA) to modulate plasma LH concentrations under a variety of hormonal conditions (reviewed by Barraclough and Wise, 1982). Although NA has not, of late, received the attention bestowed upon other putative neurochemical mediators within this system, substantial new information has accrued over recent years and, reassuringly, the importance of NA in influencing the activity of the GnRH network appears to have stood the test of time. The purpose of this review is to provide a summary of the neuroanatomical and functional analyses undertaken with respect to the role of NA in regulating LH secretion in female rats. Through this, I hope to provide an updated view of how we may consider NA to act within the GnRH network.

Noradrenergic pathways to the GnRH neurones

It is only relatively recently that studies have examined precisely which noradrenergic neurones within the brain are likely to be involved in regulating GnRH neurones (Fig. 1). Using retrograde tracing techniques, Wright and Jennes (1993) demonstrated that it was essentially only the brainstem NA neurones of the ventrolateral medulla (A1 cell group) and nucleus tractus solitarii (A2 cell group) that projected to the immediate vicinity of the GnRH cell bodies within the rostral preoptic area of the rat. This finding, which is in good agreement with other similar studies examining noradrenergic inputs to the preoptic area as a whole (Ricardo and Koh, 1978; Day et al., 1980), is also in accord with electrophysiological evidence of projections from the A1 region to the preoptic area (Kaba et al., 1983; Kim et al., 1987) and microdialysis investigations which have shown increased NA release within the preoptic area after electrical stimulation of either the A1 or A2 cell groups (Herbison et al., 1990; Fernandez-Galaz et al., 1994).

However, the synaptic relationship between noradrenergic terminals and GnRH neurones in the preoptic area has been more difficult to ascertain. Although noradrenergic terminals can be found in the vicinity of the GnRH cell bodies and catecholamine-containing terminals are found to make synapses with GnRH neurones, no clear picture has emerged from electronmicroscopic investigations as to whether it is actually noradrenergic terminals that make synaptic contact with GnRH neurones (Leranth et al., 1988; Chen et al., 1989). A recent study has reported the presence of alpha adrenergic receptor immuno-reactivity in both GT-1 cells and GnRH neurones (Lee et al., 1995). If confirmed, this would shift the balance of opinion...
of any noradrenergic influence on GnRH terminals remain unfluenced on GnRH cell bodies, while the origin and relationship as the source of indirect and, possibly, direct noradrenergic in-
subpopulations of the brainstem A1 and A2 neurones appear to have the same effect on pulsatile LH secretion as an increase in adrenergic receptor activity. As both experimental manipulations will effectively ‘clamp’ adrenergic receptor activity at constant high or low levels, one possible explanation of this seemingly paradoxical phenomenon would be that fluctuating patterns of adrenergic receptor activity are essential for pulsatile GnRH release. Our recent theoretical modelling experiments indicate that the pattern of noradren-
ergic input within the GnRH network may be critical in de-
termining the parameters of pulsatile GnRH release (Brown et al., 1994). However, the precise function of this episodic noradrenergic activity within the GnRH network is not clear and, although a clear coincidence of NA and GnRH release is found in monkeys (Terasawa et al., 1988), no similar temporal relationship between fluctuating episodes of NA release and pulsatile LH secretion has been detected in rats (Jarry et al., 1990).

It would appear then that the pulsatile nature of GnRH secretion is dependent upon an appropriate degree of fluctuating adrenergic receptor activity within the vicinity of the GnRH cell bodies; acute perturbation of this input, in either direction, will disrupt the normal functioning of the GnRH network. This behaviour is most appropriately described as permissive. When present in appropriate amounts, NA enables the GnRH network as a whole to operate maximally without contributing any linear directional influence within the circuitry. In other words, NA does not exert a conventional stimulatory or inhibitory action (in which there is a linear relationship between neurotransmitter concentration and network output) but, instead, appears to promote and enable activity between other neurones within the network. Although the maximal influence of a permissive regulator within a network will always be confined by the properties of the neurones it modulates, it can, nevertheless, set the ‘gain’ of network output up to a maximal point through modest changes in its pattern or amount of release. However, acute and large changes in adrenergic receptor activity, as induced in experimental manipulation paradigms, will move network activity outside a range compatible with normal functioning and will collapse GnRH network output. The proposal that NA is a permissive regulator within the network is entirely compatible with the results from several chemical and neuroanatomical lesion studies in which pulsatile LH secretion has been shown to recover fully from near total destruction of the ascending noradrenergic pathways (Clifton and Steiner, 1985; Leonhardt et al., 1991). As reasoned above, these studies indicate that NA is not in itself driving the pulsatile pattern of GnRH release but rather ‘enabling’ it to occur. Under certain pathological conditions, this permissive role within the GnRH network can quite clearly be undertaken by other factors. The permissive action of NA within the GnRH

![Fig. 1. Noradrenergic pathways to GnRH neurones. Projections to GnRH cell bodies arise principally from brainstem A1 and A2 neurones which make direct and indirect connections. The origin of noradrenergic influences on GnRH terminals is not well established.](image-url)
network has been indicated by many different avenues of investigation in rats, is also suggested in primates (Terasawa et al., 1988; Pau et al., 1989), and now seems established.

Noradrenaline and gonadal steroids

Evidence indicates that specific brainstem NA neurones are oestrogen-receptive. Receptor autoradiographic (Heritage et al., 1977) and immunocytochemical studies in rats and sheep (Simonian and Herbison, in press) have shown that many A1 and A2 neurones express oestrogen receptors in a topographically distinct manner within the brainstem. Further results from in vivo investigations have provided positive correlations between oestrogen status and noradrenaline turnover or release in both the preoptic area and median eminence (Advis et al., 1980; Honma and Wuttke, 1980; Wise et al., 1981; Adler et al., 1983; Demling et al., 1985). As oestrogen has been shown to increase the electrical excitability of A1 neurones projecting to the preoptic area (Kaba et al., 1983) as well as immediate early gene expression (Jennes et al., 1992) and tyrosine hydroxylase mRNA content (Liau et al., 1992) in A2 cells, it seems reasonable to suggest that oestrogen may enhance noradrenergic transmission within the GnRH network. Our recent work highlights the importance of noradrenergic neurones within the A2 group in this respect as oestrogen receptors are detected in A2 neurones projecting to the vicinity of the GnRH neurones but not in similarly projecting A1 neurones (Herbison and Simonian, 1996). It is of note that the oestrogen-receptive A2 neurones projecting to the vicinity of the GnRH cells do not synthesize neuropeptide Y, the neurochemical commonly co-expressed by noradrenergic neurones. Such observations provide a neuroanatomical substrate for the observed oestrogen dependence of NA release in the preoptic area, although, once again, the basis and nature of changes in the median eminence remain unknown. Turnover of NA within the median eminence is particularly sensitive to changes in circulating progesterone concentrations (Wise et al., 1981) but it is not known whether brainstem noradrenergic neurones express progesterone receptors.

One of the most intriguing early observations with NA was that its influence on LH secretion in female rats was apparently dictated by the gonadal steroid status of the animal. The infusion of NA into the third ventricle reduced LH secretion in ovariectomized rats but promoted LH release in animals primed with gonadal steroids (Gallo and Drouva, 1979; Leung et al., 1982). Together with evidence for steroid-dependent changes in NA release (Advis et al., 1980; Honma and Wuttke, 1980; Wise et al., 1981; Adler et al., 1983), this led to the idea that NA may have a central, indeed pivotal, role in determining the so-called ‘positive’ and ‘negative’ feedback effects of oestrogen on GnRH neurones. However, over recent years, a growing number of neurochemicals, such as neuropeptide Y, neurotensin and galanin, have been shown to exhibit exactly the same phenomenon (see Kafka, 1993) and it looks increasingly as though this inhibitory versus stimulatory LH response is more likely to reflect the activation state of a ‘core’ group of neurones within the GnRH network rather than anything specific about the neurotransmitter under examination.

There is, nevertheless, evidence indicating that gonadal steroids modulate the number of adrenergic receptors and intracellular coupling (see Etgen et al., 1993) as well as NA-evoked immediate early gene expression in the hypothalamus and preoptic area (Conde et al., in press). It has been noted that the stimulatory LH response requires higher concentrations of intraventricular alpha adrenergic agonists (but not NA itself) than does the inhibitory response, while beta adrenergic receptor inhibition of LH is evident only in ovariectomized rats (Leung et al., 1982; Taleisnik and Sawyer, 1986). Furthermore, the stimulatory effect of NA on LH secretion desensitizes quickly, while its inhibitory action in ovariectomized rats does not (Gallo, 1984). Hence, gonadal steroids are likely to influence the NA component of the GnRH network in pre- and post-synaptic fashions by altering both NA release and adrenergic receptor functioning, respectively.

However, an important observation has been that the alpha adrenergic-mediated enhancing effect of NA on LH release can rapidly revert to an alpha adrenergic-mediated repression once the LH surge begins (Bergen and Leung, 1988). This, together with the preceding argument in favour of a permissive role for NA within the GnRH network, suggests that the direction of influence of NA upon the GnRH network and LH secretion is determined, in the most part, by the excitability of neurones upon which NA impinges. In other words, NA exerts a non-directional permissive influence within the network. When GnRH network output is high, as it is after ovariectomy or at the time of the LH surge, NA is active in enabling maximal output. At times when the GnRH network exhibits low activity, NA can be used to activate components of the network that enable a high output state. From this type of network behaviour analysis, it is apparent that NA should be considered as a permissive regulator that favours high output states of the GnRH network. Within the context of gonadal steroid actions on the network, the most plausible role for the gonadal steroid modulation of NA release and adrenergic receptor functioning would be to regulate the effectiveness of its permissive influence within the network and thus alter the ‘gain’ or efficiency of GnRH network output.

Noradrenaline and the generation of the preovulatory LH surge

The LH surge in rats is generated through the interplay of a circadian input and rising concentrations of oestrogen on the day of pro-oestrus. Studies in sheep indicate that the GnRH network undergoes substantial change leading up to the time of the surge and that it transcends from producing a relatively low frequency pulsatile output to one in which massive GnRH secretion occurs (Evans et al., 1995). Experimental evidence indicates a role for NA in helping the network exhibit this ‘surge’ behaviour. Prominent among these findings has been the observation of increased NA turnover or concentrations within the vicinity of the GnRH cell bodies and terminals before, and at the time of, the steroid-induced or pro-oestrous LH surge (Honma and Wuttke, 1980; Rance et al., 1981; Wise et al., 1981; Demling et al., 1985; Mohankumar et al., 1994). This increase in NA release within the preoptic area is likely to result, in part, from the biosynthetic and electrical activation of oestrogen-receptive A2 neurones by rising oestrogen concentrations. Oestrogen induces expression of the immediate early gene Fos in A2 neurones (Jennes et al., 1992) and increased numbers of Fos-positive A2 neurones are found
on the morning of pro-oestrus (Conde et al., 1995). Neurones exhibit increased concentrations of Fos when electrically activated and this pattern of Fos expression in A2 neurones correlates well with the increased NA concentrations reported in the preoptic area on the morning before the LH surge (Demling et al., 1985). A further mechanism likely to play a role in increasing NA concentrations at pro-oestrus is the gradual removal of a presynaptic inhibitory opioid influence on noradrenergic terminals in the preoptic area (Kalra and Kalra, 1984).

An emerging theme is that, as found in other regions of the hypothalamus (Dietl et al., 1993), NA release in the preoptic area exhibits a circadian periodicity (Demling et al., 1985) and a diurnal pattern of Fos expression is observed in A1 neurones (Conde et al., 1995). As the diurnal changes in NA release within the preoptic area are greater in gonadal steroid-treated rats compared with ovariectomized animals (Demling et al., 1985), it is possible that the A1 inputs to this area are responsible for the circadian profile of preoptic NA release while the oestrogen receptor-expressing A2 inputs may provide the additional gonadal steroid-dependent NA release. However, at present, the nature of this circadian pattern of NA release has yet to be established, as has its relationship to the circadian ‘trigger’ responsible for generating the GnRH surge in rats.

The effects of the increase in NA at pro-oestrus may be twofold; on the one hand it may facilitate the change in the pattern and activity within the GnRH network, while on the other it seems likely to mediate part of the stimulatory action of oestrogen on GnRH mRNA expression (Weesner et al., 1993; Fig. 2). With respect to the latter, it is worth noting that investigators have reported increasing endogenous NA concentrations or turnover within the vicinity of the GnRH cell bodies before the onset of the LH surge (Rance et al., 1981; Demling et al., 1985; Mohankumar et al., 1994). Others (He et al., 1993) have demonstrated that GnRH mRNA expression is increased 1 h after intraventricular NA administration and, hence, the endogenous NA increase in the preoptic area on pro-oestrus appears well-positioned in a temporal sense to aid in the increased expression of GnRH mRNA which occurs before the onset of the LH surge (Porkka-Heiskanen et al., 1994; Petersen et al., 1995).

With respect to the electrical activation of GnRH neurones, I have suggested that NA promotes the high output state of the network. How this is achieved is not known and will likely remain a mystery until it is possible to make direct recordings from GnRH and associated neurones. By analogy with the actions of NA elsewhere in the brain (Waterhouse et al., 1988), NA may facilitate electrical activity within the network by increasing the signal-to-noise ratio of specific synapses and may even act as a ‘gate’ to enable ‘silent’ excitatory inputs to function. Such electrophysiological manifestations of the permissive

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**Fig. 2.** Proposed sequence of events (1–5) and pathway by which noradrenaline facilitates GnRH biosynthesis and secretion to help generate the LH surge in pro-oestrous rats. Oestrogen acts on many components of the GnRH network (blue cells) including the brainstem A2 neurones (red cells). (Black nuclei represent nuclei containing oestrogen receptors.) Note that GnRH neurones (yellow cell) do not express oestrogen receptors. (●) noradrenaline; (●) GnRH.
influence of NA are likely to underly the experimental observations where adrenergic receptor antagonists have been found to block the actions of various neuropeptides/neurotransmitters on LH secretion (see Kalra, 1993). These results are often interpreted as if there is a serial arrangement between the neurochemical under question, NA and the GnRH neurone. However, it is much more likely that it is a parallel relationship between the neurochemical and NA that has been revealed. By removing the permissive influence of NA within the GnRH network, the effect of the neurochemical becomes silent or lost in the background noise.

The temporal difference between the gradual increment in preoptic NA concentrations before the LH surge and the abrupt increase in GnRH electrical activity at the onset of the LH surge would not favour any direct ‘triggering’ influence of NA on the electrical activity of GnRH neurones and, again, this emphasizes the permissive role of NA. It is of note that the enhancing role of NA within this network only becomes apparent at the time of puberty (Clough et al., 1988) and the failure to exhibit LH surges in older animals is correlated with an absence of the afternoon increase in NA release within the preoptic area (Mohankumar et al., 1994).

Conclusions

Although it is only possible, at present, to describe the role of NA within the GnRH network in terms of network behaviour (that is, LH or GnRH output), this type of analysis makes clear the permissive or ‘enabling’ role for NA within this network. Such a role means that, although it does not determine directly the mode of GnRH output, it is able to alter the efficiency of network functioning and thus output via the GnRH neurones. Although not yet established, it seems likely that other components of the network, in particular the fast acting amino acid neurotransmitters, may serve the more direct or ‘core’ function of acutely starting and stopping the electrical activity of the GnRH neurones. A clear association of the permissive role of NA with the high output states of the GnRH network is seen in surging rats and it, thus, seems reasonable to suggest that the noradrenergic components of the network are part of the neural machinery used by oestrogen under normal conditions to bring about the electrical and biosynthetic events resulting in the GnRH/LH surge. As constituents of a critical brain region at which visceral and other peripheral stimuli are integrated, the brainstem noradrenergic neurones are also ideally positioned to modulate the overall functioning of the GnRH network in response to relevant internal homeostatic and environmental stimuli. Future efforts to establish the electrophysiological actions of NA on GnRH cells and their associated input neurones are likely to represent the next major advance in our understanding of the noradrenergic regulation of GnRH neurones.

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