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Review

Function-related structural plasticity of the GnRH system
A role for neuronal–glial–endothelial interactions

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ABSTRACT

As the final common pathway for the central control of gonadotropin secretion, GnRH neurons are subjected to numerous regulatory homeostatic and external factors to achieve levels of fertility appropriate to the organism. The GnRH system thus provides an excellent model in which to investigate the complex relationships between neurosecretion, morphological plasticity and the expression of a physiological function. Throughout the reproductive cycle beginning from postnatal sexual development and the onset of puberty to reproductive senescence, and even within the ovarian cycle itself, all levels of the GnRH system undergo morphological plasticity. This structural plasticity within the GnRH system appears crucial to the timely control of reproductive competence within the individual, and as such must have coordinated actions of multiple signals secreted from glial cells, endothelial cells, and GnRH neurons. Thus, the GnRH system must be viewed as a complete neuro-glial–vascular unit that works in concert to maintain the reproductive axis.

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1. Introduction

The hypothalamus is a brain structure useful for the study of hormone- and activity-dependent plasticity. Research into the GnRH system appears to be particularly fascinating and challenging in this regard. Numerous regulatory homeostatic and external factors converge on GnRH neurons to control gonadotropin secretion and thereby achieve levels of fertility appropriate to the organism. Current models of neuronal plasticity stress the importance of transient electrical and biochemical events associated with the excitation process [44,135]. However there is increasing evidence that activation is accompanied by other important physical phenomena. Over the past three decades, it has indeed become clear that fluctuating physiological conditions have the power to reversibly alter the structural relationships between neuronal and non-neuronal cell types, as well as the functional pathways over which information is transmitted. Function-related plasticity was first discovered in the magnocellular hypothalamo-neurohypophysial system; the activation or inactivation of this system and its downstream physiological consequences is associated with microstuctural changes [77,232]. In this review, we will consider these aspects of the neuroendocrine control of GnRH release and the cell–cell communication processes involved in their regulation.

2. The GnRH system

GnRH is the master regulator of sexual maturation and reproduction in vertebrate [81,158,171,229]. In rodents, the cell bodies of GnRH neurons are diffusely distributed in the forebrain and are particularly abundant in the preoptic region; in primates, including humans, they are also present in the tuberal region of the hypothalamus. The neuroendocrine fraction of GnRH neurons sends axons to the median eminence of the hypothalamus, where they release the neurohormone into the pituitary portal blood vessels for delivery to the anterior pituitary. At the adenohypophysis, GnRH elicits the secretion of the gonadotropins LH and FSH, which stimulate gametogenesis and gonadal steroid secretion and thus support reproductive physiology (Fig. 1).

Because GnRH neurons are the final common target for the central control of reproduction, their activity is regulated by a complex

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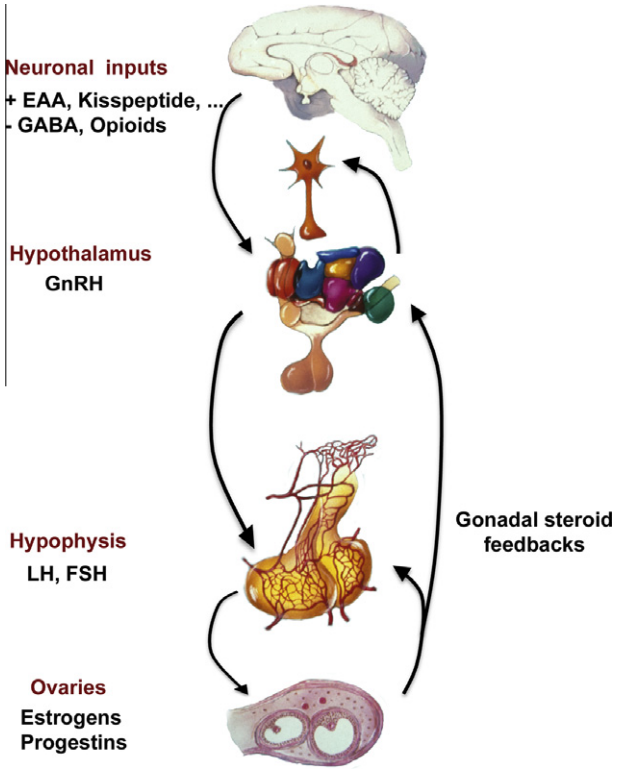

Fig. 1. Neuronal control of the pituitary gonadal axis. As hypothalamic GnRH neurons are the final common pathway for central control of gonatropin secretion, they are subjected to a complex array of excitatory and inhibitory transsynaptic inputs that modulate their activity. GnRH neuroendocrine neurons project to the median eminence where they make contact with basal lamina and open into the pericapillary space of the primary hypophyseal portal plexus. Upon reaching the pituitary portal system, GnRH travels to the pituitary to stimulate the synthesis and secretion of pituitary gonadotropins: luteinizing hormone (LH) and follicle stimulating homone (FSH). Blood-borne LH and FSH act on target cells in the gonads (here the ovaries) to direct production of gametes, as well as the secretion of steroid hormones. Within the brain, gonadal steroids influence GnRH secretion via neuroendocrine feedback loops. EAA, excitatory amino acids and GABA, gamma-aminobutyric acid.

array of excitatory and inhibitory transsynaptic inputs [24,55,81,155,222,229]. Notably, the multiple neuronal networks involved in the control of GnRH secretion are subjected to the direct modulatory influence of gonadal steroids [82,83,134,148,194]. However, there is now a growing body of evidence indicating that, concurrently with these transsynaptic regulatory mechanisms, cell–cell interactions involving non-neuronal cells such as astrocytes, specialized ependymoglial cells named tanycytes, and vascular endothelial cells might be of critical importance for the regulation of GnRH secretion [12,68,152,153,180]. Indeed, in the hypothalamus as in most areas of the central nervous system, the classical one-way dialogue at the chemical synapse that forms the functional unit for the transmission of information between the nerve terminal and its target is being re-evaluated on the strength of recent demonstrations that glial cells, the presumed electrically silent co-habitants of the nervous system, might be a critical third element of the synapse [7,8,13,78,128,169,242]. Within this organization, further modular structure can be detected; in particular, neuro-glio-vascular units have been proposed, in which individual astrocytic glia support the function of certain neuronal populations and territories, and communicate with associated segments of the microvasculature [79,87]. These microfunctional domains are likely to play an important role in maintaining a precisely regulated microenvironment for reliable neuronal signaling in an ever-changing physiological context. These new concepts in neuroscience are fundamental to understanding how events that involving the neurons, astroglia and vascular endothelial cells of the GnRH neuroendocrine network are orchestrated to bring forth functionally meaningful episodes of GnRH release at key stages of animal physiology, i.e., puberty, ovulation and seasonal breeding (Fig. 2).

3. Morphological plasticity

At all levels – somatic, dendritic and median eminence terminal zone – the GnRH neuroendocrine system displays an increasingly recognized degree of structural plasticity that is correlated with changes in the animal's physiological state and, thus, with the altered functional properties of the system. Whereas plasticity at the GnRH cell body appears to result from dendritic and synaptic contact remodeling likely to require astrocyte intermediacy, plasticity in the terminal field involves interactions between neuronal, glial and endothelial cells.

3.1. At the GnRH cell bodies

3.1.1. Puberty

GnRH neurons are peculiar hypothalamic neurons because, unlike the other parvicellular neurosecretory neurons that arise from the third ventricle neuroepithelium [127], they are born in the olfactory pit, subsequently migrate to the septal region and reach their final destination in the hypothalamus by the time of birth in all examined mammalian species including humans [185,204,205,233,249,250]. Thereafter, the function, morphology, biosynthetic capacity, and synaptic connectivity of GnRH neurons mature during postnatal development to promote sexual maturation and initiate puberty [159]. Puberty is initiated by events within the central nervous system and that are set in motion independently of gonadal influence [158,171,224,229]. As a consequence of these events, the pulsatile release of GnRH into the portal vasculature increases and pituitary gonadotropin output is stimulated, resulting in the initiation of the pubertal process. Over the past two decades, the exciting concept that developmental changes in the function of the GnRH neuronal network might be tightly linked with the structural remodeling of GnRH neurons themselves and/or their attendant afferent inputs was only addressed by a few studies. Early immunocytochemical studies showed that the number of GnRH neurons bearing spine-like processes [89,104] increases during postnatal development in both male and female rats [251,252]. Recent studies by Herbison and collaborators using biocytin filling of green fluorescent protein-tagged GnRH neurons in acute brain slice preparations [30], extended these findings by showing that spine density in GnRH neurons increases twofold between the second week of postnatal life and adulthood both at the level of somata and at proximal dendrites in transgenic mice [48]. This increase in spine density correlates well with the increase in glutamatergic stimulation of GnRH neurons that is thought to be an essential component of the transsynaptic mechanism controlling GnRH neurosecretion at puberty [23,237]. It is also concomitant with the maturation of the electrical response of GnRH neurons to kisspeptin [76], a recently identified neuropeptide that is required for the onset of puberty [49,50,209], as well as with the arrival of neuronal projections from the arcuate nucleus of the hypothalamus in the preoptic region [22]; these neuronal projections are known to form close appositions with GnRH soma and dendrites [38,235] and to play an essential role in regulating the secretion of LH [68,82]. Herbison and colleagues also showed that in addition to changes in spine density, a specific subset of GnRH neurons is subjected to a biphasic pattern of remodeling in their dendritic tree during postnatal

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