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Research article

IS OXYTOCIN A KEY HORMONE FOR GENE REGULATION AND PHYSIOLOGICAL FUNCTION IN POSTMENOPAUSAL WOMEN; AN INQUEST INTO POSSIBLE MECHANISMS?

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ABSTRACT: Oxytocin (OT) is a pituitary hormone and acts on the oxytocin receptor which are expressed in the brain, heart, kidney and blood vessels. OT has been implicated in its role in social bonding, and oxytocin's role in the parasympathetic nervous system includes the control of memory and learning processes and of various types of behaviour such as feeding, locomotion, as well as maternal and sexual behaviour. Oxytocin is also suggested to participate in the control of cardiovascular functions, thermoregulation, and pain threshold and fluid balance. Inefficient thermoregulation leads to hot flashes, and is associated with memory loss is a common symptom of menopause. Several studies suggest that the use of oxytocin and additional substances that amplify its effects can be used for treating weight changes, mood swings, hot flushes, somatic discomfort, dry and ulcerous mucous membranes, fissures, and bone loss during pre-menopause, menopause itself and post menopause. This review suggests its possible role in gene regulation and physiological function in post menopausal women and the possible mechanisms.

Key words: Oxytocin, menopause, gene, osteoporosis, stress

INTRODUCTION

Oxytocin, a hypothalamic neuropeptide, induces uterine contractions during parturition and milk ejection during lactation via activation of the oxytocin receptor, a G protein-coupled receptor (Gimpl & Fahrenholz, 2001). Prior to the onset of labor, uterine muscle becomes exquisitely sensitive to oxytocin due to dramatic increases in the expression of oxytocin receptors (OTR) (Kimura, 1996) whose activation promotes myometrial shortening. Recently, the role of oxytocin has expanded given the discovery of OTR gene expression in diverse tissues such as the pituitary, kidney, ovary, testis, thymus, heart, vascular endothelium, osteoclasts, myoblasts, pancreatic islets, adipocytes, several types of cancer cells (Gimpl & Fahrenholz, 2001) smooth muscle and epithelial compartment of the human epididymis. Evidence also suggests oxytocin may serve as an acute phase response protein after injury. There is growing evidence to the role of OT in postmenopausal women (Tyagi, 2010). Light *et al* (2005) reported that in postmenopausal women participating in a hormone replacement therapy (HRT) trial, greater treatment-induced increases in oxytocinergic activity (indexed by plasma levels of an OT precursor) were associated with greater post-treatment reductions in BP and vascular resistance reactivity to a battery of experimental stressors including speech, stroop and cold pressor tasks. More recently, it has been (Taylor *et al* 2006) reported that although postmenopausal women self-selected for HRT had higher plasma OT compared with non-treated women, higher OT was not related to blood pressure or heart rate reactivity to the Trier Social Stress Test (TSST). Similarly, it was reported that in postpartum lactating and non-lactating women and reproductive aged control women, OT levels were not associated with blood pressure or heart rate reactivity to the TSST, but lactation was related to greater parasympathetic cardiac control ((Altemus *et al*, 2001, Heinrichs *et al* 2003). In women, plasma OT signals relationship stress and is associated with elevated cortisol; it does not appear to significantly affect cortisol or blood pressure responses to acute stress.

Women in the post-menopausal period and OVX rats present an increase in sympathetic activity with higher α1-adrenergic activation and peripheral vasoconstriction associated with a reduction in nitric oxide (NO) synthesis, possibly due to estrogen deficiency. As a result, it was suggested that both the lower basal HR in OVX-EC rats and attenuation of cardiovascular responses induced by hemorrhage in the OVX-EC group found in the present study could be a consequence of estrogen effect. This review article analyses the role of OT in gene regulation and physiological activity in post menopausal women.

Oxytocin and CD 38 in post menopausal women:

A novel protein reported to be related to OT neurotransmission is CD38, a transmembrane glycoprotein expressed on the majority of natural killer cells, T cells, B cells, and macrophages. The view of CD38, besides its major role in triggering proliferation and immune responses in lymphocytes, is of a promiscuous receptor and cell surface enzyme involved in several other functions, such as signal transduction, cell adhesion, and catalytic activity. CD38 is expressed in a variety of tissues besides lymphoid cells, such as brain, pancreas, muscle, bone, kidney, and gut. The levels of expression are variable, and the function for most of the tissues not related to the immune system remains unknown. It has been shown that CD38 is critical for social behavior and for regulating OT secretion in mice (Higashida et al, 2008). The demonstration that CD38 knockout mice showed deficits in maternal nurturing and social behavior and that the plasma levels of OT, but not vasopressin, were strongly reduced in these mice. Further it has been shown that CD38 knockout mice displayed compatible phenotypes to mice with compromised OT systems, such as social amnesia and disruption in depolarization, and in calcium ion elevation (Salmina et al, 2010).The CD38 gene is located on the short arm of chromosome 4 (4p15) and consists of eight exons. There is a large intron (approximately 40 kb) between exons 1 and 2 while exons 2–8 span on approximately 36 kb. A recent genome-wide linkage scan found the 4p15 region to have suggestive evidence for linkage to ASD. Several polymorphisms have been described in the CD38 gene, and several were reported to be associated with Type II diabetes, systemic lupus erythematosus, and premenopausal and postmenopausal bone mineral density. Thus it can be postulated that oxytocin may mediate its actions through CD38 in postmenopausal women (Figure 1).

OT and cardiovascular homeostasis in postmenopausal women:

Regular exercise seems to be particularly beneficial in menopausal women (Bonaiuti *et al*, 2002), whose lack of ovarian steroids has detrimental effects on bone mass and progression of cardiovascular diseases. The incidence of cardiovascular diseases rises immensely in women after menopause (Staffileno *et al* 2001), where a fourfold higher prevalence of hypertension has been documented compared with premenopausal women. Exercise has been shown to improve the metabolic and lipid profile and reduces inflammation and cell adhesion molecules in postmenopausal women, even in the absence of caloric restriction (Wegge *et al* 2004). Furthermore, postmenopausal women who engage in intermittent, moderate-intensity physical training experience a significant reduction in BP, with a decreased risk of pressure-related cardiovascular complications (Light *et al*, 2005). Increased oxytocinergic activity was recently linked to lowered BP and vascular resistance during stress in postmenopausal women on estrogen replacement therapy. Another important feature of OT is its role in cell proliferation. OTR mediates cell growth inhibition when coupled with G_i protein; therefore, an antihypertrophic effect of OT on the heart cannot be excluded. Additionally, the biological activities of OT may be mediated by natriuretic peptides (Mukkadam Daher, 2006) or NO. Low oxytocin serum levels appeared to be associated with severe osteoporosis, independently of other factors associated with osteoporosis or known to regulate oxytocin serum levels, such as estradiol or leptin, reinforcing the concept that oxytocin may be involved in the patho-physiology of postmenopausal osteoporosis (Breuil *et al*, 2011).

OT stress and HPA

Plasma OT has been shown to be associated with elevated cortisol at the beginning of the challenge protocol. In response to the stress tasks, women with both high and low levels of plasma OT showed the expected increase in cortisol followed by a decline in cortisol levels during recovery ; however, this pattern was not significantly connected to plasma OT levels.

This pattern appears contrary to a large experimental animal literature and a modest human literature relating OT to lower HPA axis activity (Gimpl & Fahrenholz, 2001). A possible reconciliation of these divergent findings stems from the fact that past research has not consistently disentangled the effects of OT from the effects of affiliative contact or its anticipation. The reduced stress responses attributed to OT may be due instead to its affiliative consequences and/or to OT's impact on other aspects of the affiliative neurocircuitry; for example, modulation of pathways implicating reward, such as the mesolimbic dopamine and opioid systems (Vongpatanasin, 2009). Positive social contact or its anticipation may activate these aspects of the affiliative neurocircuitry, producing the stress-reducing effects that have been attributed to OT (Young *et al*, 2001). Merely having elevated OT levels does not appear to be protective against cortisol or BP responses to stress, an important qualification to the literature that has documented the stress-protective effects of OT. Thus OT is involved in stress management and social affiliation in post menopausal women.

Oxytocin and gene regulation:

This biological effect of OT operates through its cognate receptor, the OT receptor (OXTR). The OTR is a 389-amino acid polypeptide that modulates a number of behaviors, including stress response, anxiety, social memory and recognition, sexual and aggressive behaviors, and maternal behavior (Lee et al., 2009). The human OTR gene is located on chromosome 3p25.3 spanning approximately 19 kbp, and is composed of three introns and four exons (Inoue *et al*., 1994). A single-nucleotide polymorphism (SNP) within intron 3 involving an adenine (A)/guanine (G) transition (rs53576) has recently been associated with different socio-emotional phenotypes (Bakermans-Kranenburg and Van Ijzendoorn, 2008; Tost et al., 2010). Intranasal administration of OT enhances human trust behavior rather than trustworthiness or risk behaviors (Kosfeld et al., 2005), for which the biological effect of OT operates through its OTR. The OT mRNA in the rat shows an increase in poly (A) tail length in response to the activation of the hypothalamoneurohypophysial system, e.g., during pregnancy, lactation, and dehydration. This could augment mRNA stability and may be an additional level of OT gene control (Zingg, 1989, Carter & Murphy, 1991). Hexanucleotide AGGTCA motifs and variations thereof are present in the proximal 5′-flanking region of cloned OT genes. This motif is part of binding sites for all members of the nuclear receptor superfamily, except the glucocorticoid, mineralocorticoid, progesterone, and androgen receptor. Various combinations of this motif exist, ranging from single hexanucleotides, direct or inverted repeats with spacing varying from one to at least six nucleotides. Thus potentially several members of the nuclear receptor family including many orphan receptors could interact with the OT gene and regulate its expression. The human and rat OT promoters could be stimulated by the ligand-activated estrogen receptors ERα and ERβ, the thyroid hormone receptor THRα, and the retinoic acid receptors RARα and RARβ in a variety of cells (Parker *et al* 1993). However, it is important to note that these results were obtained from cotransfection experiments in cell lines, i.e., under nonphysiological circumstances. Gonadal steroids play an important role in the regulation of uterine OT receptors. In the days preceding birth, the ratio of plasma progesterone to estrogen falls. These changes in the steroid concentrations may occur in most mammals. At least in humans, progesterone withdrawal has not been determined. The steep drop of circulating progesterone occurs after placental delivery. Alteration of sex steroid metabolism in the fetoplacental unit appears to occur in women and primates (Larcher *et al*, 1995).

OT interaction with other hormones:

As shown in bovine and in sheep, maturation of the fetal hypothalamus leads to an increased secretion of CRH, which in turn stimulates the pituitary to secrete ACTH. Subsequently, ACTH stimulates the fetal adrenal to release cortisol. Additionally, OT-induced contractures of the myometrium in late pregnancy could lead to temporary decreases in blood flow and transient episodes of fetal hypoxia, which also may provoke a fetal stress response (Fuchs *et al* 1995). Cortisol then increases the activity of the key enzyme cyctochrome P-450c17α (CYP 17A1), which promotes placental pregnenolone turnover into estrogens. In primates, CRH is additionally synthesized by the placenta and stimulates the fetal adrenal to secrete dehydroepiandrosterone sulfate (DHEAS), the precursor of placental estrogen (Mecenas *et al* 1996). In each case, the ratio of estrogen to progesterone increases in the maternal plasma concomitantly with increases in the synthesis of connexin-43, formation of gap junctions, increased production of prostaglandins from intrauterine tissues, and an upregulation of OT receptors. Finally, the uterine quiescence that was maintained by the high progesterone level ceases, and parturition can occur.

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In addition, several reports have suggested that estrogen has modulatory effects on cardiovascular function, as evidenced by the cardiovascular changes observed in postmenopausal women, OVX rats and, possibly, females of other species during senescence (Clark *et al* 2004, Reckelhoff & Fortepiani 2004). OT has been shown to potentiate the effects of carbachol on lacrimation (Tyagi, 2010). Upregulation of OT receptors and an increased expression of gap junctions also occur in the hours or days preceding human labor onset. Obviously, estrogens and progesterone act in opposing fashion on the function, expression, and/or regulation of OT receptors. The mechanism for the sudden and sometimes unpredictable responsiveness to OT of the myometrium is still mysterious (Mitchell & Chibbar, 1995, Richard & Zingg, 1990). As Kimura (1996) pointed out, the reaction of the uterus to OT in the same patient could vary from day to day. To induce labor at term, in some patients, OT is completely ineffective even at high doses, whereas in others a minimal dose can induce hypertonus of the uterus. However, despite the striking steroid dependence of the OT system, the promoter of the human OT receptor gene does not contain a classical steroid responsive element. Several observations indicated that progesterone promotes uterine relaxation and inhibits the function of the OT receptor system by both genomic and nongenomic mechanisms. Even in the absence of protein synthesis, progesterone induces a reduction in uterine OT binding. Moreover, progesterone-mediated downregulation of OT receptors was not accompanied by a decrease in OT receptor gene expression (Soloff *et al*, 1983). The mechanisms of how progesterone acts nongenomically are still unknown but are of fundamental importance. Oxytocin may also regulate the carbohydrate metabolism and intake of sugars in postmenopausal women and this can be stated based on the some reports which suggest that deficiency of oxytocin gene in the mice leads to enhanced sucrose intake (Bellings *et al* 2006, Amico *et al* 2005).

Thus, this review article has explored the various possibilities of oxytocin action in human physiology and in conclusion it can be stated that oxytocin can act in multiple ways to regulate gene and physiological function in post menopausal women.

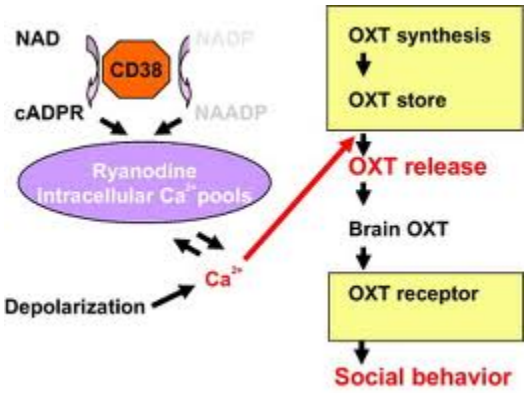

Figure 1: Interaction of oxytocin with CD38 molecule

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REFERENCES

AB. Salmina, O. Lopatina, M. V. Ekimova, S. V. Mikhutkina, H. Higashida (2010). CD38/Cyclic ADP-ribose System: A New Player for Oxytocin Secretion and Regulation of Social Behaviour. Journal of Neuroendocrinology Volume 22, Issue 5, pages 380–392

Altemus M, Redwine LS, Leong YM, Frye CA, Porges SW and Carter CS (2001). Responses to laboratory psychosocial stress in post partum women. Psychosom.Med.,63: 814-821.

Amico JA, Vollmer RR, Cai HM, Miedlar JA, Rinaman R. Enhanced initial and sustained intake of sucrose solution in mice with an oxytocin gene deletion. Am J of Physiology: Regulatory, Integrative, Comp Physiol 289:R1798-R1806, 2005.

Breuil V, Amri EZ, Panaia-Ferrari P, Testa J, Elabd C, Albert-Sabonnadière C, Roux CH, Ailhaud G, Dani C, Carle GF, Euller-Ziegler L. (2011). Oxytocin and bone remodelling: relationships with neuropituitary hormones, bone status and body composition., Joint Bone Spine. 78(6):611-5.

Billings LB, Spero JA, Vollmer RR, Amico JA. (2006). Oxytocin null mice ingest enhanced amounts of sweet solutions during light and dark cycles and during repeated shaker stress. Behavioral Brain Research 171;134-141

Bonaiuti D, Shea B, Iovine R, Negrini S, Robinson V, Kemper HC, Wells G, Tugwell P, Cranney A. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev 3: CD000333, 2002.

Bakermans-Kranenburg, M. J., and Van Ijzendoorn, M. H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. Soc. Cogn. Affect. Neurosci. 3, 128–134.

Clark JT, Chakraborty-Chatterjee M, Hamblin M, Wyss JM, Fentie IH. Estrogen depletion differentially affects blood pressure depending on age in Long-Evans rats. Endocrine 25: 173-186, 2004.

Carter DA, Murphy D (1991) Rapid changes in poly(A) tail length of vasopressin and oxytocin mRNAs form a common early component of neurohypophysial peptide gene activation following physiological stimulation.Neuroendocrinology 53:1–6.

Fuchs AR, Fields MJ, Freidman S, Shemesh M, Ivell R (1995) Oxytocin and the timing of parturition. Influence of oxytocin receptor gene expression, oxytocin secretion, and oxytocin-induced prostaglandin F2α and E2release. Adv Exp Med Biol 395:405–420.

Gimpl G, Fahrenholz F: (2001). The oxytocin receptor system: structure, function, and regulation. Physiol Rev, 81(2):629-683.

Higashida H, Jin D, Liu H-X, Lopatina O, Yokoyama S, Koizumi K, Hashii M, Islam MS, Hayashi K, Munesue T. (2008). Social memory, maternal care, and oxytocin secretion, but not vasopressin release, require CD38 in mice. In: BridgesRS, ed. Neurobiology of Parental Brain. Amsterdam: Elsevier, : 361–375.

Heinrichs M, Baumgartner T, Kirshbaum C, Ehlert U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychological stress. Biol Psychiatry;54:1389 –98

Inoue, T., Kimura, T., Azuma, C., Inazawa, J., Takemura, M., Kikuchi, T., Kubota, Y., Ogita, K., and Saji, F. (1994). Structural organization of the human oxytocin receptor gene. J. Biol. Chem. 269, 32451–32456.

Kimura T, Takemura M, Nomura S, Nobunaga T, Kubota Y, Inoue T, Hashimoto K, Kumazawa I, Ito Y, Ohashi K, et al.: (1996). Expression of oxytocin receptor in human pregnant myometrium. Endocrinology, 137(2):780-785.

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., and Fehr, E. (2005). Oxytocin increases trust in humans. Nature 435, 673–676.

Light KC, Grewen KM, Amico JA, Brownley KA, West SG, Hinderliter AL, Girdler SS. (2005). Oxytocinergic activity is linked to lower blood pressure and vascular resistance during stress in postmenopausal women on estrogen replacement. Horm Behav. 47: 540–548,

Lee, H. J., Macbeth, A. H., Pagani, J. H., and Young, W. S. III. (2009). Oxytocin: the great facilitator of life. Prog. Neurobiol. 88, 127–151.

Larcher A, Neculcea J, Breton C, Arslan A, Rozen F, Russo C, and Zingg HH. (1995). Oxytocin receptor gene expression in the rat uterus during pregnancy and the estrous cycle and in response to gonadal steroid treatment. Endocrinology 136: 5350–5356,

M G Tyagi, (2010) "Oxytocin revisited: a critical hormone for gene regulation and physiological activity in post menopausal women" International symposium "Gene to Vial concept for biotechnology based healthcare molecules" 7 – 10 FEBRUARY

Mukaddam-Daher S. (2006).Atrial natriuretic peptides as therapeutic targets. Expert Opinion on Therapeutic Targets 10: 239–252,

Mecenas CA, Giussani DA, Owiny JR, Jenkins SL, Wu WX,Honnebier BO, Lockwood CJ, Kong L, Guller S, Nath aniels PW (1996)Production of premature delivery in pregnant rhesus monkeys by androstenedione infusion. Nat Med 2:443–448.

MG Tyagi. (2007). Oxytocin potentiates carbachol induced lacrimation in female Wistar rats. Biomed.Res., 18 (2), 103-105

Mitchell BF, Chibbar R (1995) Synthesis and metabolism of oxytocin in late gestation in human decidua. Adv Exp Med Biol 395:365–380.

Light KC, Grewen KM, Amico JA, Brownley KA, West SG, Hinderliter AL, Girdler SS (2005). Oxytocinergic activity is linked to lower blood pressure and vascular resistance during stress in postmenopausal women on estrogen replacement. Hormones and Behavior, 47(5):540-548

Parker MG, Arbuckle N, Dauvois S, Danielian P, White R(1993).Structure and function of the estrogen receptor. Ann NY Acad Sci 684:119–126.

Richard S, Zingg HH (1990). The human oxytocin gene promoter is regulated by estrogens. J Biol Chem.265:6098–6103.

Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. Hypertension 43: 918-923, 2004.

Staffileno BA, Braun LT, Rosenson RS. (2001).The accumulative effects of physical activity in hypertensive postmenopausal women. J Cardiovasc Risk 8: 283–290,

Soloff MS, Fernstrom MA, Perisamy S, Soloff S, Baldwin S, and Wieder M. (1983). Regulation of oxytocin receptor concentration in rat uterine explants by estrogen and progesterone. Can J Biochem Cell Biol 61: 625–630

Taylor SE, Gonzaga GC, Klein LC, Hu P, Greendale GA, Seeman TE (2006). Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. Psychosom Med. Mar-Apr;68(2):238-45.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., Weinberger, D. R., and Meyer-Lindenberg, A. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. Proc. Natl. Acad. Sci. U.S.A. 107, 13936–13941.

Vongpatanasin W. (2009). Autonomic regulation of blood pressure in menopause, Semin Reprod Med 27: 338-45

Wegge JK, Roberts CK, Ngo TH, Barnard RJ. (2004) Effect of diet and exercise intervention on inflammatory and adhesion molecules in postmenopausal women on hormone replacement therapy and at risk for coronary artery disease. Metabolism 53: 377–381,

Young LJ, Lim MM, Gingrich B, Insel T. Cellular mechanisms of social attachment. Horm Behav 2001;40:133– 8.

Zingg HH, Lefebvre DL (1989) Oxytocin mRNA: increase of polyadenylate tail size during pregnancy and lactation. Mol Cell Endocrinol.65:59–62.