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New concepts of the central control of reproduction, integrating influence of stress, metabolic state, and season

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ABSTRACT

Gonadotropin releasing hormone is the primary driver of reproductive function and pulsatile GnRH secretion from the brain causes the synthesis and secretion of LH and FSH from the pituitary gland. Recent work has revealed that the secretion of GnRH is controlled at the level of the GnRH secretory terminals in the median eminence. At this level, projections of kisspeptin cells from the arcuate nucleus of the hypothalamus are seen to be closely associated with fibers and terminals of GnRH cells. Direct application of kisspeptin into the median eminence causes release of GnRH. The kisspeptin cells are activated at the time of a natural "pulse" secretion of GnRH, as reflected in the secretion of LH. This appears to be due to input to the kisspeptin cells from glutamatergic cells in the basal hypothalamus, indicating that more than 1 neural element is involved in the secretion of GnRH. Because the GnRH secretory terminals are outside the blood–brain barrier, factors such as kisspeptin may be administered systemically to cause GnRH secretion; this offers opportunities for manipulation of the reproductive axis using factors that do not cross the blood-brain barrier. In particular, kisspeptin or analogs of the same may be used to activate reproduction in the nonbreeding season of domestic animals. Another brain peptide that influences reproductive function is gonadotropin inhibitory hormone (GnIH). Work in sheep shows that this peptide acts on GnRH neuronal perikarya, but projections to the median eminence also allow secretion into the hypophysial portal blood and action of GnIH on pituitary gonadotropes. GnIH cells are upregulated in anestrus, and infusion of GnIH can block the ovulatory surge in GnRH and/or LH secretion. Metabolic status may also affect the secretion of reproduction, and this could involve action of gut peptides and leptin. Neuropeptide Y and Y-receptor ligands have a negative impact on reproduction, and Neuropeptide Y production is markedly increased in negative energy balance; this may be the cause of lowered GnRH and gonadotropin secretion in this state. There is a complex interaction between appetite-regulating peptide neurons and kisspeptin neurons that enables the former to regulate the latter both positively and negatively. In terms of how GnRH secretion is reduced during stress, recent data indicate that GnIH cells are integrally involved, with increased input to the GnRH cells. The secretion of GnIH into the portal blood is not increased during stress, so the negative effect is most likely effected at the level of GnRH neuronal cell bodies.

1. Introduction

Reproduction is driven by the secretion of GnRH from the brain, which stimulates the synthesis and secretion of the gonadotropins, LH, and FSH from the anterior pituitary [1,2]. The function of GnRH neurons is controlled and modulated by a wide range of neuronal systems within the brain, which transmit feedback signals of sex steroids and mediate effects of stress, metabolic status and season [3–5]. Recent data have led to a significant advance in our understanding of how GnRH synthesis and secretion is

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controlled by modulatory neuronal systems in the brain. To a large extent, this is due to the recognition of the roles played by kisspeptin and gonadotropin inhibitory hormone (GnIH). In addition, new information on the nature of the projections of GnRH neurons to the neurosecretory zone in the median eminence and the demonstration of direct action of neuromodulators at the level of the secretory terminals behoves a revision of the way reproduction is controlled by the brain. This review will focus on our knowledge of how metabolic status, season, and stress are able to modulate the function of GnRH neurons and will be biased toward findings in the sheep as an experimental model.

2. GnRH neurons and anatomical evidence of modulatory afferents

To develop a working model for the regulation of GnRH neurons by season, stress and metabolic status, it is important to know which neuronal systems in the brain project to these cells. For many years, the putative modulatory afferents that regulate GnRH neurons was directed toward input at the level of the cell bodies in the preoptic area. As discussed in the following, we now need to revise our model of neuronal circuitry that controls GnRH cells because of demonstrable regulation at the level of the neurosecretory terminals in the median eminence. Earlier work concentrated on determination of input to GnRH cell bodies or dendrites, as previously detailed [6]. One may be confident of direct contact demonstrated by electron microscopic display of synaptic contacts of afferents identified by immunohistochemistry, but there are distinct species differences that need to be appreciated. For example, the demonstration of input to GnRH cells from proopiomelanocortin (POMC)- derived peptides (adrenocorticotropin and β-endorphin) that were reported for the nonhuman primate and rat, respectively, suggests that there are projections from the POMC cells of the arcuate nucleus (ARC) to the GnRH cells in the preoptic area (POA) [6]. The same is unlikely to be true for the sheep because there are minimal direct projections from cells of the ARC to the POA in this species [7,8]. This does not mean that ARC cells are irrelevant in terms of control of GnRH neurons, as will be discussed in the following. It is possible that there are serial circuits from the former to the latter that have not been described in domestic animal species.

More recent work describing neuronal afferents to the GnRH cell bodies has been assisted by confocal microscopy and identification of relevant factors not recognized before 2000. In particular, GnIH was shown to be a regulator of the reproductive axis in that year [9], and the major role that kisspeptin plays in the control of reproduction became known in 2003 [10,11]. These 2 RF-amide peptides play a significant role in the regulation of GnRH neurons by season, stress, and metabolic status and will be discussed in detail. Expansion of the earlier work on afferents to GnRH neurons is given in Table 1, which indicates receptors expressed in these cells. Although work in this area over the last 20 yr has expanded our knowledge with molecular and immunohistological analysis, the definitive methodology of electron microscopy is rarely employed because it is arduous and expensive. Notably, GnRH cells do not express estrogen receptor-α (ERα), which has been demonstrated as the signaling isoform of the receptor that is responsible of feedback to the GnRH cells, in rodents at least [47,48]. To the knowledge of the authors, only 1 study has been performed in the sheep to ascertain whether feedback regulation in this species is via ERα or ERβ [49], and this is discussed below with reference to control of seasonal breeding. It would be instructive to use more recently generated specific ligands for the two receptor subtypes and to ascertain whether feedback effects or behavioral effects are seen when these are placed in specific regions of the hypothalamus known to be involved in relay of the sex steroid feedback to GnRH neurons.

Now that we accept that particular ERα-expressing cell types are responsible for feedback signaling to GnRH neurons, this provides a basis for the deciphering of the effects of season, stress, and metabolic status on GnRH secretion. The cell types that express ERα in the ovine brain have been documented to some extent [5], and working models for reproductive function rely on this knowledge. Cells producing kisspeptin are of most relevance to control of GnRH cells by estrogen, by virtue of their high level of expression of ERα. GnRH cells express the kisspeptin receptor (KissR), and kisspeptin cells provide direct input to GnRH cell bodies. Importantly, however, input of kisspeptin neurons is from the population of cells found in the POA and not from those of the ARC [7]. The kisspeptin cells in the POA of the ovine brain are primarily involved in the positive feedback effect of estrogen that causes the preovulatory surge in GnRH and LH secretion [50], whereas the former are involved in negative feedback regulation and seasonal change. The role of kisspeptin and GnIH in the regulation of GnRH secretion in sheep has been reviewed extensively [3,5,51–53] and will not be dealt with in detail herein; specific details as to the involvement of these 2 peptides in seasonality, stress, and metabolic effects will be discussed.

3. Seasonal control of GnRH secretion

Seasonality is due to altered patterns of melatonin secretion from the pineal gland, which is dictated by day:night cycles [54]. As to how and where melatonin acts is an important question, and this has been the subject of significant investigation in a number of laboratories and in a number of species that will not be reviewed here.

3.1. Estrogen feedback and seasonality

The demonstration in 1977 that the negative feedback effect of estradiol on pulsatile LH secretion in ovariectomized (OVX) ewes is enhanced at the time when normal animals are in seasonal anestrus [55] was a milestone discovery. It was later shown that this effect is at the level of GnRH secretion [56], but as indicated previously, the GnRH cells do not express ERα. Despite identification of various types of cell in the POA and the hypothalamus that express ERα, none of these emerged as bone fide candidates for the transmission of negative feedback regulation of GnRH cells by estradiol. although this seasonal change in negative