INTRODUCTION

Bipolar disorder (BD) is a major health concern, with life time prevalence in the United States estimated to be as high as 16.2%. Furthermore, the World Health Organization states that major depressive disorders (MDD) is the second largest global health burden ***(Kessler et al., 2005).***

Although a number of pharmacological agents are available to treat depression, approximately 30–40% of patients do not respond to them and in those who do benefit there is a delayed onset of action. Therefore, a major emphasis in modern psychiatric research is to uncover the underlying etiology of mood disorders, and to develop novel efficacious antidepressant treatments ***(Matthews et al., 2005).***

Neuropeptides, which have discrete synthesis and receptor sites, have emerged as viable research candidates, with respect to both the pathophysiology and treatment MDD ***(Holsboer et al., 2008).***

Originally considered as a "maternal hormone" based on its role in the regulation of reproductive functions and maternal behavior, oxytocin is mainly synthesized in magnocellular neurons of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei and is secreted into the periphery *via* the posterior pituitary where it mediates effects on uterine contractions, milk ejection in lactation and cardiovascular control ***(Neumann et al., 2006).***

Recent evidence has implicated oxytocin in numerous complex behaviors, particularly anxiolysis, oxytocin may be of therapeutic benefit in these patients, as well as those with only anxiety ***(Kennedy et al., 2008).***

Oxytocin inhibits stress-induced activity in the hypothalamic-pituitary axis in rats, and plays an important role in the response to stress through its close association with corticotrophin-releasing factor. Some studies supported the finding of lower plasma oxytocin levels in patients with major depressive disorders ***(Neumann et al., 2006).***

Oxytocin and its receptors appear to hold the leading position among the neurotransmitters having a role in "happiness." If not "happiness," at least it seems to be an important brain compound in building trust, which is necessary in developing emotional relationships, a process also referred to as social bonding ***(Rotzinger et al., 2010).***

AIM OF THE WORK

To assess a possible role for serum oxytocin in affective disorders, depression and mania.

OXYTOCIN

Oxytocin is a nonapeptide, which can be found in most bony vertebrate species and exhibits in its structure, as well as in the locations of main cell groups in the brain ***(Murphy et al., 2008).***

Although oxytocin has an established role as a circulating hormone involved in parturition and lactation, it can also act as a neurotransmitter and neuromodulator by interacting with the central oxytocin receptors within the brain ***(Murphy et al., 2008).***

Oxytocin can be found in brain regions that are involved in social emotions and social reward such as amygdala and the tegmental area. Accumulating evidence indicate that oxytocin is a key mediator of complex emotional and social behaviors, including attachment, social recognition, and aggression in humans. Several studies have found associations between oxytocin and neuropsychiatric disorders such as depression and autism ***(Kirsch et al., 2005).***

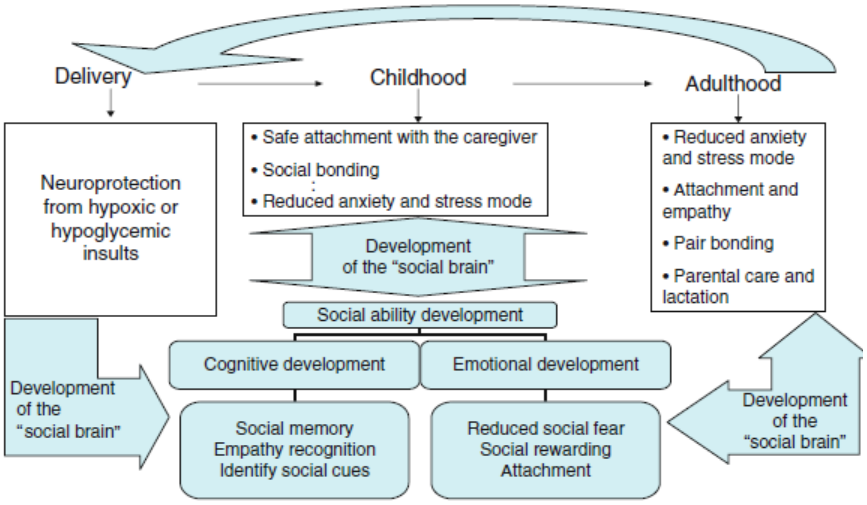

Figure (1): Possible roles of oxytocin during different periods of life ***(Kirsch et al., 2005).***

1. Biochemistry:

All neurohypophysial hormones are nonapeptides with a disulfide bridge between cysteine residues 1 and 6. This results in a peptide constituting a six-amino acid cyclic part and a COOH-terminal a-amidated three-residue tail. These peptides are classified into vasopressin and oxytocin families based on the amino acid at position 8 ***(Goodson et al., 2008).***

The vasopressin family contains a basic amino acid and the oxytocin family contains a neutral amino acid at this position ***(Goodson et al., 2008).***

In all vertebrates, the arginine vasopressin-like and oxytocin-like peptides are produced by populations of magnocellular and parvocellular neurons located in the preoptic

area and anterior hypothalamus. These cell groups project to the neurohypophysis as well as to the adenohypophysis, allowing the nonapeptides to exert a wide range of peripheral effects. Some of these effects are actions that may be integrated with the central regulation of social behaviors ***(Goodson et al., 2008).***

2. Genes, Receptor Structure and Physiology

In all species, oxytocin and vasopressin genes are located on the same chromosomal locus but are transcribed in opposite directions. The intergenic distance between these genes ranges from 3 to 12 kb in different species ***(Henry et al., 2008).***

The human gene for oxytocin-neurophysin I encoding the oxytocin prepropeptide is mapped to chromosome 20p13 and consists of three exons ***(Henry et al., 2008).***

As noted earlier, oxytocin is synthesized primarily in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. Following its synthesis, oxytocin is transported mainly along the neuronal axons to the posterior pituitary lobe, where it is stored until its secretion in neuronal terminals. Later, oxytocin is released to regulate parturition and lactation. Oxytocin is also released in brain structures that are relevant to emotions and social interaction ***(Young et al., 2009).***

In rodents, oxytocin receptors are found in the olfactory bulb, which is related to social cognition, in the central and lateral amygdala which are related to social stress and in the nucleus accumbens which is related to social reward ***(Insel et al., 2007).***

In humans, expression is prominent in the basal nucleus of Meynert, the nucleus of the vertical limb of the diagonal band of Broca, the ventral part of the lateral septal nucleus, the preoptic anterior hypothalamic area, the posterior hypothalamic area, the substantia nigra pars compacta, the substantia gelatinosae of the caudal spinal trigeminal nucleus and of the dorsal horn of the upper spinal cord, as well as in the medio-dorsal region of the nucleus of the solitary tract ***(Leng et al., 2008).***

Mechanism of action of oxytocin

Activation of oxytocin neurones after stressful stimuli, food intake and social stimuli Oxytocin is primarily synthesised in the paraventricular or supraoptic nucleus of the hypothalamus and released from the neurohypophysis into the general circulation, and it plays essential roles in parturition and lactation. In addition, parvocellular oxytocin neurons project to various brain areas, including the nucleus of the solitary tract, dorsal motor nucleus of the vagus, the ventromedial hypothalamus, medial preoptic areas, ventral tegmental area, nucleus accumbens and bed nucleus of the stria terminalis ***(Takayanagi et al., 2008).***

Oxytocin is released not only from axon terminals in these brain areas, but also from dendrites or cell bodies, resulting in both local and remote actions after diffusion to various brain regions where the oxytocin receptor is expressed. Oxytocin has been implicated in the control of stress responses,

analgesia, energy metabolism and social behaviours, including the recognition of conspecifics, mother–infant attachment, sexual behaviour, pair-bonding and inter-male social behaviour. The present review focuses on the roles of oxytocin in the control of stress, energy metabolism and social recognition ***(Takayanagi et al., 2008).***

- **Activation of oxytocin after food intake:**

Oxytocin neurones in the hypothalamus are also activated after food intake. Food intake induces gastric distension, the release of a peripheral satiety signal, cholecystokinin octapeptide (CCK) and possibly an increase in plasma osmolality, and these factors are known to increase plasma oxytocin concentrations in rats ***(Fanneli et al., 2009).***

In humans, the intake of a fatty meal or CCK administration has been shown to facilitate oxytocin release ***(Lee et al., 2009).***

- **Activation after social stimuli**

Oxytocin neurones in the hypothalamus have been suggested to be activated after social interactions, including parent–infant bonding, pair-bonding, oxytocin concentrations in cerebrospinal fluid or plasma are positively correlated with social behaviour in monkeys. Social interactions are also associated with the oxytocin system in humans. Plasma oxytocin concentrations have been shown to be associated with

parental behaviours in humans. Plasma oxytocin concentrations increase after performing a task requiring intimate trust (i.e. secret sharing by writing an important secret of their life with each other) in humans. Interactions with pet dogs also facilitates oxytocin release from the posterior pituitary in the dog owners ***(Groppe et al., 2013).***

Synthesis, storage, release, and metabolism

The oxytocin peptide is synthesized as an inactive precursor protein from the *OXT* gene. This precursor protein also includes the oxytocin carrier protein neurophysin I. The inactive precursor protein is progressively hydrolyzed into smaller fragments (one of which is neurophysin I) via a series of enzymes. The last hydrolysis that releases the active oxytocin nonapeptide is catalyzed by peptidylglycine alpha-amidating monooxygenase (PAM) ***(Sheldrick et al., 2008).***

The activity of the PAM enzyme system is dependent upon vitamin C (ascorbate), which is a necessary vitamin cofactor. By chance, sodium ascorbate by itself was found to stimulate the production of oxytocin from ovarian tissue over a range of concentrations in a dose-dependent manner Many of the same tissues (e.g. ovaries, testes, eyes, adrenals, placenta, thymus, pancreas) where PAM (and oxytocin by default) is found are also known to store higher concentrations of vitamin C ***(Hornig et al., 2005).***

Oxytocin is known to be metabolized by the oxytocinase, leucyl/cystinyl aminopeptidase. Other oxytocinases are also known to exist. Amastatin, bestatin (ubenimex), leupeptin, and puromycin have been found to inhibit the enzymatic degradation of oxytocin, though they also inhibit the degradation of various other peptides, such as vasopressin, met-enkephalin, and dynorphin A ***(Mizutani et al., 2006).***

- **Physiological roles of oxytocin:**

1. Anti-stress and anxiolytic actions of oxytocin

Stressful stimuli disturb homeostasis of the body physically and psychologically. In response to stressful stimuli, various responses take place in the body and the roles of the stress responses can be categorised into at least two categories: one is suppressive and keeps other stress responses from overshooting, whereas the other is stimulatory and facilitates other stress responses. Oxytocin released in response to stressful stimuli might represent the former ***(Morsette et al., 2008).***

2. Roles in adaptation to chronic stress

Animal studies have also shown that oxytocin plays an essential role in adaptation to chronic repeated stress. Acute restraint stress delays gastric empty and accelerates colonic transit. This acute stress-induced gastrointestinal dysmotility is no longer observed after chronic repeated exposures to stressful stimuli. This restored motility after chronic stress is reversed by an intracerebroventricular injection of an oxytocin receptor antagonist or by oxytocin deficiency ***(Bakerseville et al., 2010).***

- **Targets for anti-stress or anxiolytic actions:**

Sites of anxiolytic actions of oxytocin remain to be determined, although several sites have been proposed, including the median raphe nuclei, central amygdala, hypothalamic PVN, lateral septum and dorsal hippocampus. Approximately half of the serotoninergic neurones in the pontine raphe nucleus express oxytocin receptors, and local oxytocin administration facilitates serotonin release ***(Budden et al., 2014)***. Anxiolytic actions of oxytocin are impaired by a serotonin 2A / 2C receptor antagonist, suggesting that oxytocin reduces anxiety via facilitating serotonin release ***(Lee et al., 2005).***

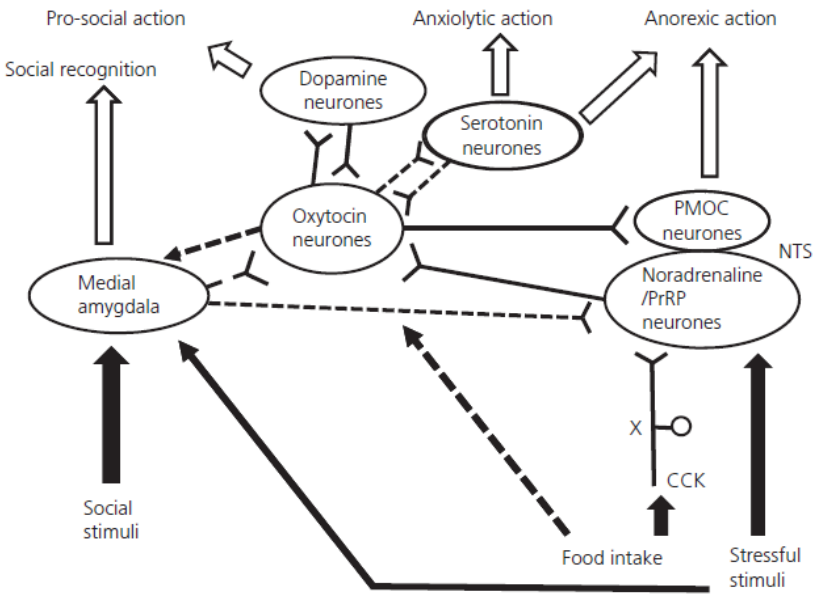

Figure (2): Action of oxytocin on different neurons ***(Lee et al., 2005).***

3. Role in food intake:

Oxytocin has anorexic actions via the activation of oxytocin receptors. Consistent with the data, patients with Prader–Willi syndrome, a condition characterised by deficits in oxytocin neurones, show hyperphagia and obesity ***(Simmons et al., 2005).***

4. Roles in food preference:

The roles of endogenous oxytocin in food intake have been shown to depend on dietary macronutrients (carbohydrates, lipids and proteins) A sucrose-enriched diet induces the activation of oxytocin neurons and increases oxytocin mRNA compared to the effects of a high-fat diet. The administration of an oxytocin receptor antagonist increases the intake of sucrose but not that of standard chow, high-fat diet or total calories in mice ***(Simmons et al., 2005)***. Oxytocin-deficient mice show an increased preference for carbohydrates such as sucrose,starch and polycose. All of these findings suggest that oxytocin plays an important role in the control of carbohydrate intake ***(Slattery et al., 2008).***

5. Roles in energy consumption:

Oxytocin is also involved in energy consumption. Oxytocin administration induces hyperthermia, and oxytocin receptor-deficient animals showed a reduced response in energy consumption after reduced energy consumption might contribute to the late-onset obesity observed in oxytocin-deficient or oxytocin receptor-deficient mice ***(Thind et al., 2005).***

6. Role in parturition:

Oxytocin and the oxytocin receptor have two important roles in labour. Evidence in all mammalian species suggests that neurohypophysial oxytocin plays a role in the expulsive phase. Data supporting a role for oxytocin in the initiation of labour is less established but remains likely ***(Challis et al., 2008).***

The effects of oxytocin are therefore mediated by tissue specific oxytocin receptor expression, which leads to direct contractile effects in myometrium and prostaglandin formation in the decidua. There is a dramatic increase in oxytocin receptor expression in these tissues in late pregnancy and pharmacological inhibition delays delivery, which suggests that, in contrast to oxytocin, the oxytocin receptor may be essential for normal labour ***(Fuchs et al., 2008).***

7. Role in Milk ejection:

Stimulation of Oxytocin receptors produces an increase in contractions of the myoepithelial cells that are localized on the surface of the alveoli and along the ducts of the mammary gland. When the myoepithelial cells on the alveoli contract, their compression increases intra-alveolar pressure. Contraction of the myoepithelial cells on the ducts results in duct shortening and widening, reducing resistance to the passage of milk ***(Caldwell et al., 2009).***

An important factor in the response of the breast to oxytocin in the post-partum period is a 100-fold increase in the mammary receptors for oxytocin at this time, but unlike the increase in uterine receptors which occurs ante-partum, that of the breast does not appear to be under the influence of oestrogen ***(Richard et al., 2011).***

The human oxytocin response to suckling is not simply confined to stimulation of the nipple, and conditioned reflexes also are superimposed. Thus, ***Mecker et al. (2008)*** found that oxytocin release occurred in many women before the tactile stimulus of suckling was applied and was related to such factors as the baby crying. On the other hand it has long been known that certain stresses such as fear can inhibit milk ejection in women ***(Love et al., 2013)***.

It is considered that most of the stress-induced inhibition of milk ejection is due to central reduction in oxytocin concentrations and, certainly, there is experimental evidence in primates that behavioural stress will inhibit oxytocin release ***(Kenderick et al., 2007)***.

8. Hypophysiotrophic actions of oxytocin

- **ACTH secretion** It is now well recognized that arginine vasopressin stimulates the release of ACTH both in vitro ***(Qiao et al., 2001)*** and in vivo ***(Rivera et al., 2009)*** so that vasopressin is regarded as an important cofactor in the

regulation of ACTH secretion. The hypophysiotrophic action of oxytocin is, however, less well established. Anatomically, there is co-localization of oxytocin and CRH within the perikarya of the paraventricular nucleus of the rat ***(Sams et al., 2007)***, and nerve fibres from this nucleus containing oxytocin have been identified in the external lamina of the median eminence ***(Wuarin et al., 2009)***.

Of particular importance is the finding of very large amounts of oxytocin in the hypophyseal portal blood of the rat and of the rhesus monkey, where the concentration is over 2000 pmol/l. Moreover, high affinity receptors for oxytocin have been identified in the anterior pituitary of the rat ***(Ulas et al., 2008).***

It has been shown that, in vitro, oxytocin enhances the release of ACTH from dispersed rat anterior pituitary cells in a dose dependent manner, although it is less potent than vasopressin ***(Sams et al., 2007).***

- **Prolactin secretion** In experimental animals both oxytocin and prolactin are released during suckling and this has raised the possibility that oxytocin is involved in the regulation of prolactin secretion. In the rat, oxytocin stimulated the release of prolactin both in vitro and in vivo using concentrations similar to those present in hypophyseal portal blood ***(Westhoff et al., 2008).***