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Review

Gonadotropin-releasing hormone (GnRH) and its natural analogues: A review

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Abstract

The pivotal role of gonadotropin-releasing hormone (GnRH) during the hormonal regulation of reproductive processes is indisputable. Likewise, many factors are known to affect reproductive function by influencing either GnRH release from hypothalamus or pituitary gland responsiveness to GnRH. In veterinary medicine, GnRH and its agonists (GnRHa) are widely used to overcome reduced fertility by ovarian dysfunction, to induce ovulation, and to improve conception rate. GnRHa are, moreover, integrative part of other pro-fertility treatments, e.g. for synchronization of the estrous cycle or stimulation for embryo transfer. Additionally, continuous GnRH which shows desensitizing effects of the pituitary-ovarian axis has been recommended for implementation in anti-fertility treatments like inhibition of ovulation or reversible blockade of the estrous cycle. Just as much, another group of GnRH analogues, antagonists, are now in principle disposable for use.

For a few decades, GnRH was thought to be a unique structure with a primary role in regulation gonadotropins. However, it became apparent that other homologous ligands of the GnRH receptor (GnRHR) exist. In the meantime, more than 20 natural variants of the mammalian GnRH have been identified in different species which may compete for binding and/or have their own receptors. These GnRH forms (GnRHs) have apparently common and divergent functions. More studies on GnRHs should contribute to a better understanding of reproductive processes in mammals and interactions between reproduction and other physiological functions. Increased information on GnRHs might raise expectations in the application of these peptides in veterinary practice. It is the aim of this review to discuss latest results from evolutionarily based studies as well as first experimental tests and to answer the question how realistic might be the efforts to develop effective and animal friendly practical applications for endogenous GnRHs and synthetic analogues.
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Contents

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1. Introduction to gonadotropin-releasing hormone

GnRH belongs to a group of neuropeptides originally discovered and successfully isolated as factors of hypothalamic origin that control secretions of the anterior pituitary gland. GnRH influences reproductive processes, mainly by regulating pituitary gonadotropin synthesis and release, which in turn modulate steroidogenesis and gametogenesis. This pivotal role may explain why the interest in GnRH is still going on since its primary structure was revealed in pigs [1] and sheep [2]. GnRH is expressed, apart from hypothalamus, in numerous peripheral tissues including gonads and placenta [3–10]. Hypothalamic and extrahypothalamic GnRH are known as integrated part of multiple paracrine/autocrine axes. Hypothalamic GnRH, however, is in the focus of attention of the present review.

There are currently 23 identified naturally occurring GnRH analogues (GnRHs) across the vertebrate species [11–13]. These variants show multiple substitutions in their amino acid (AA) sequence when compared with the mammalian GnRH (mGnRH), and they were widely distributed in tissues suggesting that they have acquired significant functions through the phylogeny. GnRHs have been explored during last years in various classes of vertebrates, mainly in fishes and mammals, but also in protochordates, that are phylogenetically distant from mammalian vertebrates. The species-related designation of single GnRH isoforms may be difficult to survey and confusing under circumstances. In this review mGnRH will always be designated, according to [14], ‘‘GnRH-I’’, chicken GnRH-II (cGnRH-II) ‘‘GnRH-II’’, and salmon GnRH (sGnRH) ‘‘GnRH-III’’. Other GnRHs will be preferably discussed by citing the traditional names which have been introduced in the literature. It was assumed that dogfish GnRH, GnRH-II, and GnRH-III are ancient forms which could be likely found in invertebrates [15]. At this stage, the exploration of the primary structure of GnRHs has been completed only in tunicates and octopus. More information seems to be necessary to complete the phylogenetic tree of GnRH and to characterize the ontogenic development of single GnRHs in different species [16].

GnRH-I and its variants are thought to have neuroendocrine, as well as neurotransmitter and neuromodulatory functions [13,17]. The neuroendocrine axis plays the central role in the control of reproduction, and GnRH-I is well known to integrate internal and external signals of the nervous system to reproductive system [15]. In invertebrates, a similar role of GnRHs may have evolved resulting in systems that assure the maintenance of species under changing environments. However, GnRH-I also acts as a neuromodulator probably by down-regulation of its neighboring genes for particular protein-tyrosin phosphatases [18]. This GnRH-I function could be an important link of the common molecular mechanism underlying the diverse functions of GnRHs.

It is evident that at least two of these natural GnRHs are present in more than 80 vertebrate species [12–14,19–21]. A better understanding is, however, still needed to evaluate the specific contribution of GnRHs to the control of mammalian reproduction by GnRH-I in mammals. The practical usefulness of GnRH-I and its synthetic analogues (agonists and antagonists) has achieved a high level. It is the purpose of the present review to discuss in this context the prospects for GnRH-II and other GnRHs although the exact functions of these peptides are yet to be defined [22].

2. Biosynthesis and storage of GnRH-I and its natural analogues

Like many other proteins and peptides, GnRH-I and its analogues are enzymatically processed from larger precursors (Fig. 1). The complementary DNA consists of the decapeptide, extended at the amino (N) terminus by a signal peptide, and at the carboxy (C) terminus by a Gly-Lys-Arg sequence followed by the GnRH-associated peptide (GAP).

In the proGnRH-I, the GAP sequence is 56 AA long but it shows, like the signal peptide, considerable variations between several mammals [3] like that of pro-GnRHs of other species [23,24]. GAP which is

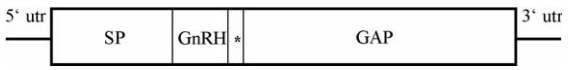

Fig. 1. Schematic representation of the prepro-GnRH precursor proteins. The 5′-untranslated region (5′ utr) is followed by the signal peptide (SP), the GnRH, processing signal (*), the GnRH-associated peptide (GAP), and the 3′-untranslated region (3′ utr). Adapted to Sherwood et al. [3].

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