



## Role of Neuropeptide RFRP-3 in Ageing

Sumit Sethi<sup>1\*</sup> and Chandra Mohini Chaturvedi<sup>2</sup>

<sup>1</sup>Interdisciplinary Laboratory for Clinical Neuroscience (LiNC), Department of Psychiatry, Universidade Federal de São Paulo – UNIFESP, São Paulo, **BRAZIL**

<sup>2</sup>Department of Zoology, Banaras Hindu University, Varanasi 221 005, INDIA

\*E-mail: [sumitsethi92@gmail.com](mailto:sumitsethi92@gmail.com)

### 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<sub>2</sub>) 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.

RFRP3 in testicular activities in adult mice. *J. Endocrinol.*, **223**(1):79-91.

Elo T, Sipilä P, Valve E, Kujala P, Toppari J, Poutanen M and Härkönen P, 2012. Fibroblast

## REFERENCES

Anjum S, Krishna A and Tsutsui K, 2014. Inhibitory roles of the mammalian GnIH ortholog

- growth factor 8b causes progressive stromal and epithelial changes in the epididymis and degeneration of the seminiferous epithelium in the testis of transgenic mice. *Biol. Reprod.*, **86**(5):157.
- Jegou B, Laws AO and de Kretser DM, 1983.** The effect of cryptorchidism and subsequent orchidopexy on testicular function in adult rats. *J. Reprod. Fertil.*, **69**(1):137-145.
- Kauffman AS, 2004.** Emerging functions of gonadotropin-releasing hormone II in mammalian physiology and behaviour. *J. Neuroendocrinol.*, **16**(9):794-806.
- Levy S and Robaire B, 1999.** Segment-specific changes with age in the expression of junctional proteins and the permeability of the blood-epididymis barrier in rats. *Biol. Reprod.*, **60**(6):1392-1401.
- Pop OT, Cotoi CG, Pleșea IE, Enache SD, Popescu FC, Enache MA and Pleșea RM, 2011.** Correlations between intralobular interstitial morphological changes and epithelial changes in ageing testis. *Rom. J. Morphol. Embryol.*, **52**(1 Suppl):339-347.
- Quennell JH, Rizwan MZ, Relf HL and Anderson GM, 2010.** Developmental and steroidogenic effects on the gene expression of RFamide related peptides and their receptor in the rat brain and pituitary gland. *J. Neuroendocrinol.*, **22**(4):309-316.
- Roch GJ, Busby ER and Sherwood NM, 2014.** GnRH receptors and peptides: skating backward. *Gen. Comp. Endocrinol.*, **209**:118-134.
- Stevenson TJ, Hahn TP, MacDougall-Shackleton SA and Ball GF, 2012.** Gonadotropin-releasing hormone plasticity: a comparative perspective. *Front. Neuroendocrinol.*, **33**(3):287-300.
- Syntin P and Robaire B, 2001.** Sperm structural and motility changes during aging in the Brown Norway rat. *J. Androl.*, **22**(2):235-244.
- Takemura S, Ichikawa H, Naito Y, Takagi T, Yoshikawa T and Minamiyama Y, 2014.** S-allyl cysteine ameliorates the quality of sperm and provides protection from age-related sperm dysfunction and oxidative stress in rats. *J. Clin. Biochem. Nutr.* **55**(3):155-161.
- Tsutsui K, Saigoh E, Ukena K, Teranishi H, Fujisawa Y, Kikuchi M, Ishii S and Sharp PJ, 2000.** A novel avian hypothalamic peptide inhibiting gonadotropin release. *Biochem. Biophys. Res. Commun.*, **275**(2):661-667.
- Sethi S, Tsutsui K and Chaturvedi CM, 2010a.** Temporal phase relation of circadian neural oscillations alters RFamide-related peptide-3 and testicular function in the mouse. *Neuroendocrinology*, **91**(2):189-199.
- Sethi S and Chaturvedi CM, 2015.** Physiological evidence of an inverse correlation between the gonadal function and RFRP-3 neurons in mice. *Int. J. Bioassays*, **4**(6):4022-4024.
- Sethi S, Tsutsui K and Chaturvedi CM, 2010b.** Age-dependent variation in the RFRP-3 neurons is inversely correlated with gonadal activity of mice. *Gen. Comp. Endocrinol.* **168**(3): 326-332.
- Ubuka T, Ueno M and Ukena K, Tsutsui K, 2003.** Developmental changes in gonadotropin-inhibitory hormone in the Japanese quail (*Coturnix japonica*) hypothalamo-hypophysial system. *J. Endocrinol.*, **178**(2):311-318.

---

How to Cite this Article:

**Sumit Sethi<sup>1</sup> and Chandra Mohini Chaturvedi, 2015.** Role of Neuropeptide RFRP-3 in Ageing. *Bioscience Discovery*, **6**(2):70-72.