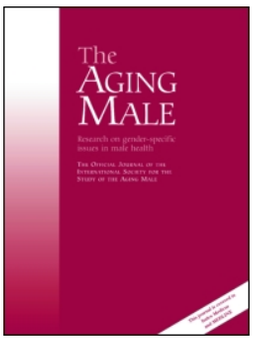

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REVIEW ARTICLE

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Are We missing out the role of oxytocin in overactive bladder syndrome?

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ABSTRACT

Overactive bladder (OAB) is characterized by the storage symptoms of urgency with or without urgency incontinence. Although there is no clear cause of this idiopathic disease, overall prevalence of OAB symptoms in individuals aged 40 years old is more than 15%. Oxytocin, which is one of the most powerful contracting neuropeptide, was also shown to exhibit high intrinsic contractile activity on detrusor muscle. Oxytocin receptor antagonists that inhibit of bladder activity might offer new insights into the treatment of OAB.

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Introduction

According to the International Continence Society "urgency, with or without urge incontinence, usually with frequency and nocturia" can be described as the overactive bladder (OAB) syndrome [1]. The term can be used if there is no proven infection or obvious pathology. It is generally accepted that OAB is a highly prevalent disorder that increases with age in both sexes and that has a profound impact on quality of life [2–4]. In a multinational European study, Milson et al. investigated 16,776 men and women by phone or direct interviews. The overall prevalence of OAB was found as 15.6% in men and 17.4% in women [5]. Overactive bladder is a common problem among older adults, affecting up to 40% of men and 30% of women ages 75 years and older [6].

The management of OAB is complex, and a wide range of conservative treatments has been offered, including bladder training, biofeedback, behavioral changes (e.g. decrease in coffee intake), anticholinergic agents, S3 sacral neuromodulation, and peripheral electrical stimulation [1,7]. Currently, anti-muscarinic agents are the first-line choice for the pharmacologic treatment of OAB [1,8]. The rationale for treating OAB with anti-muscarinic agents is based on the fact that detrusor contractions are primarily mediated via muscarinic receptors, specifically subtype M2 and M3 [8–10]. Clinical efficacy of these treatments remains an open issue and several experimental and clinical studies were carried out in the last years improving the results and decreasing the side effects of medical treatment [1,9,11,12].

The hypothalamic hormone oxytocin (OT), long known for its role in lactation and parturition, is increasingly recognized as a key mediator in a range of physiologic processes in different organs in both sexes [13–17]. The fact that OT is found in equivalent concentrations in the "posterior pituitary gland" and "plasma" of both sexes suggests that OT has further physiological functions. Multiple physiological stimuli impact OT secretion in both sexes. OT pulse characteristics (pulse height and pulse mass) correlate positively with measures of social support and negatively with avoidant attachment style and with measures of interoception [13].

The effect of aging and sex on OT innervation of the brain was studied by means of immunocytochemistry, comparing the major innervated areas in rats. In the two distinctive studies performed with 35 years of interval, demonstrated that there is no age or sex differences in OT cell bodies or fibers throughout the different parts of brain [18].

In females, lactation and parturition are the main physiological states during which OT is secreted in pulses [19]. Although, in men, peripheral levels have been shown to increase during sexual arousal, OT is

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secreted in a pulsatile manner in healthy men during a resting state [13]. In females with normal menstrual cycle, plasma OT levels in the morning after overnight fasting were significantly higher (4.5 ± 2.6 pg/mL) in the follicular phase than they were (2.1 ± 1.3 pg/mL) in the luteal phase [20]. Plasma OT levels were higher in the follicular and ovulatory phases than they were in the luteal phase. In the luteal phase, the mean OT concentration was higher during sleeping than during waking; however, in the follicular phase a variation of plasma OT level was higher during waking than during sleeping.

In healthy males, plasma OT level in the morning after overnight fasting was 3.5 ± 1.7 pg/mL, which was higher during sleeping than during waking. But the variation of plasma C levels during waking was larger than that during sleeping [20]. Plasma OT levels did not show cyclic changes in a year, but they were higher in summer than in winter. Plasma OT levels rose significantly after estradiol administration in normal females and males and did not change significantly after progesterone, and estradiol and progesterone administrations. A significant positive correlation was observed between plasma OT level and the ratio of estradiol to progesterone concentrations in plasma in females and males [20].

It is suspected that in females with normal menstrual cycle, estrogen or LH-RH stimulates OT secretion which is inhibited by progesterone, and that testosterone or LH-RH stimulates OT secretion in normal males [20]. On the other hand, a transient elevation of OT secretion during waking in both females and males may be attributed to stimuli other than the sex hormones. The results also suggest that OT secretion is affected by mechanism related to the hypothalamus-pituitary-gonadal system, and by mechanisms other than the system [20].

OT receptors are found in different organs including the uterus, ovary [21], kidney [22], pancreas [23], testis, epididymis, prostate, and also the bladder [24–26]. It was demonstrated that OT induced high intrinsic contractile activity on detrusor muscle, in both *in vitro* and in vivo studies [26,27]. In view of its powerful contracting action on different organs, especially in pelvic area including bladder, literature proposes OT receptor antagonists as a promising candidate for OAB treatment. In this mini-review, we will evaluate potential role of OT in pathogenesis of OAB by evidences in literature.

The potential role of OT in the pathogenesis of OAB

The posterior pituitary gland peptide OT and OT-like hormones facilitate reproduction in all vertebrates at several levels. Previous studies demonstrated that OT exerts a wide spectrum of central and peripheral effects [16]. The expression of OT and its receptor has now been identified in a variety of peripheral tissues [14–16,24,28,29]. In addition to systemic OT, the peptide is also produced locally (e.g. testis, epididymis, and prostate) [14,24]. OT has been shown to enhance the contractility of the tubules; therefore, the responsiveness to OT was higher at a certain stage of the spermatogenic cycle, around the time when the sperm are shed into the lumen [30]. Interestingly, along with the complex neurological pathways, some non-neuronal factors OT and sex hormones have been also demonstrated to take part in the peripheral regulation of epididymal contractility [29].

In an animal study, OT levels were found as raised in the prostatic tissue of dogs with benign prostatic hyperplasia (BPH) and the increase in peptide was accompanied with increased 5 alpha-reductase activity [30]. In a different study, Herbert et al. showed that OT receptor expression was drastically increased with age in both smooth muscle and epithelium of the prostate [14]. Additionally, OT concentrations were elevated in prostate tissue of patients with BPH [14]. It was suggested that OT is involved in the contraction of the prostate and the resulting expulsion of prostatic secretions at ejaculation [30].

More than thirty years ago, Romine and colleagues were the first to investigate evidence of OT-receptors in the urinary bladder experimentally [26]. OT was shown to exhibit high intrinsic contractile activity on isolated strips of detrusor muscle of the rabbit [26]. Pandita et al. demonstrated intrathecal OT induced stimulation and OT antagonist inhibited bladder activity in normal, conscious rats [27]. Pandita et al. also showed that OT caused a concentration dependent contraction in isolated detrusor strips [27]. The concentration response curve was concentration dependently shifted to the right by the OT antagonist. In recent decade, some studies showed the importance of OT on OAB that was regulated by OT either straight or subsidiary [31–34]. In this mini-review, we will overview the potential role of OT in the pathogenesis of OAB.

The potential role of OT via prostaglandins in the pathogenesis of OAB

Prostaglandins (PGs) are hormones that are produced, released, and effective locally; such agents are called autocoids. One of the earliest recognized effects of PGs was the stimulation of myometrial contractions.

Besides stimulating uterine myometrial contraction, OT causes the release of PGs from different organs including bladder [35]. PGs are locally synthesized in the bladder muscle and mucosa [36]. This synthesis is initiated by stretch of the detrusor muscle, bladder nerve stimulation, bladder mucosa damage, and inflammation mediators. PGs are released from the bladder into the general circulation in response to distension. In regard to PG related changes in the micturition reflex, it was envisaged that they might act directly on the afferent nerves to modulate firing and so, trigger micturition at lower bladder volumes [34].

The effects of PGs in the bladder have been studied in numerous studies. These studies have shown that bladder infusion with PGE_2 enhances the micturition reflex and that urine levels of PGE_2 are increased in patients with OAB [37,38]. More data supporting the involvement of PGE_2 in detrusor activity came from a study showing that intravesical instillation with PGE_2 increased frequency of micturition and increased basal intravesical pressure in normal, conscious rats [39].

Because increases in PGs release are thought to be involved in OAB, OT might serve a dual role in OAB by stimulating detrusor activity both directly and indirectly through stimulation of PGs synthesis [35].

The potential role of OT via estrogens in the pathogenesis of OAB

Anecdotal evidences suggest that chronic bladder pain improves while breastfeeding [40]. Fascinatingly, an objective data validated and showed that lactating rats were less sensitive to urinary bladder distension than controls [28]. So, what does happen during lactation? In a clinical study, Battin et al. studied blood hormone levels of nursing subjects during the first six months postpartum [41]. Battin et al. found that the mean estradiol levels as low at ten days postpartum (7.2 pg/mL; Normal range: 35–400 pg/mL [42]), then gradually rose to a mean level of 47.3 pg/mL at 180 days postpartum; additionally, in four subjects who were amenorrheic during the study period, the mean estradiol levels remained low (4.25 pg/mL) [41].

Could there be a relation between low estradiol levels and less sensitive urinary bladder? Recent evidence suggests that estrogens modulate the expression of the neuropeptide gene for OT [29]. Nearly ten years ago, it was demontrated that in vivo administration of estrogen to castrated rats increased the number of OT binding sites and the level of OT receptor mRNA in the myometrium and ventromedial nucleus of the brain [15]. OT, along with their cognate receptors, have also been demonstrated to act, in an estrogen dependent autocrine and paracrine loop, to regulate epididymal contractile activity in rabbit, and at least partially, in humans [29]. Gender, age, obesity, alcohol, and caffeine intake have been shown or proposed to be risk factors for the prevalence and/or severity of the OAB syndrome [43]. Women who consumed an average of 200 milligrams or more of caffeine ($>$ 2cups) a day had elevated (70% more) estrogen levels when compared to women who consumed less [44]. According to previous studies, it is likely that higher estradiol develops higher OT levels in different organs [15,29].

The potential role of OT via altered dopamine-OT pathways in the pathogenesis of OAB

Parkinson's disease (PD) is a common movement disorder associated with the degeneration of dopaminergic neurons in the substantia nigra. In addition to the movement disorder, patients with PD often show non-motor disorders. Pelvic organ" dysfunctions (bladder, bowel, and sexual dysfunction) is one of the most common autonomic disorders in PD [31].

Dopamine is an important neuromodulator that exerts widespread effects on the central nervous system function. In different studies, OT is proposed to be a key neural substrate that interacts with central dopamine systems [31–33,39]. OT is a circular nonapeptide synthesized primarily within paraventricular nucleus and the supraoptic nucleus of the hypothalamus. The posterior lobe of the pituitary contains axonal projections originating from the hypothalamus, which secrete OT for release into circulation. While OT regulates dopamine release in extra-hypothalamic regions, oxytocinergic neurons are susceptible to modulation by dopamine themselves as they also express dopamine receptors [33]. Earlier, the investigators proposed a new dysregulation of OT which was occurring via altered dopamine-OT pathways [31–33]. This sense can be interpreted as OT is an important factor of OAB which is commonly seen in PD patients as non-motor component of disease. Of course, this will lead to the potential role of OT via altered dopamine-OT pathways in the pathogenesis of OAB, and as a OT-receptors as a candidate in treatment of OAB.

The potential role of OT in depressive symptoms in OAB patients

Animal research indicates that central OT facilitates adaptive social attachments and modulates stress and

anxiety responses [45]. It is well-known that OAB patients have a restricted social life and furthermore significantly more depressive symptoms [46,47]. Cyranowski et al. compared patterns of peripheral OT release exhibited by depressed and non-depressed women [17]. Investigators revealed that depressed women are more likely than controls to display a dysregulated pattern of peripheral OT release [17]. Although it is not easy to decide which came first, the depressive symptoms or the OT, the fact is at least 15% of the population in the older ages (≥40 years old) suffer OAB [5,46]. Additionally, behavioral studies demonstrated that OT has a substantial role in social attachment, affiliation and sexual behavior. It has emerged that disturbances in peripheral and central OT levels have been detected in some patients with dopamine-dependent disorders [32].

Conclusion

The etiology and triggers of OAB have long remained elusive. Literature supports the importance and the role of OT in OAB by stimulating detrusor activity either directly or indirectly or both. The studies proposed in the present report suggests use of OT-receptor antagonists may offer new inroads into the treatment and the pathogenesis of this clinically perplexing disease, i.e. OAB. In summary, central or peripheral OT pathways/receptors may serve as a potential therapeutic target to alleviate the symptoms of OAB patients and increase their quality of life.

Disclosure statement

No potential conflict of interest was reported by the authors.

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