PHARMACOTHERAPY

Orgasm, Serotonin Reuptake Inhibition, and Plasma Oxytocin in Obsessive-Compulsive Disorder. Gleaning From a Distant Randomized Clinical Trial

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ABSTRACT

Introduction: Serotonin reuptake inhibitors (SRIs) are widely used for the treatment of psychiatric disorders, including obsessive-compulsive disorder (OCD). SRIs commonly cause delayed orgasm, the mechanism of which is poorly understood. Oxytocin is involved in sexual function and is interconnected with serotonin within the brain. SRIs are reported to affect the oxytocin system, but possible relations between SRI-induced changes of sexual function and oxytocin are unexplored in humans. In a randomized, double-blinded, placebo-controlled trial of OCD, the anti-obsessive efficacy and adverse events of SRIs and oxytocin measurements were studied.

Aims: To identify possible correlates between oxytocin levels and sexual function; find out whether sexual side effects correlate with levels of oxytocin and/or paroxetine and clomipramine; and test whether changes in sexual functioning are related to an anti-obsessive response.

Methods: Reported sexual function and oxytocin plasma levels at rest were studied in 31 adults (15 men and 16 women) with OCD who participated in a randomized, double-blinded trial comparing the SRIs clomipramine and paroxetine with placebo. Sexual adverse effects were quantified by a clinician-administered semistructured interview. Anti-obsessive response was based on the Yale-Brown Obsessive-Compulsive Scale.

Main Outcome Measures: Ratings on the Sexual Symptom Checklist, plasma oxytocin, serum paroxetine and clomipramine levels, and Yale-Brown Obsessive-Compulsive Scale scores.

Results: Baseline oxytocin levels were positively correlated with baseline OCD severity, but not with sexual functioning. Impaired orgasm at week 6 was reported by 73% of SRI-treated and 20% of placebo-treated patients ($P = .03$). Impaired orgasm was related to higher oxytocin levels after 4 weeks of SRI treatment ($P < .01$) but not to SRI concentrations. In men, an association between impaired orgasm and anti-obsessive treatment response was found ($P = .028$).

Conclusion: This pilot study suggests that some collateral effects of SRIs, particularly delayed orgasm, might be influenced by changes within the oxytocinergic system and are related to anti-obsessive mechanisms. Early-onset delayed orgasm in SRI-treated patients could serve as a predictor for OCD treatment response.

Key Words: Obsessive-Compulsive Disorder; Oxytocin/Plasma; Serotonin; Clomipramine; Paroxetine; Serotonin Uptake Inhibitors; Response Prediction; Adverse Effects; Randomized Controlled Trial; Sexual Physiology

INTRODUCTION

Antidepressant-Induced Sexual Dysfunction, Serotonergic, and Oxytocinergic Mechanisms

In clinical practice, treatment with potent serotonin reuptake inhibitors (SRIs; eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-noradrenaline reuptake inhibitors, and the tricyclic antidepressant clomipramine) is commonly associated

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with sexual side effects. The frequency of these side effects has been debated, because in major depression (the most common indication for SRIs) sexual dysfunction constitutes a typical symptom of the disorder. However, in patients without sexual dysfunction at baseline, SRIs often induce decreased libido and delayed orgasm and/or ejaculation.[1,2] The specificity of serotonergic mechanisms is evident, because serotonergic antidepressants cause a much higher rate of sexual dysfunction than noradrenergic drugs, especially concerning orgasmic function.[2,3] Thus, SRIs seem to affect most specifically orgasmic function, which is further supported by the fact that SSRIs (eg, paroxetine and dapoxetine) currently constitute first-line pharmacologic treatment of premature ejaculation.[4] Despite the usefulness of this side effect of SSRIs in andrology, in psychiatric practice, it is mainly viewed as an undesired adverse effect. In any case, further knowledge of the neurochemical mechanisms is warranted. Concerning the role of various serotonin (5-hydroxy-tryptamine [5-HT]) receptors, agonists on 5-HT_{1A} receptors have been found to facilitate, whereas 5-HT_{1B} agonists have been found to inhibit or delay, ejaculatory functions in rats.[5–7] Not only direct effects of changed serotonergic transmission, but also indirect effects of serotonin, such as inhibited dopamine release,[8] or increased prolactin levels[9] have been mechanistically implicated. However, serotonin has increasingly been shown to interact with the hypothalamic-neurohypophyseal hormone oxytocin, which clearly is involved in sexual functions, although its role in human sexuality is insufficiently defined.[10–12] Serotonin increases the hypothalamic mRNA expression of oxytocin by stimulating 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} receptors[13] and increases oxytocin release by 5-HT_{1A}, 5-HT_{2C} and 5-HT_4 receptors.[14] Plasma oxytocin increases rapidly after SSRI administration in rats,[15] and the therapeutic effect of SSRIs might be mediated by oxytocin.[15,16] Conversely, oxytocin might modulate the release of serotonin in mice[17] and humans.[18] SSRI treatment leads to downregulation of 5-HT_{1A} receptors after approximately 1 week,[19,20] thereby potentially decreasing oxytocin activity. Because 5-HT_{1A} receptor activation releases oxytocin and facilitates ejaculation in rats, de Jong et al[21] suggested that SSRI-induced delayed orgasm might be related to downregulation of 5-HT_{1A} receptors and decreased oxytocin activity.

However, it should be noted that, with few exceptions,[10,11,18] these studies were performed in rodents, and to our knowledge, no human studies relating oxytocin and serotonin measurements with sexual function are available. Two single cases of male sexual dysfunction (not caused by SSRIs) were reportedly improved by intranasal oxytocin[22,23]; however, when intranasal oxytocin was administered to 10 male volunteers, a moderate but significant delay of ejaculation was recorded.[11]

Serotonin and Oxytocin in Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is a psychiatric disorder that frequently has a long-term course and does not include sexual dysfunction among its typical symptoms. Some specific symptoms (eg, obsessions related to contamination, religion, or sexuality) can interfere with sexual function,[24] but sexual obsessions have been found in only 13% of adult patients with OCD.[25] In a direct comparison of sexual dysfunction, patients with OCD were more similar to healthy controls than to patients with a major depressive disorder.[26] Because of early findings that the potent SRI clomipramine has a specific anti-obsessive effect,[27] pathophysiologic research on OCD has focused on serotonin.[28,29] Currently, SRIs are the main pharmacologic anti-obsessive treatment, but a clinical problem is the long delay of therapeutic response.[30] Interestingly, Ackerman et al[31,32] found relations between sexual side effects of SRIs and the anti-obsessive clinical response, with early-onset sexual dysfunction being the side effect most consistently predicting a response to the SSRI fluoxetine.

Oxytocin also has been implicated in the pathophysiology of OCD.[33,34] In a previous study, we investigated how SRIs change oxytocin levels in patients with OCD.[35] We found higher plasma oxytocin levels after 4 weeks of treatment in SRI responders compared with non-responders.

Accordingly, drug-induced sexual effects are common in SRI-treated patients, but the mechanisms of these effects are insufficiently studied. A putative role of oxytocin is unsubstantiated in humans, because, to our knowledge, oxytocinergic measurements in relation to sexual functions in SRI-treated humans have not been reported.

AIMS

While investigating SRI treatment of OCD, we had the opportunity to study oxytocin in relation to SRI-induced sexual side effects. Our aims were to:

1. Identify possible correlates between baseline oxytocin plasma levels and baseline sexual function;
2. Find out whether the degree of sexual side effects correlates with plasma levels of oxytocin, with changes of oxytocin induced by treatment, and/or with serum levels of paroxetine and clomipramine;
3. Test whether incident changes of sexual functioning have any relation to the anti-obsessive clinical response.

METHODS

Patients

In a 12-week, multicenter, randomized, double-blinded, parallel-group drug trial comparing flexible doses of the SRIs paroxetine (20—60 mg daily) and clomipramine (50—250 mg daily) and placebo for the treatment of OCD, our center included 43 patients with OCD.[36] Of these, 36 patients participated in a site-specific biochemical extension of the trial,[35,37] including plasma levels of oxytocin (at baseline and 1 and 4 weeks after treatment) and serum concentration of the