Assessment of follicular-fluid neurotrophin levels as predictor for ovarian reserve in women undergoing assisted reproductive technology for different etiologies of infertility

Thesis

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List of Abbreviations

AFC : Antral follicle count

AMH : Antimullarian hormone

ART : Assisted reproduction technology

BDNF : Brain-derived neurotrophic factor

BMI : Body mass index

CBAVD : Congenital bilateral absence of the vas deference

CCCT : Clomphine citrate challenge test

COH : Controlled ovarian hyper stimulation

d-(OPU) : Day of ovum pickup

DG : Dentate gyrus

ET : Embryo transfer

FF- BDNF : Follicular fluid brain derived neurotrophic factor

GAST : GnRHa stimulation test

GNRH : Gonadotropin releasing hormone

HSG : Hystrosalpingogram

ICSI : Intra cytoplasmic sperm injection

IVF : Invitro fertilization

kDa : Kilo dalton

LBR : Live birth rate

MOV : Mean of ovarian volume

MPA : Medroxy progesterone acetate

OHSS : Ovarian hyper stimulation syndrome

ORT : Ovarian reserve test

PCOS : Polycystic ovarian syndrome

RCT : Randomized control trail

TMET : Trans myometrial embryo transfer

TRK : Tyrosin Kinase receptor

TVS : Trans vaginal sonography

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Introduction

Growing evidence indicates that Brain-derived neurotrophic factor (BDNF) is a27-kDa polypeptide that belongs to the neurotrophin family binding with high-affinity protein kinase receptors (Trk) and the unselective p75NGFR receptor. The BDNF gene has a complex structure with multiple regulatory elements and four promoters that are differentially expressed in central or peripheral tissue **(Tapia-Arancibia et al., 2004).**

Neurotrophins are a family of growth factors that are involved in the development of the central and peripheral nervous system **(Levi-Montalcini, 1987).**

Although they were initially thought to be restricted to the nervous system, it now is well known that they affect non-neuronal cells, as cells of the endocrine system **(Yamamoto et al., 1996).**

Brain-derived neurotrophic factor (BDNF), is major member of the neurotrophin family, and together with its receptor, it is found in both rodent and mammalian (including human) ovaries. It has a wide range of functions in the ovary, from support of early survival of germ cells to control of steroidogenesis and extrusion of polar bodies, as well as ovulation **(Seifer et al., 2006).**

Neurotrophins are expressed in human ovaries and strongly suggest that they play a role in folliculogenesis and cytoplasmic competence of oocytes **(Seifer et al., 2006).**

This is further supported by a recent study showing that plasma BDNF levels change during the menstrual cycle and that concentrations fall steadily after menopause **(Begliuomini et al., 2007).**

Follicular fluid BDNF levels are different for each etiological factor of infertility as patients with a history of endometriosis had significantly lower mean levels of follicular fluid BDNF compared with control group (male factor of infertility) **(Erkan Buyuk, 2008).**

Aim of the Work

The aim of this study is to detect of FF neutrophin level in different types of infertility and using it as a predictor for ovarian response.

Brain-derived Neurotrophic Factor (BDNF)

Definition:

Brain-derived neurotrophic factor (BDNF) is a27-kDa polypeptide that belongs to the neurotrophin family binds with high-affinity to protein kinase receptors (Trk) and the unselective p75NGFR receptor. **(Tapia-Arancibia et al., 2004).**

It is well known to play an important role in the survival, differentiation, and outgrowth of select peripheral and central neurons during development and in adulthood **(McAllister et al., 1999; Sohrabji and Lewis, 2006).**

Secretion and storage:

BDNF is present in the human plasma and, since platelets represent a major storage site of BDNF in peripheral blood, serum levels are higher than plasma levels **(Lommatzsch et al., 2005).**

Irrespective of the yet unknown mechanism, there is also accumulating evidence that BDNF serum levels are affected by altered BDNF release or utilization in the central nervous system **(Staats et al., 2005).** As described above neurodegenerative disorders, such as Alzheimer's

and Parkinson's diseases, appear to be associated with decreased levels of BDNF in the brain **(Connor et al., 1997; Parain et al., 1999),** although low serum levels of BDNF are thought to characterize major depression **(Karege et al., 2002),** schizophrenia **(Toyooka et al., 2002)** and eating disorders, such as bulimia and anorexia nervosa **(Nakazato et al., 2003; Monteleone et al., 2005).**

Function:

Brain-derived neurotrophic factor (BDNF) modulates hippocampal plasticity, hippocampal-dependent memory and has been suggested to be involved in the pathophysiology of different mental disorders **(Tan et al., 2005).**

BDNF has also been shown to play an important role in activity-dependent synaptic plasticity in the hippocampus **(Kang and Schuman, 1995; Korte et al., 1995)** where, as in the dentate gyrus (DG) **(Messaoudi et al., 1998),** it is known to produce a lasting potentiation of synaptic efficacy probably involving calcium-induced calcium release (CICR) **(Balkowiec and Katz, 2002; Kramar et al., 2004).** Moreover, BDNF enhances glutamatergic synaptic transmission in hippocampal cultures through a presynaptic mechanism **(Li et al., 1998).**

It is possible that these effects may, in turn, enhance specific learning and memory processes and help reduce cognitive deficits associated with aging and neurodegenerative disease **(Gibbs, 1999).** In fact, recent findings show that cellular events involved in memory encoding initiate BDNF signaling through synaptic TrkB, thereby ensuring that learning will trigger neurotrophic support **(Musumeci and Minichiello, 2011).**

Mechanism of action:

Recent studies revealed an important role of BDNF in the regulation of glutamatergic synapses and glutamate receptor activity **(Carvalho et al., 2008),** which may represent one important link between BDNF and hippocampal function. Glutamate receptor function is essential for memory functions, and the hippocampal pyramidal layers are densely packed with glutamate-containing excitatory neurons. These neurons are involved in the induction of long-term potentiation (LTP) and long-term depression (LTD), which are the cellular and molecular mechanisms underlying memory **(Tamminga et al., 2010).**

Role of BDNF in CNS:

BDNF expression in the central nervous system (CNS) is modified by various kinds of brain insult (stress, ischemia, seizure activity, hypoglycemia, etc.) **(Lindvall et al., 1994)** and alterations in its expression may contribute to some pathologies such as depression, Alzheimer's, and Parkinson's disease **(Connor et al., 1997; Parain et al., 1999; Karege et al., 2002).**

Recent studies also suggest that BDNF is a biomarker of impaired memory and general cognitive function in aging women **(Komulainen et al., 2008).**

Several authors have attributed various problems in health and wellbeing to the impaired adaptation of individuals to their environment, as a consequence of a dysfunctional hypothalamic–pituitary–adrenal (HPA) axis (the major pathway for regulating stress responses) and its cortisol production **(Corbett et al., 2009).** On the other hand, it has been shown in some experimental studies that BDNF regulates the HPA response to stress **(Angelucci et al., 2005; Duman and Monteggia, 2006).**

Relation of BDNF and different hormons:

ESTROGENS AND BDNF

In vitro studies, estrogens have multiple functions in the brain. Some reports suggest the involvement of BDNF in modulating estrogen actions **(Scharfman and MacLusky, 2006). Sohrabji et al. (1995),** showed that estrogen could regulate the expression of BDNF via the estrogen response element on the BDNF gene **(Murphy et al., 1998).**

In vivo studies it has been reported that 28 weeks after ovariectomy in rats, BDNF mRNA levels are significantly reduced in almost all hippocampal layers and the cortex **(Singh et al., 1995).** Estradiol replacement essentially reversed this effect in the hippocampus, suggesting a regional divergence in ovarian steroid requirements for BDNF expression. In addition, it has been reported that the levels of BDNF mRNA fluctuated significantly during the estrous cycle in CA1, CA3, and CA4 areas of the hippocampus. The highest levels were detected on the morning of diestrus 2, when progesterone levels are relatively low, and the lowest levels were detected on the afternoon of pro-estrus, when progesterone levels were highest **(Gibbs, 1998).**