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Oxytocinergic activity is linked to lower blood pressure and vascular resistance during stress in postmenopausal women on estrogen replacement

Kathleen C. Light[a,*], Karen M. Grewen[a], Janet A. Amico[b], Kimberly A. Brownley[a], Sheila G. West[c], Alan L. Hinderliter[a], Susan S. Girdler[a]

[a]*School of Medicine, University of North Carolina at Chapel Hill, CB #7175, Medical Research Building A, Chapel Hill, NC 27599-7175, USA*
[b]*School of Medicine and School of Pharmacy, University of Pittsburgh, PA 15260, USA*
[c]*Pennsylvania State University, University Park, PA 16802, USA*

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Abstract

Estrogen administration results in increased release of the oxytocin (OT) prohormone reflected by increases in oxytocin intermediate peptide (OT Int) in both animal models and humans, and sequential treatment of ovariectomized rats with estrogen/progesterone then progesterone withdrawal leads to increased hypothalamic OT mRNA. Blood pressure (BP) reductions have been related to increased exogenous and endogenous OT in rats and to higher endogenous OT activity in premenopausal women, but not previously in postmenopausal women. Thus, we used plasma obtained at rest and during a speech stressor from 54 postmenopausal women who participated in a 6-month randomized trial of oral conjugated estrogens vs. placebo to examine effects of estrogen replacement therapy (ERT) on plasma OT and OT Int levels and their relationships to changes in BP during the trial. ERT alone and with progesterone (but not placebo) led to significant increases in plasma levels of OT Int, but no change in plasma OT levels. Women showing greater increases in OT Int during treatment showed greater decreases in BP and total vascular resistance during a series of behavioral stressors compared to women with moderate or no increases in OT Int, even after controlling for effects related to treatment condition or to changes in plasma estradiol. The findings suggest that enhanced oxytocinergic activity may contribute to BP decreases associated with ERT in more responsive postmenopausal women.

Keywords: Oxytocin; Estrogen; Postmenopausal; Hormone replacement; Blood pressure; Marriage

Introduction

Oxytocin (OT) is a mammalian neuropeptide known for its role in breastfeeding (milk ejection), childbirth (uterine contractions), maternal behavior, and male–female pair-bonding among species that form such bonds (Insel, 1997; Jenkins and Nussey, 1991; Pedersen et al., 1982). There is a growing literature, however, indicating that OT also has substantial and enduring effects on blood pressure (BP) regulation. In animal models, OT administration has been associated with sustained decreases in BP and diminished stress responses (Holst et al., 2002; Petersson, 2002; Petersson et al., 1996, 1999a,b; Uvnas-Moberg, 1998a,b). OT knock-out mice demonstrate chronic hypotension but greater stress-related BP increases, including sustained 24-h BP increases during chronic stress, suggesting that OT is involved in tonic BP maintenance and regulation of the stress-induced pressor response (Bernatova et al., 2004; Michelini et al., 2003). The BP-reducing effects of enhanced OT activity in rats may be potentiated by female steroid hormones, and if OT activity is increased early in life, BP decreases and reduced stress responses persist into

* Corresponding author. Fax: +1 919 966 0708.
E-mail address: Kathy_Light@med.unc.edu (K.C. Light).

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adulthood (Holst et al., 2002; Petersson et al., 1999b). Endogenous OT activity in both infant rats and their dams is enhanced by maternal licking and warm contact, but also experimentally by stroking with a brush (Holst et al., 2002; Pedersen and Boccia, 2002). In an initial translational study involving mothers of infants, we demonstrated that BP levels before, during and after a speech stressor were lower in those mothers who showed plasma OT increases vs. those who showed OT decreases following baby holding and cuddling (Light et al., 2000). Subsequently, in a protocol involving warm contact with their spouses/partners that preceded a stressor, we found that among 59 premenopausal women who were *not* postpartum, higher plasma OT levels were linked to greater frequency of partner hugs at home during the past month, and appeared to be a partial mediator of the relationship between hug frequency and lower resting BP levels (Light et al., in press). In another study with 38 premenopausal women and their spouses/partners, greater partner support was linked to higher plasma OT levels in both men and women, and OT appeared to mediate the reduced sympathetic activity (indexed by lower plasma norepinephrine levels) shown by women with greater partner support (Grewen et al., in press).

These results from our three studies linking greater plasma OT levels with lower BP and norepinephrine in premenopausal women are consistent with evidence from rats that increased oxytocinergic activity may lower BP over the short term by acting directly on the vasculature and heart, or over the longer term by altering central α_2-adrenergic tone, which then leads secondarily to reduced sympathetic outflow to both vessels and heart (Diaz-Cabale et al., 2000; Gutkowska et al., 2000; Jankowski et al., 2000; Petersson, 2002; Petersson et al., 1996, 1998). Some postmenopausal women, particularly those with mild hypertension and those less than 5 years since onset of menopause, experience beneficial BP decreases while on estrogen replacement therapy (ERT) that are associated with (and appear to be a consequence of) decreases in total vascular resistance (Brownley et al., 2004; da Costa et al., 2004; Light et al., 2001; Seeley et al., 1999; van Ittersum et al., 1998). Although the primary mediator of such BP decreases is presumed to be estradiol's direct effect on the vasculature, other secondary factors such as increased oxytocinergic activity may also help to lower BP (Petersson, 2002; Petersson et al., 1999b). However, no study to date in humans has attempted to relate oxytocinergic activity to an index of vascular constriction, and no study has examined relationships of oxytocinergic activity to BP in postmenopausal women.

OT is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus as a larger precursor. The gene for OT was identified by Land et al. (1983) as having the structure of oxytocin–glycine–lysine–arginine–neurophysin. As this larger precursor is transported from the hypothalamus to the posterior pituitary, biologically active OT and neurophysin are formed from the precursor as endopeptidases induce cleavage. Amico and Hempel (1990) found that both humans and other primates administered estrogen showed no increase in plasma OT itself but did show increases in plasma levels of an OT intermediate peptide form (OT Int) between the precursor and OT, that of oxytocin–glycine. Oxytocin–glycine, along with similar prohormones (oxytocin–glycine–lysine and oxytocin–glycine–lysine–arginine) that may also be formed during proteolytic cleavage of the precursor, have together been referred to as OT-X (Morris et al., 1992). Although the final OT Int peptide that has only the additional glycine appears to lack the milk ejection and uterine contractile effects of OT, Amico and Hempel (1990) suggested that estrogen-induced increases in circulating levels of the OT Int may provide an important indicator of the priming effect of estrogen on release of the prohormone, laying the groundwork for subsequent increases in levels of the OT peptide when other necessary enzymatic and amidation elements are present. Early studies that reported increases in plasma OT levels with endogenous or exogenous estrogen typically used less specific antibodies with cross-reactivity for both OT and OT-Int (Amico et al., 1981, 1985). More recent research has shown that increased estrogen and progesterone followed by declining progesterone leads to increased OT Int and hypothalamic oxytocinergic activity (indexed by hypothalamic OT mRNA and peptide levels), but does not increase pituitary or plasma OT (Amico and Hempel, 1990; Amico et al., 1997, 2000; Crowley et al., 1995; Blyth et al., 1997).

Thus, based on reserve plasma samples from an earlier randomized double-blind, placebo-controlled study, plasma OT and OT Int peptide levels were determined in 54 postmenopausal women both before and after 6 months of either placebo or ERT with oral conjugated estrogens (Premarin). This study evaluated the following hypotheses. First, ERT induces greater increases in plasma OT Int (but not OT) compared to placebo. Second, assuming that OT Int increases that are induced by ERT reflect enhanced hypothalamic oxytocinergic activity with its potential effects on BP and adrenergic activity, women who show greater ERT-induced increases in OT Int are expected to show greater reductions in BP during rest and stress, even after adjustment for effects of treatment-induced increases in plasma estradiol levels.

Methods

Participants

The present report is based on 54 of the 69 naturally and surgically postmenopausal women aged 40–69 who participated in a randomized, double-blind, placebo-controlled trial of the effects of ERT on cardiovascular