Article

Role of nerve growth factor and FSH receptor in epithelial ovarian cancer

Dr Chinmoy K Bose obtained his MD qualification in Obstetrics and Gynaecology from Ramakrishna Mission Seva Prathisthana, Kolkata, India, in 1989. His sub-speciality training, registrarship and PhD (1996) in gynaecological oncology were completed in the Chittaranjan National Cancer Institute, Kolkata. Later Dr Bose won a Royal Society fellowship at St Bartholomew's Hospital, London, UK. He is a practising gynaecological oncologist and works as a Specialist Medical Officer in the Kolkata Municipal Corporation. He is a peer reviewer for international journals and has many publications. He works on the role of gonadotrophins, their receptors and nerve growth factor in epithelial ovarian cancer and non-linear science in endocrine feedback.

Dr Chinmoy K Bose

Chinmoy K Bose
8D Mathur Sen Garden Lane, Kolkata 700 006, India
Correspondence: Tel +91 33 227 23264; Fax +91 33 222 40201; e-mail: ckbose@hotmail.com

Abstract

The neurotrophins (NT) including nerve growth factor (NGF) are a family of related growth factors that are of major importance in the regulation of neuronal survival and differentiation. In the ovary, they can help in follicular maturation and ovulation by inducing the FSH receptor (FSHR). Current literature shows that perimenopausal ovarian surface epithelium (OSE) can also express FSHR. By G protein link, this FSHR is capable of precipitating neoplasia of OSE, which is the commonest in the ovary. NT are implicated as the cause of this aberrant expression of FSHR in OSE. By central action NT can lower serum FSH, as is found in ovarian cancer. Thus, NGF deregulates expression of FSHR in OSE and secretion of FSH from the pituitary. This phenomenon may hold the key to the hitherto unexplained carcinogenic process of sporadic epithelial ovarian cancer.

***Keywords*:** *epithelial ovarian cancer, follicle-stimulating hormone receptor, FSH, nerve growth factor, ovarian surface epithelium*

Introduction

Although originally discovered in the nervous system as nerve growth factor (NGF) (Levi-Montalcini and Angeletti, 1966), many members of the neurotrophin (NT) family are expressed in the cardiovascular, immune, endocrine and reproductive systems (Tessarollo, 1998).

The neurotrophin family consists of NGF, brain-derived neurotrophic factor or BDNF, NT-4/5, NT-3, their respective receptor tyrosine kinases (Trk A for NGF, Trk B for BDNF, and NT-4/5, Trk C for NT-3) and non-specific receptor p75. Several of its members are expressed in the mammalian ovary and influence ovarian function including ovulation, steroid secretion and follicular development (Mayerhoffer *et al.*, 1996). NGF is also involved in the differentiation process by which ovarian follicles become responsive to gonadotrophins (Romero *et al.*, 2002) through formation of biologically active FSH receptor (FSHR) in early neonatal life. However, their role in the postmenopausal ovary is not yet established.

Fallacy of the theory of FSH and receptor involvement in ovarian cancer

Looking at the high gonadotrophin levels of menopause, Biskind and Biskind (1944) proposed the gonadotrophin theory for epithelial ovarian cancer (EOC). This was substantiated by several in-vitro experiments. However, in recent studies, FSH in postmenopausal epithelial ovarian cancer patients was found to be significantly lower (Blaakaer *et al.*, 1992; Menon *et al.*, 1999; Bose *et al.*, 2001), even in the preclinical phase of the disease (Helzlsoeur *et al.*, 1995). Levels of LH were found to be unchanged in those studies. Hence, the gonadotrophin theory itself suffered a setback (Paskeviciute *et al.*, 2002). Interestingly, there are quite a few studies where FSHR was detected in an abnormal place such as postmenopausal ovarian surface epithelium (OSE) and EOC (Zheng *et al.*, 1996; Parrot *et al.*, 2001; Wang *et al.*, 2003). This has prompted attempts to establish a novel role for NGF in EOC.

The hypothesis

Transmembrane heterotrimeric FSHR couples with guanine nucleotide, activates adenylyl cyclase and may cause growth disorder and neoplasia. So, it seems appropriate to question whether the two phenomena of high FSHR and low serum FSH have a common and important relationship in causation of such cancer. However, alternative intracellular signalling pathways besides or in addition to generation of cAMP have been described following FSHR activation (Babu *et al.*, 2000). In fertility research, new small molecules have been studied, which might supersede existing weakly stimulating doses of FSH to elicit responses equivalent to a maximally effective dose of FSH on follicular stimulation for ovulation and steroidogenesis (Palmer *et al.*, 2005). That is why Fleming (2005) has commented that trying to increase the response of FSH using a converse approach may be too complex and too risk-prone to undertake.

One group trivializes the finding of low FSH in such a situation by concluding that sex hormone or inhibin produces this lowering (Blaakaer *et al.*, 1992; Arslan *et al.*, 2003). However, no study has satisfactorily substantiated this. But a finding like this cannot and should not be ignored, however innocuous it may appear (Bose 2004, 2005). This is because it may herald a deeper cytokine irregularity having a dissociated effect in the endocrine feedback mechanism of the hypothalamic pituitary ovarian axis. NGF with its effect in inducing FSHR and its influence on the central nervous system may be the missing link, and its role is worth investigation. Neurotrophins have already been detected in the hypothalamus and pituitary (Petit *et al.*, 2002). Gibbs (2003) described the decrease in tyrosine kinase A (*Trk A*) mRNA detected in the medial septum of brain as a function of ageing and menopause. Loss of NGF production appeared to be involved in the development and progression in pituitary tumours secreting prolactin (Missale *et al.*, 1999). Sympathetic overactivity of chronic stress (Dorfman *et al.*, 2003) or unknown reasons causing an increase in target-derived (ovarian) or central-derived NGF can induce aberrent FSHR expression in OSE, and can also cause significant lowering of FSH in postmenopausal EOC in the absence of sex hormone. Thus, NGF signalling dysregulates FSHR signalling in the ovary directly, and promotes growth disorder and neoplasia in OSE (**Figure 1**). It is the intermediary in the negative feedback of low sex hormone where low NGF promotes high FSH.

Mechanism of FSHR expression

This expression of FSHR is such a basic mechanism inside the ovary that it can rarely be missed, and its importance cannot be overemphasized. It is in the central position of ovarian activity. So, search for its cause will take a natural ontogenic course in the fetal and neonatal period. It may be described as the begining of expression of a 'responsiveness-to- gonadotrophin' mechanism. It has been shown that, unlike in the adult ovary, gonadotrophin is not the reason for its receptor expression in early fetal and neonatal life, where adrenergic and peptidergic sympathetic nerves come into play. Factors found responsible for such expression are nerve growth factor (NGF), vasoactive intestinal peptide (VIP), catecholamines, cAMP and its analogues, activin, insulin-like growth factor (IGF) and transforming growth factor β (TGF-β). In adult life, FSH itself and all the above

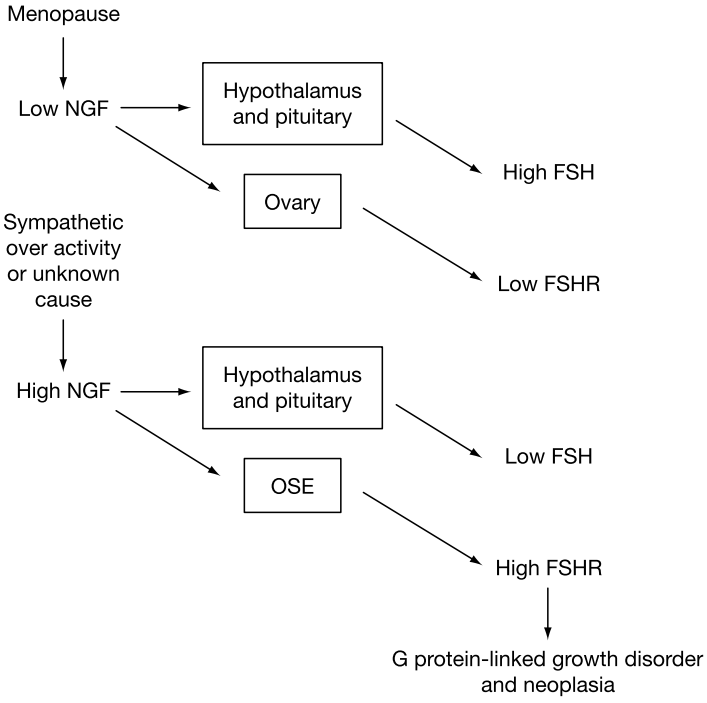

Figure 1. Flow chart of the hypothesis. NGF, nerve growth factor; OSE, ovarian surface epithelium; FSHR, FSH receptor.