

## Review Article

# The multifarious oxytocin: a review

Arpita Kapur<sup>1\*</sup>, Vinay Kapur<sup>2</sup>

<sup>1</sup>Department of Anaesthesiology, Civil Hospital, Panchkula, Haryana, India

<sup>2</sup>Department of Medicine, HS Judge Institute of Dental Sciences, Panjab University, Chandigarh, India

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### \*Correspondence:

Dr. Arpita Kapur,

E-mail: [kapur.arpita@gmail.com](mailto:kapur.arpita@gmail.com)

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### ABSTRACT

Oxytocin over centuries has always been regarded as the drug of paramount importance during childbirth. Oxytocin, a peptide hormone facilitates parturition and breastfeeding. These nine amino acid peptides have presently been found to be associated with a wide variety of pathophysiological functions associated with social behaviours. It has been recently recognised as an important modulator of human social behaviour. Its correlation as a common factor important in various neuropsychiatric disorders such as schizophrenia, personality disorders and autism, mood and anxiety disorders has been highlighted. Anticipatory role of oxytocin in osteoporosis, diabetes and cancer has been coaxing the researchers for developing new therapeutic modalities. Over a course of past 100 years, oxytocin has come a long way from being an insipid agent used as an aid in labour and delivery to the drug of neuropsychiatric conditions. This review article summarises the varied functions of oxytocin, its apt dosing when used therapeutically and reinforcement of development of new lines of treatment involving the use of oxytocin and antagonists for multiple human disorders.

**Keywords:** Autism, labour, Oxytocin, Post-partum haemorrhage, Schizophrenia

### INTRODUCTION

Oxytocin is a naturally occurring peptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. Part of it is transported as secretory granules to the posterior pituitary gland for subsequent release into the bloodstream to reach the peripheral targets and the rest is directly spread into other brain areas as a neurotransmitter.<sup>1</sup> Human studies confirm the role of oxytocin as a social hormone in addition to its importance in parturition, milk let down and maternal bonding.<sup>2,3</sup> Oxytocin decreases anxiety and cortisol release in response to social stress, reduces amygdala activity to frightening and threatening visual images or emotional faces.<sup>4,5</sup> Oxytocin exhibits very weak

antidiuretic properties which mandates its infusion in an isotonic solution.<sup>6</sup> Pharmacokinetics of oxytocin reveals its inactivation by enzyme chymotrypsin in gastrointestinal tract which emphasizes on its administration via intravenous, intramuscular or transmucosal route via nasal spray. Onset of action of intravenous oxytocin is 1-2 minutes with a half-life of approximately 15 minutes.<sup>7</sup> When given intramuscularly, onset is 2-4 minutes and action last for 30-60 minutes.<sup>8</sup> Frequent dosing and a chance of crossing the blood brain barrier is enabled by intranasal route of administration.<sup>9</sup> In this review article, authors shall follow the whole course of long journey of oxytocin from its origin to present day status and take a cursory look into its unfolding prospective.

### Oxytocin in augmentation of labour

Oxytocin is the most extensively used uterotonic drug for augmenting labour or to maintain uterine contractility during labour.<sup>10</sup> The process of stimulating the uterus to increase the frequency, duration and intensity of contractions after the onset of spontaneous labour is known as augmentation of labour. Oxytocin has been commonly used as a method to augment delayed labour when poor uterine contractions are assessed to be the underlying cause. Uterine motility depends on the formation of the contractile protein actomyosin in the presence of myosin light chain kinase; the  $\text{Ca}^{2+}$  dependent phosphorylating enzyme. Oxytocin by binding with oxytocin receptor promotes contractions by increasing the intracellular  $\text{Ca}^{2+}$  which in turn activates myosin light chain kinase. Oxytocin acts on specific receptors in the muscle lining of the uterus and the concentration of these receptors increases tremendously during pregnancy, reaching peak in early labour at term.<sup>11</sup> Studies have shown that obese women are more likely to have prolonged labour resulting in larger, more frequent applications of both synthetic oxytocin and cervical ripening methods.<sup>12</sup> Effects of oxytocin on labour induction also appear to be blunted by obesity. In a study conducted by Carlson NS et al, it was shown that obese parturients with higher BMI had significantly higher mean oxytocin infusion rates when compared to obese women with lower BMI while both were spontaneously labouring healthy, nulliparous without pre labour rupture of membrane.<sup>13</sup> Around 70% of obese parturients exhibit metabolic dysregulation with changes in circulating hormones from adipose tissues like leptin, apelin, visfatin, ghrelin, adiponectin and free fatty acids. Obesity therefore results in altered physiology which results in oxytocin regulation and response. All these factors may affect the myometrial contractility, and the variation in expression and function of the oxytocin receptors present in human myometrium caused by increased BMI.<sup>14,15</sup> Selin L et al, found no advantages for routine use of high dose ( $>6$  mIU/min) oxytocin in the augmentation of labour.<sup>16</sup> Low dose (3.3 mIU/min) oxytocin regimen is recommended to avoid unnecessary cardiovascular events of tachysystole and fetal distress. To induce labour, oxytocin doses in the range of 1-6 mIU/min are widely used. This is equivalent to approximately 0.3 IU per hour.

### Oxytocin in third stage of labour in normal vaginal delivery

Post-partum haemorrhage (PPH) still remains as a major global cause of maternal morbidity and mortality. Since, PPH occurs suddenly in low risk pregnancies also, both prophylactic and therapeutic approaches are essential for minimizing blood loss and preventing PPH in all parturients at delivery.<sup>17</sup> The active management of third stage of labour (AMTSL) comprises of prophylactic administration of a uterotonic agent prior to placental separation, early cord clamping and traction and uterine massage. Since uterine atony is responsible for more than

80% of PPH cases, the administration of a uterotonic agent seems to be a mandatory component of AMTSL to prevent PPH.<sup>17</sup>

The third stage of labour is facilitated by the use of oxytocin which thus decreases the risk of post-partum haemorrhage. Guidelines recommend administration of intramuscular oxytocin 10 IU to mother and controlled cord traction after vaginal delivery during the third stage of labour. This has reduced the incidence of PPH significantly.<sup>18</sup>

Through intravenous route, oxytocin 5 IU diluted to 5 ml in normal saline can be given slowly over 1-2 minutes to achieve the uterotonic effect. Nipple stimulation or breast feeding as early as possible has been postulated to be a stimulus for release of oxytocin and consequent uterine contractions. The uterine contractions reduce bleeding during third stage of labour.<sup>19</sup> The same has been recommended by FOGSI (The Federation of Obstetric and Gynaecological Societies of India) as a possible adjuvant method for physiological prevention of PPH. However, more studies with adequate sample sizes are required to be undertaken to assess the impact of nipple stimulation in comparison to uterotonic agents like oxytocin.

Thus, routine prophylactic administration of oxytocin as a component of AMTSL reduces blood loss and incidence of PPH without much increase in the incidence of adverse effect.<sup>20</sup>

### Oxytocin during caesarean section

Oxytocin is administered to the parturient intravenously during caesarean section to significantly reduce the incidence of post-partum haemorrhage. Two categories of parturients land up in caesarean section. First category includes the elective caesarean section in which the patient is not in labour and has not received any prior oxytocin. Second category includes the labouring patients being taken up for caesarean section. Labouring patients in whom oxytocin is administered there is down regulation of receptors and therefore decreased responsiveness of uterine oxytocin receptors results in higher oxytocin requirement.<sup>21</sup> While evaluating the risk/benefit of prophylactic oxytocin, one must be aware of its adverse effects which could be myocardial ischaemia, hypotension, increased cardiac output, tachycardia, flushing, nausea, vomiting and mild antidiuretic effect. Haemodynamic effects of oxytocin can be minimized by slow intravenous injection of oxytocin. Fast injection of oxytocin results in greater increase in heart rate and decrease in mean arterial pressure with no difference in blood loss at a dose of 5 IU.<sup>22</sup> Recent trials have shown that doses of oxytocin below the commonly used 5 IU are equally effective and associated with fewer complications. A dose of 0.3-1 IU oxytocin given slowly over 1 minute, followed by an infusion of 5-10 IU/hour for 4 hours represents an

evidence based approach for women at relatively lower risk of post-partum haemorrhage at elective caesarean section.<sup>23</sup> In case of caesarean section in labouring parturient, a slow 3 IU bolus of oxytocin followed by an infusion of 5-10 IU/hour for 4 hours is supported by limited evidence.<sup>23</sup> Many anaesthesiologists avoid repeated bolus administration of oxytocin due to oxytocin receptor desensitization in labouring parturients thus preferring the use of second line uterotonic protocols.<sup>24</sup>

### Oxytocin in breastfeeding

As soon as the baby sucks at the breast, sensory impulses are transmitted from nipple to the mother's brain. As a result, the anterior and posterior lobes of the pituitary secrete prolactin and oxytocin respectively. Prolactin is responsible for the milk secretion by the cells of the alveoli. The milk collected in the alveoli then flows into the ducts.<sup>25</sup> At times milk is ejected in fine streams. This is known as "let down reflex" or the "milk ejection reflex" or oxytocin reflex. Oxytocin reflex becomes conditioned to the mother's emotions and sensations like sight, smell or touch of her baby. Baby should therefore be kept in skin to skin contact with the mother. Oxytocin induces a state of calmness and reduces stress.<sup>26</sup> Skin to skin contact helps both breastfeeding and emotional bonding.<sup>27</sup> Many women stop expressing milk earlier in post-natal period because they get disheartened by their apparently poor milk production. This may correlate more to inadequate production of oxytocin than of prolactin. Oxytocin secretion being sensitive to psychological stimuli is easily inhibited by stress. Oxytocin production is stimulated by various sensory stimuli from the infant which are missing in case of mother expressing milk in neonatal unit for her preterm neonate. A study of nasal oxytocin in such mothers reported a dramatic effect of oxytocin on milk production in primigravid mothers.<sup>28</sup> Intranasal oxytocin has been shown to benefit women with quadriplegia who have lost the neuronal connection between hypothalamus and nipple.<sup>29</sup> Numerous studies suggest that oxytocin given during labour has a negative effect on breastfeeding, possibly it reduces sucking behaviour in the newborns in a dose dependent manner.<sup>30</sup>

### Oxytocin as love hormone

Reproductive endocrinologists have found that the oxytocin is not just the hormone of labour, it is the love hormone too. Oxytocin's role in social recognition, bonding and orgasm has also been investigated. Social bonding is responsible for survival of species as it favours reproduction and imparts safety against predators and environmental variations and enhances further brain development.<sup>31</sup> Lack of socialization results in various physical and mental disorders. Oxytocin and its receptors are important for "happiness" and building trust. It is an important brain substance for building trust and development of emotional relationships and thus social bonding. Moreover, oxytocin has been shown to be

involved in a plethora of social and affective disorders, physiological and pathophysiological behaviours including attachment security, paternal behaviour, mating and motherhood to autism and obsessive-compulsive disorder.<sup>32</sup> Plasma oxytocin levels have been found to be higher amongst individuals who admit being in love. Oxytocin increases sexual receptivity and can counteract impotence and can be expected to have an important role in treatment for male infertility in days to come. The erectile tissues i.e. corpus cavernosum and corpus spongiosum are one of the main peripheral targets of oxytocin. It is thought to be associated with ejaculation by the contraction of ejaculatory tissues namely bladder neck, prostatic urethra, and ejaculatory duct.<sup>33</sup> Studies have found increases in plasma oxytocin at orgasm in both males and females.<sup>34</sup> The maternal behaviour is specifically because of oxytocin. Virgin female sheep infused with oxytocin in cerebrospinal fluid shows maternal behaviour towards foreign lambs.<sup>35</sup>

### Oxytocin and autism spectrum disorders (ASD)

Autism spectrum disorder (ASD) is a neuro-developmental disorder whose primary symptoms include deficits in social interaction and communication along with restricted and repetitive behaviours. Prevalence of ASD is 1 in 100 at present, still no medication has been established for treatment of its symptoms. Modahl C et al, found that children with autism have lower plasma oxytocin levels in comparison to healthy controls of the same age group.<sup>36</sup> A defect in peptide processing of oxytocin was shown in a follow up study of autistic individuals with decreased plasma oxytocin associated with increased extended peptide inactive forms of oxytocin derived from the same prohormone.<sup>37</sup> Therefore, exogenous oxytocin administration has been suggested to be effective in reversing social and communicative dysfunction in individuals with ASD. Guastella A et al, carried out a study with finding that typically developed male adults who were administered 24 IU of oxytocin gazed more frequently and longer at the eye region.<sup>38</sup> Oxytocin might facilitate interpersonal communication by improving eye contact as eye contact is critical for the same. Various behavioural studies undertaken suggest that oxytocin improves wide variety of social behaviours including facial or vocal recognition of emotion, gazing at the eyes, and trust in another person, this facilitates socially acceptable behaviour while reducing repetitive behaviour.<sup>39</sup> Various neuroimaging studies taken up to elucidate the mechanism of benefits of oxytocin administration on ASD individuals found significant changes in brain activation by oxytocin administration resulting in behavioural improvement. Domes G et al, studied the effect of 24 IU oxytocin on neural response in house and face matching tasks, followed by magnetic resonance screening.<sup>40</sup> They found that amygdale activation was significantly increased in ASD individuals. However, in typically developed individuals, oxytocin administration reduced activation of amygdala. Based on these, it was concluded that oxytocin reduced

responsiveness of amygdala when suppressing fear and stress in normal individuals, while increased its responsiveness for face/place recognition in individuals with ASD. Oxytocin seems to be a promising agent that needs to be explored to detect changes in well validated measures of social perception, social cognition and repetitive behaviours.

### Oxytocin and schizophrenia

Schizophrenia is a heterogeneous, debilitating, neuropsychiatric disorder characterized by positive and negative symptoms and cognitive deficits. The currently available antipsychotic drugs provide significant relief from the positive symptoms like auditory and visual hallucinations, delusions, dis-organized behaviour or speech with little therapeutic effects on the negative symptoms and cognitive deficits resulting in poor prognosis. Recently, studies have shown that stimulation of oxytocin system might produce therapeutic effects on all the symptom domains of schizophrenia. Many studies have found an inverse relationship between the degree of negative symptoms (avolition, anhedonia, asociality, alogia) and levels of plasma oxytocin and oxytocin levels in cerebrospinal fluid.<sup>41</sup> Studies have shown, the booming ability of oxytocin to enhance trust towards strangers provides a possible mechanism for its therapeutic role in paranoid delusions (positive symptoms). Cacciotti-Saija C et al, reported that addition of twice daily intranasal oxytocin administration to six weeks of social cognitive training in patients with early psychosis showed a positive correlation with reduction of negative symptoms (scale for assessment of negative symptoms) and cognitive deficits.<sup>42</sup> Therapeutic effects of oxytocin can provide a ray of hope to patients of schizophrenia and their families that oxytocin may provide relief especially from the debilitating negative symptoms and cognitive deficits. This will probably in near future allow the schizophrenics to lead more fulfilling lives.

### Oxytocin and affective disorders

Affective psychiatric disorders have a substantial comorbidity existing between major depressive disorders (MDD) and anxiety. Major depressive disorder is characterized by depressed mood, anhedonia (loss of interest or pleasure in previously rewarding stimuli), sleep disturbances, anxiety and sexual dysfunction. Oxytocin has now been implicated in a plethora of behaviours and neurochemical processes. The actions of oxytocin are mediated through oxytocin receptor which is a G protein-coupled receptor coupled to phospholipase C. This receptor is extensively distributed in the central nervous system.<sup>43</sup> Recent evidence has shown role of oxytocin in complex behaviours particularly anxiolysis.<sup>44</sup> Oxytocin may be of benefit in patients of MDD with comorbid anxiety or those with anxiety only. Anxiolytic action of oxytocin may be mediated through 5HT receptor activation. Early life stress has been found to result in increased anxiety and depression related

behaviours and the severity of the response to stress exposure in adulthood. Adverse early life experiences result in altered activity of the brain oxytocin system in adulthood, also its receptors and thus increase the possibility of developing mental disorders later in life. In support of this, oxytocin has been shown to increase the sense of attachment security in adult males who suffer from insecure attachment patterns, which are usually the result of adverse early life experiences and can also result in the development of MDD.<sup>45</sup> Oxytocin knockout mice have altered social interactions, which can be reversed by intra medial amygdala oxytocin infusion.<sup>46</sup> This study findings suggested that oxytocin may be important for both the development of social withdrawal/anxiety in MDD and that exogenous oxytocin may be of therapeutic benefit in MDD patients with low attachment security. A possible mechanism of action of oxytocin in treatment of MDD is due to its interaction with serotonergic system, 5HT1A and 2A specific agonists have been shown to dose dependently increase plasma oxytocin levels. SSRI treatment leads to loss of libido and anorgasmia resulting in poor compliance. Sexual stimulation in males and females causes an increase in plasma oxytocin levels. Thus, combining oxytocin with SSRI treatment may help to reduce the concurrence of sexual dysfunction caused by former and therefore improve compliance to antidepressant treatment.

The potential of its synergistic actions and multiple interactions with other neurotransmitters and neuropeptide systems determine the importance of oxytocin for the fine-tuned balance of emotionality, stress coping and complex social interactions, that shape our personality and mental wellbeing.

### Oxytocin and osteoporosis

Oxytocin has a peripheral, direct and significant action on the skeleton through its stimulation of osteoblast formation and modulation of osteoclast formation.<sup>47</sup> The last phase of pregnancy and lactation correspond to most of the fetal and postnatal bone growth because of which mother is likely to lose ~120 g of calcium from her own skeleton. Hormonal adaptations comprising of low estrogen and elevated parathormone levels facilitate maternal hyper resorption of bones and inter-generational calcium transfer.<sup>48</sup> However, shortly after this profound bone loss, the mother's skeleton is rapidly repleted else pregnancy and lactation related osteoporosis would occur. Oxytocin has been shown to maintain an increased cell activity in bone, stimulating the proliferation of both forming and resorbing cells with well controlled the amount of bone resorption. The complimentary genetic and pharmacologic approaches reveal oxytocin as new anabolic regulator of bone mass and might have utility in treatment for human osteoporosis.<sup>49</sup> Bone loss due to bone resorption is accompanied by increased bone marrow adiposity since osteoblasts and adipocytes share the same precursor cells since an inverse relationship has been shown to exist between the two lineages. Both



oxytocin and carbetocin (an oxytocin analogue) negatively modulate adipogenesis while promoting osteogenesis in both human multipotent adipose-derived stem (hMADS) cells and human bone marrow mesenchymal stromal cells. Clinically, lower plasma oxytocin levels were seen in postmenopausal women with osteoporosis than their healthy counterparts.<sup>50</sup> Oxytocin administration therefore holds promise as a potential therapy for this disease. Oxytocin analogues can emerge as anabolic stimuli to restore the skeletal loss occurring after pregnancy and lactation or in postmenopausal women.

### Oxytocin in diabetes and obesity

Oxytocin has emerged as a modality for the treating diabetes and obesity. Oxytocin treatment lessens the cardiomyocyte death induced by ischemia-reperfusion by triggering pro-survival pathways within injured cardiomyocytes. Oxytocin treatment decreases cardiac apoptosis, fibrosis, and hypertrophy. In addition, oxytocin stimulates glucose uptake in both cardiac stem cells and cardiomyocytes and increases cell resistance to diabetic conditions. Role of oxytocin in lowering of body weight by mechanisms involving increased energy expenditure, reduced adiposity and food intake has been shown. Reduction in body weight and composition can be obtained by central, peripheral and intranasal oxytocin administration. In addition, an oxytocin effect as a prosocial hormone may provide additional benefit in the treatment of complex diseases such as diabetes and metabolic syndrome.

The oxytocin mediated cardio-protection include activation of the natriuretic peptides and nitric oxide both increasing formation of cGMP in the heart, activation of cAMP activated protein kinase and by inhibition of excess of reactive oxygen species produced as a consequence of ischemia. Considering the efficacy of intranasal oxytocin delivery in stimulating the synthesis of central and peripheral oxytocin, and in reducing obesity and hedonic eating habits, investigation into the role of combined intranasal oxytocin treatment and exercise training are warranted. Consequently, treatment with oxytocin might potentially improve cardiovascular outcome in patients at risk for heart failure especially in association with obesity and diabetes.<sup>51</sup>

### Oxytocin and cancer

Recently, research has focused on unravelling the involvement of oxytocin in cancer, and its potential role as a cancer biomarker. Oxytocin effects may depend on cell type, concentration of the hormone, its interactions with other hormones in the microenvironment and the precise localization of its receptor on the cell membrane. Future research is needed to further elucidate the involvement of oxytocin in cancer, and whether it could be a clinical cancer biomarker or therapeutic target.<sup>52</sup>

## CONCLUSION

In the current review, authors have detailed the tale of the multifarious oxytocin beginning right before pregnancy, continuing during birth and later, travelling from brain to the heart and throughout the body, modulating a wide range of physiological functions and emotions like love, affection, attraction, happiness and hatred after stress. The nonapeptide appears to play a pivotal role in modulating social behaviour and the evidence for its role in broad range of neuro psychiatric disorders is accumulating. Biochemical, pathophysiological, psychological studies are expected to reinforce the development of new drugs comprising oxytocin agonists and antagonists for treatment of various disorders such as osteoporosis, diabetes, cancer etc.

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