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Review

Translational control of gene expression in the gonadotrope

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ABSTRACT

The study of gene expression in gonadotropes has largely focused on the variety of mechanisms regulating transcription of the gonadotropin genes and ancillary factors that contribute to the overall phenotype and function of these cells in reproduction. However, there are aspects of the response to GNRH signaling that are not readily explained by changes at the level of transcription. As our understanding of regulation at the level of mRNA translation has increased, it has become evident that GNRH receptor signaling engages multiple aspects of translational regulation. This includes activation of cap-dependent translation initiation, translational pausing caused by the unfolded protein response and RNA binding protein interaction. Gonadotropin mRNAs and the mRNAs of other factors that control the transcriptional and signaling responses to GNRH have been identified as targets of regulation at the level of translation. In this review we examine the impact of translational control of the expression of gonadotropin genes and other genes relevant to GNRH-mediated control of gonadotrope function.

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1. Introduction

The development and regulation of reproductive tissues is a complex task that operates through a variety of regulatory mechanisms. In mammals, the reproductive endocrine axis, consisting of the hypothalamus, pituitary, and gonad, (H–P–G axis) is controlled by a number of feed-forward and feedback signals that impact each level. The regulatory signals range from the synaptic and peptidergic control of the hypothalamic neurons producing the primary releasing factor, gonadotropin-releasing hormone (GNRH), interaction of GNRH and other factors such as activin and insulin modulating pituitary gonadotropin output, and finally

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the impact of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) on the cognate cells of the testis and ovary that dictate germ cell maturation and feedback factor production such as sex steroids, activin, and inhibin. There is increasing evidence that there are regulatory signals originating outside the Hypothalamus–Pituitary–Gonad axis that impact gonadotropin production by the pituitary. Inflammatory stress and obesity are both associated with decreased gonadotropins. The interaction of these cues ultimately defines gonadotropin output and there is an emerging appreciation for the role of the pituitary in interpreting multiple signals. Much of the study of gonadotropin gene expression has been focused on the primary regulation of gonadotropin gene transcription. However, gonadotropin production is not easily explained solely on the basis of transcriptional control and a more complete description of gonadotropin gene expression must incorporate other modes of gene regulation, including the regulation of protein synthesis. A number of studies have implicated translational control in the regulation of gonadotropes and gonadotropin production. Further, the increasing appreciation for the role of stress responses and maintenance of endoplasmic reticulum (ER) homeostasis in secretory cells of all types through the unfolded protein response (UPR) suggests that these processes, which largely operate through translational control, may also play a role in gonadotrope biology as well. This review will discuss our current understanding of translational control of gene expression in the gonadotrope.

2. Translational control in human disease

As our understanding of the mechanisms of translational control has increased, it has become clear that a number of diseases involve some component of the regulated translation or the unfolded protein response (Scheper et al., 2007; Walter and Ron, 2011). A variety of conditions lead to disrupted or alternatively regulated translation in mammalian cells. Lytic viral infection results in accumulation of protein in the ER. Some viruses, such as Hepatitis B, manipulate the activation of UPR signaling proteins to elicit an ER proliferative response to aid in viral replication and assembly (Li et al., 2007). Other viruses disrupt normal translational initiation by cleavage of factors necessary for translation initiation such as eukaryotic translation initiation factor 4G(EIF4G) and polyA Binding Protein (PABP) (Lloyd, 2006). Other than compromise by infectious agents, dysregulated protein synthesis is identified in a number of diseases in which tissues are exposed to chronic stress, taxing the ability of the cell to maintain homeostasis. One common example of this is the degenerative disease retinitis pigmentosa, which is caused by accumulation of misfolded rhodopsin in retinal photoreceptor cells. Retinitis pigmentosa is associated with a number of other pathologies including mis-sense mutations of numerous RNA processing enzymes and membrane proteins, suggesting an overall sensitivity of photoreceptors to accumulated mis-translated or unfolded protein (Lin and Lavail, 2010). Neurodegenerative diseases also appear to have a significant relationship to disorders of protein translation (Chang et al., 2007). Most similar to the secretory cells of the reproductive endocrine axis, the impact of increased demand on pancreatic beta cells in Type II diabetes mellitus leads to chronic activation of the UPR that eventually causes loss of some members of the population, increasing demand on the remaining cells, thus establishing a recurring and elevating cycle of increased demand and cell loss that ultimately causes a near or complete loss of insulin production (Fonseca et al., 2011). Overall the wide range of disease types suggests different tissues exhibit different levels of sensitivity to disruption of translation and ER homeostasis, resulting in a variety of consequences.

3. Evidence for translational control in the hypothalamus–pituitary–gonad axis

Although disorders of pituitary function or tumors of pituitary origin are well studied, their origins have not been directly attributed to dysregulated protein synthesis or disruption via the UPR, nor has this perspective been examined carefully. There is suggestion in a number of studies that gonadotropin secretion is reduced under conditions of high BMI, stress, or hyperinsulinemia (Arroyo et al., 1997; Pagan et al., 2006; Jain et al., 2007) and the post-translational modification of secreted gonadotropins is altered under these conditions (Srouji et al., 2007). It is also documented that inflammation can reduce gonadotropin output. Although it is yet to be conclusively demonstrated, the known impact of inflammatory cytokines and lipopolysaccharides on UPR activation presents the possibility that some aspect of reduced pituitary gonadotropin release under conditions of stress may be due to the translational impact of UPR activation.

3.1. Evidence in animal models

The study of gonadotropin subunit mRNA synthesis in rats provides a strong suggestion that processes other than transcriptional regulation contribute to gonadotropin production. Early examination of the changes in gonadotropin mRNA levels in hemipituitaries subjected to tonic or pulsatile GNRH stimulation showed measurable changes of up to fourfold in LH transcription rate (Shupnik, 1990). Though significant, these rates were less than the typical changes in LH secretion seen during the LH surge or under exogenous GNRH stimulation (Blake et al., 1972; Arimura et al., 1974; Legan and Karsch, 1975). In GNRH-stimulated male rats, LH beta (*Lhb*) steady-state mRNA levels were found to be increased approximately 40% after stimulation with GNRH, although LH secretion was found to be increased by approximately 100 fold (Burger et al., 2001, 2002). The nonlinear increase in protein release by the pituitary indicates that increased gonadotropin production cannot be explained by strict correspondence to increased mRNA. The relatively low level of steady state mRNA response is corroborated by a number of microarray studies that failed to show an increase in *Lhb* mRNA after GNRH stimulation that exceeded the typical 2-fold cutoff for declaring significance (Blake et al., 1972; Legan and Karsch, 1975; Kakar et al., 2003; Zhang et al., 2006; Lawson et al., 2007). Overall, these accumulating observations provide the foundation for the hypothesis that GNRH engages post-transcriptional regulatory processes including the protein synthetic machinery to increase gonadotropin production and release.

3.2. Evidence in cell model systems

The regulation of post-transcriptional processes is not well-established in the gonadotrope despite the potential to be a major means of gene regulation. GNRH impacts both mRNA synthesis rates and half-life of *Lhb* mRNA (Shupnik, 1990; Bouamoud et al., 1992; Weiss et al., 1992). The glycoprotein hormone subunit alpha gene (*Cga*) mRNA was shown to be stabilized by GNRH treatment of the immature gonadotrope cell line αT3-1 (Weiss et al., 1992; Chedrese et al., 1994). Although reports focused on understanding gonadotropin synthesis in the context of transcriptional regulation, evidence emerged shortly thereafter that post-transcriptional control may also contribute to gonadotropin synthesis. Early studies of GNRH receptor (GNRHR) expression showed regulation of receptor synthesis activity despite no change in mRNA content after GNRH stimulation (Tsutsumi et al., 1993, 1995). GNRHR synthesis increased in GNRH-stimulated cells and in *Xenopus* oocytes injected with RNA isolated from these cells, indicating an RNA-based