Bioscience Discovery, 6(2):70-72, July - 2015

Print & Online, Open Access, Research Journal Available on http://jbsd.in
ISSN: 2229-3469 (Print); ISSN: 2231-024X (Online)

Short Communication

Role of Neuropeptide RFRP-3 in Ageing

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Article Info

Received: 08-06-2015,

Revised: 22-06-2015,

Accepted: 03-07-2015

Keywords:

GnIH, RFRP-3, DMH, Testosterone, Reproduction

Abstract

Progressive development and growth of gonad occur in parallel with somatic growth until the attainment of puberty. Regressive variations start performing in the seminiferous tubules with aging. Testicular development of male mice is under the direct regulation of hypothalamic gonadotropin-releasing hormone (GnRH). Now, evidence arose from work in the quail which isolated and identified a factor named gonadotropin-inhibitory hormone (GnIH) that inhibited gonadotropin release in the same species. This short communication demonstrates that the gonadal quiescence in sexually immature mice and a decline in reproductive performance in aging mice are inversely correlated with increased and increasing expression of immune-reactive RFamide-related peptide-3 in the dorso-median region of the hypothalamus. Further, it is also quite possible that, decreased level of this peptide may lead to reproductive development and increased gonadal activity, although further experimental study is required to identify such mechanism of action involving both GnRH and GnIH like activity in relation to age-related gonadal development in mammals.

INTRODUCTION

Aging has different effects on the reproductive system. In the testes, spermatogenesis and steroidogenesis decrease with old age, as described in ageing laboratory rats (Syntin and Robaire, 2001). In addition, in the epididymal epithelium, some striking segment-specific changes occur at the histological and biochemical levels prior to the major loss of spermatogenesis (Levy and Robaire, 1999). In addition, changes in the expression of genes related to oxidative stress in the epididymis due to age have also been described (Takemura *et al.*, 2014).

Progressive development and growth of gonad occur in parallel with somatic growth until the attainment of puberty in some non-seasonal breeders. However, remarkable changes in the gonadal activity (spermatogenesis, testosterone level etc.) occur in a short span of time just before and around the puberty in these species. Thereafter, sperm production and testosterone concentration remain at the maximum level during the reproductively active period of the species' life span. Regressive/degenerative changes start appearing in the seminiferous tubules with aging. Such changes have been reported in men, rats, oxen, mice and cats but their causes remain unclear (Pop *et al.*, 2011; Elo *et al.*, 2012). Similar degenerative changes are reported to be induced by irradiation, artificial cryptorchidism and experimental autoimmunization in laboratory animals (Jegou *et*

al., 1983). Regressive testicular changes, such as those in aged men and animals, also occur spontaneously in young men resulting in infertility, although the cause remains unknown.

Testicular development of male mice is under the direct regulation of hypothalamic decapeptide gonadotropin-releasing hormone (GnRH). This releasing hormone originally isolated from mammals (Kauffman, 2004) and subsequently from birds (Stevenson *et al.*, 2012) and other vertebrates, is the primary factor responsible for hypothalamic control of gonadotropin secretions from the pituitary (Roch *et al.*, 2014). In mammals, there are two forms, GnRH-I which regulates gonadotropin secretion, and GnRH-II which appears to stimulate sexual behavior (Roch *et al.*, 2014). Gonadotropins act on the gonads to stimulate gametogenesis and sex steroid production. Gonadal sex steroid and inhibin can also modulate gonadotropin secretion via feedbacks from the gonads. But, a neuropeptide inhibitor for gonadotropin secretion was unknown in vertebrates until the discovery of hypothalamic dodecapeptide (SIKPSAYLPLRF-NH_2) termed gonadotropin-inhibitory hormone (GnIH), which directly inhibits gonadotropin release from the cultured quail anterior pituitary (Tsutsui *et al.*, 2000). The effect on gonadotropin release has subsequently been confirmed in rodents and sheep using avian GnIH or orthologous mammalian peptides (Anjum *et al.*, 2014). The structure of GnIH, its history and aspects of its functional significance are discussed in detail in the review of literature section.

Ubuka *et al.* (2003) analyzed GnIH precursor mRNA and the mature peptide during embryonic and post-hatch ages in quail diencephalon. GnIH precursor mRNA expression occurred on embryonic day 10 (E10) and showed a significant increase at E17, just before hatch. GnIH-like-*ir* neurons were localized in the PVN on E10, but GnIH-*ir* fibres did not extend to the median eminence until E17 (just before hatch), when the GnIH-*ir* neuron number in the PVN was also increased. GnIH content of the diencephalon decreased just after hatch and subsequently increased progressively into adulthood. Thus, it appears that GnIH begins to function around hatch (Ubuka *et al.*, 2003). Recently, Quennell *et al.* (2010) investigated the gene expression of RFRP and its G protein-coupled receptor over prepubertal development and in response to oestrogen. Hypothalamic RFRP and its receptor levels were measured in male and female rats aged 2, 4, 6 and 8 weeks. In female, RFRP gene expression increased with development age, peaking around the time of puberty, whereas in males, gene expression increased only between 2 and 4 weeks of age.

In spite of the identification, characterization and localization of this inhibitory peptide in mammalian system, relatively few reports are focused on the physiological aspects of this mammalian GnIH ortholog. We have recently reported the high levels of the expression of RFRP-3 neurons observed in sexually immature mice which decreased in the sexually mature condition (Sethi *et al.*, 2010a; Sethi and Chaturvedi, 2015). Hence, this short communication focuses on the expression of *ir*-RFRP-3 in mice brain with respect to aging. Interestingly, in old mice the trend got reversed with sharp increase in RFRP-3 neuronal parameters and significant decrease in testicular activity including spermatogenesis. Our study demonstrated that the gonadal quiescence in sexually immature mice and a decline in reproductive performance in old mice (concomitant with a low and decreasing testosterone level, respectively) are inversely correlated with increased and increasing expression of *ir*-RFRP-3 in the DMH (Sethi *et al.*, 2010b; Sethi and Chaturvedi, 2015). Accordingly, it is suggested that RFRP-3 might contribute to the prepubertal sexual quiescence of the gonadal axis as well as during the age-related decline in the reproductive performance. Further, it is also suggested that, decreasing or decreased level of this peptide leads to reproductive development and increased gonadal activity, although further experimental study is required to identify such mechanism of action involving both GnRH and GnIH-like activity of RFRP-3 in relation to age-related gonadal development in mammals.

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How to Cite this Article:

Sumit Sethi1 and Chandra Mohini Chaturvedi, 2015. Role of Neuropeptide RFRP-3 in Ageing. *Bioscience Discovery*, **6**(2):70-72.