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ORIGINAL CONTRIBUTION

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Plasma oxytocin levels in female fibromyalgia syndrome patients

Bestimmung der Plasma-Oxytocin-Konzentration bei Patientinnen mit Fibromyalgischem Syndrom

Summary *Objectives*: Fibromyalgia syndrome (FMS) is a chronic pain disorder, where 90% of the patients struck by the disorder are women. The neuropeptide oxytocin is known to have antinociceptive and analgesic, as well as anxiolytic and antidepressant effects, which makes this neuropeptide of interest in fibromyalgia research. The aim of this study was to assess oxytocin concentrations in female FMS patients with different hormonal status and in depressed and non-depressed patients and relate oxytocin concentrations to adverse symptoms as pain, stress, depression, anxiety and to the positive item happiness.

Methods: Thirty-nine patients and 30 controls registered these symptoms daily during 28 days and blood samples for the assessment of oxytocin were drawn twice in all patients and controls. Besides the daily ratings, depression was also estimated with the self-rating instrument Beck Depression Inventory (BDI).

Results: Depressed patients according to the BDI differed significantly with low levels of oxytocin compared to the non-depressed patients and the controls. Low levels of oxytocin were also seen in high scoring pain, stress and depression patients according to the daily ratings; however, these subgroups were small. A negative correlation was found between the scored symptoms depression and anxiety and oxytocin concentration, and a positive correlation between the item happiness and oxytocin. The oxytocin concentration did not differ between the hormonally different subgroups of patients or controls.

Conclusion: The results suggest that the neuropeptide oxytocin may, together with other neuropeptides and neurotransmitters, play a role in the integration of the stress axes, monoaminergic systems and the pain processing peptides in the pathophysiologic mechanisms responsible for the symptoms in the FMS.

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Zusammenfassung *Ziel:* Das Fibromyalgie-Syndrom (FMS) ist eine durch Schmerzen gekennzeichnete chronische Erkrankung, bei der 90% der betroffenen Patienten Frauen sind. Das Neuropeptid Oxytocin ist bekannt für seine antinozizeptive und analgetische wie auch seine anxiolytische und antidepressive Wirkung, weshalb diese Substanz von Interesse für die FMS-Forschung ist. Das Ziel dieser Untersuchung war es, die Konzentration von Oxytocin im Blut bei FMS-Patientinnen mit unterschiedlichem Hormonstatus sowie bei depressiven und nichtdepressiven Patientinnen zu messen, und die Oxytocin-Konzentration einerseits auf negative Symptome wie Schmerz, Stress, Depression und Angst, und andererseits auf den positiven Faktor Freude zu beziehen.

Methode: 39 Patientinnen und 30 Kontrollpersonen notierten diese Symptome täglich während 28 Tagen, und von allen Patientinnen und Kontrollpersonen wurden zweimal täglich Blutproben zwecks Bestimmung des Oxytocin-Plasmakonzentrationen entnommen. Neben dieser täglichen Erfassung geschah auch eine Registrierung von Depression mit Hilfe des Selbsteinschätzungsinstrumentes Beck Depression Inventory (BDI).

Resultat: Depressive Patientinnen wiesen niedrige Werte für Oxytocin auf und unterschieden sich dadurch – entsprechend dem BDI – beträcht-

lich von nichtdepressiven Patientinnen und den Kontrollpersonen. Niedrige Oxytocin-Plasmakonzentrationen wurden auch bei starkem Schmerz und Stress sowie bei depressiven Patientinnen beobachtet. Diese Untergruppen waren allerdings klein. Festzustellen war eine negative Korrelation zwischen den gemessenen Symptomen Depression und Angst und der Oxytocin-Konzentration, eine positive zwischen dem Faktor Freude und Oxytocin. Zwischen den in hormoneller Hinsicht unterschiedlichen Untergruppen von Patientinnen oder Kontrollpersonen bestand kein Unterschied der Oxytocin-Konzentration im Blut.

Zusammenfassung: Die Resultate deuten darauf hin, dass das Neuropeptid Oxytocin, zusammen mit anderen Neuropeptiden und Neurotransmittern, eine Rolle spielt in der Integration der Stressachsen, der monoaminergen Systeme und der schmerzregulierenden Peptide in den pathophysiologischen Mechanismen, die für die Symptome bei FMS verantwortlich sind.

Key words Fibromyalgia – oxytocin – pain – stress – depression

Schlüsselwörter Fibromyalgie – Oxytocin – Schmerz – Stress – Depression

Introduction

Fibromyalgia syndrome (FMS) is a common disorder in women characterized by wide-spread muscular pain and tender-points at specific sites according to the American College of Rheumatology criteria (38). Besides other symptoms, many patients also suffer from stressful and/or depressive states. Despite many years of intense research in this field, the etiology of the disorder is still unknown. However, perturbations in the serotonergic system (15, 22, 23), the pain processing systems (23, 24, 36) as well as in the stress axis (9, 10, 13) have been identified, which may reflect some of the pathophysiologic mechanisms.

The neuropeptide oxytocin is a nonapeptide produced in the paraventricular (PVN) and supraoptic (SO) nuclei of the hypothalamus. Under physiological conditions oxytocin from the magnocellular neurons is mainly transported from the PVN to the posterior lobe of the pituitary and there released into the vein system and the circulation. In contrast, oxytocin acting as a neuropeptide/neuromodulator is released from parvocellular neurons projecting elsewhere to various other brain regions. These neurons also project to the spinal cord, where they terminate on the presynaptic neurons of the sympathetic chain in the intermediolateral cell column and in the dorsal horn in the area where pain modulation takes place (21, 27). This latter function of oxytocin is not likely to contribute to changes in peripheral plasma oxytocin concentrations.

Oxytocin may also act as a potent secretagogue of adreno-corticotropin-hormone (ACTH) release at the anterior lobe of the pituitary. This is of interest, as perturbations in the hypothalamic-pituitary-adrenal (HPA) axis have been seen in FMS patients (9, 13). It has therefore been hypothesized that long-standing stress might be one important factor behind the pathophysiological mechanisms in the development to the FMS (2, 10, 19).

Oxytocin is known to have anti-nociceptive and analgesic effects (4, 17, 30) as well as anxiolytic and sedative effects (31). Research of the last years also has revealed antidepressive (3) and anti-stress effects (18, 32, 33) of oxytocin. This is of interest, as onset of FMS often coincides with some kind of physical and/or emotional stress (10, 19), and many patients perceive a high degree of distress due to daily hassles and lack of control (1,11). It is also of interest that steroid hormones, and estrogen in particular, stimulate the synthesis of oxytocin and the affinity to its receptors in certain regions (26), as 90% of the patients struck by the disorder are women. The effect pattern of oxytocin as well as the dependence of oxytocin on estrogen make oxytocin of special interest in FMS research as many of the patients also have their onset of the disorder in their fifth to sixth decade when estrogen levels decline.

This study was designed to assess oxytocin levels in subgroups of hormonally different patient subgroups and in depressed and non-depressed FMS patients and compare these to healthy age matched women, and also to relate oxytocin levels to symptoms that are associated with pain and mood in FMS patients.

Methods

Patients and controls

Forty female FMS patients, all fulfilling the American College of Rheumatology (ACR) (39) criteria for FMS, age 27–61 years (48.6 ± 7.5) were recruited from out care units belonging to the Rehabilitation and Rheumatologic Clinics at the University Hospital, Uppsala. As one patient had irregular menstrual cycles, and the patients should be divided into hormonally different subgroups, she was excluded. The total patient sample thus comprised 39 patients. The mean duration of disease was 11.9 ± 7.0 years. Some of the patients had pharma-

cological treatment with selective serotonin reuptake inhibitors (SSRI) and analgesic drugs. Since these patients were also to participate in a larger pharmacological study, the patients were asked not to use psychotropic or analgesic drug treatment three weeks before and during the time of the study. However, if necessary paracetamol 500 mg twice daily or acetylsalicylic acid 1g twice daily was allowed. Thirty age-matched healthy women were recruited to be compared with the patients as control subjects.

All patients and controls were divided into subgroups according to their hormonal state as follows: patients who had regular menstrual cycles, the cyclic patients (n = 16), patients without regular menstrual cycles, the non-cyclic (postmenopausal) patients (n = 23). The controls were divided in the same way into hormonally different subgroups. Of the 30 controls, there were 16 cyclic and 14 non-cyclic subjects. The control subjects were asked about current psychiatric history and widespread pain before entering the study. Two of those subjects were excluded due to depressive symptoms and one of these excluded persons also had wide-spread pain. All control subjects included in the study performed the same investigation as the patients according to plasma samples, daily scoring of symptoms and depression scores according to the Beck Depression Inventory (BDI).

Beck depression inventory (BDI)

To sharpen the diagnosis of depression the BDI, the self-rating instrument Beck Depression Inventory (BDI) (5, 37), was used beside the daily ratings of symptoms, where depression was one of these symptoms. The patients were divided into subgroups according to their mood and the BDI in depressed and non-depressed patients. The definition of depression in this version of BDI is as follows: mild depression scores 14–20, moderate depression scores 21–26 and severe depression scores 27 or more.

Patients having 14 or more scores at this self-rating scale were estimated to have depression (n = 17; 43.5%). The rest of the patients (n = 25) are referred to as the non-depressed patients. All included control subjects had less than 14 scores at the BDI.

Daily prospective symptom ratings

The patients and controls were asked to register several different symptoms, of which pain, depression, anxiety, stress and happiness were selected to be used in this study. The patients were asked to register their symptoms every evening during 28 days. Mean of the daily ratings were used to obtain a more true level of the symptoms over time, and also because this is a commonly used method to obtain a picture of the symptoms in the different phases of the menstrual cycle (6, 14). The symptoms were registered with whole numbers, where, for pain, 10 was “the worst imaginable pain” and 0 was “no pain at all”, every evening during 28 days. The other symptoms were estimated in the same way. The controls also estimated their symptoms over the same period of time in the same way. For the cyclic patients and controls the follicular phase was defined as days +4 to +12 and the luteal phase as days –1 to –9 of the menstrual cycle.

The median values of each symptom of each patient and control over the entire month were calculated. Then the median values of each symptom from all patients and controls in the different subgroups and phases of the menstrual cycle were calculated.

Blood samples

The patients and controls arrived at the clinical laboratory half an hour before the blood samples were drawn, which was done at 08.00–09.00 in the morning. From all patients and controls blood samples for determination of oxytocin levels were drawn twice, with an interval of 14 days. For the cyclic patients and controls, the blood was drawn at day 7 (first sample; follicular phase) and day 21 (second sample; luteal phase). For the non-cyclic patients and controls the median value of sample one and two was used. Then the median values of each subgroup of patients and controls and of the different phases, respectively, were calculated.

Oxytocin analysis

The oxytocin concentration was determined as follows: blood was drawn into chilled 7 ml tubes. Immediately 350 µl Trasylol was added and the blood was then centrifuged at 2000 rpm (Hettich Rotanda) for 10 minutes at +4 °C. The plasma was collected in mini-sorb tubes (NUNC, Denmark) and kept frozen at –20 °C before further processing.

Radioimmunoassay (RIA) technique for oxytocin

Oxytocin was measured by RIA as described by Stock & Uvnäs-Moberg (29). Plasma samples (500 µl) were purified by extraction with ice chilled acetone p.a. (2 ml) in polypropylene (p.p.) tubes. After vortexed and centrifuged 1800 x g, the top layer was transferred into a new p.p. tube. Ice-chilled petroliumether (40:60 grade, p.a.) (2 ml) was added followed by vortexing and centrifugation. This procedure was done twice. The

layer below was transferred into a new p.p. tube. After lyophilization the samples were concentrated twice when diluted with 0.05 M phosphate buffer with 1.0% BSA (bovine serum albumin) (250 µl). Oxytocin standard was cat.no. 8152, (Peninsula Laboratories, Inc., Belmont, California) and the standard range was 3.5–500 pmol/l. Standards and samples (100 µl) were incubated with anti-oxytocin (rabbit), KA-19 (Euro-Diagnostica AB, Malmö, Sweden) (1:250, 50 µl) for 24h, +4 °C. 125I-TYR2-oxytocin (3500 cpm/50 µl), cat. no. Nex-187, (DuPont NEN Research Products, Boston, MA, USA) was added and the incubation continued for another 48 h, +4 °C. KA-19 and 125I-TYR2-oxytocin were both diluted in 0.05 M phosphate buffer with 0.1% BSA. A sheep anti-rabbit antibody for precipitation of the rabbit anti-sera, Decanting Suspension 3, Cat. no. 10-6487-01 (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) was used. The limit of detection of the assay was 3.5 pmol/l and the intra-assay coefficient of variations was 16.4%.

Correlation between symptoms and oxytocin levels

All symptom scores of the daily ratings were correlated to the oxytocin levels in all patients, cyclic and non-cyclic patients, and also in the corresponding control subjects.

Statistics

All within group comparisons such as between the different phases of the menstrual cycle in the patients and controls, respectively, were performed using Wilcoxon matched pairs signed test. When pairwise comparisons were made between two different groups as between the cyclic and non-cyclic (postmenopausal) patients or when comparing the levels from the follicular and luteal phases in the cyclic patients with the corresponding controls, Mann Whitney U-Wilcoxon rank sum test was used. When comparing the oxytocin levels between different patient subgroups and corresponding controls and the oxytocin levels of the different phases of the patients with the corresponding phases of the controls, this test was also used. Comparing three distinct groups as for the oxytocin levels of depressed, non-depressed patients and controls, Kruskal-Wallis one-way analysis of variance followed by Conover's post hoc test (7) was used. All illustrations of the figures, except the correlation illustrations, are made using box-plots with quartiles (25th and 75th percentiles) (29). Correlation analyses were performed using Spearman's correlation test. To obtain a regression line, a linear correlation coefficient was calculated. In Figs. 3–5, the regression line is included to give a graphical representation of the relationship.

Results

Oxytocin levels

When comparing the oxytocin levels of the whole group of patients with the levels of the controls, there was no significant difference ($p = 0.55$), but the distribution of the oxytocin levels of the patients were larger than of the controls (Fig. 1). Nor was there any difference when comparing the levels of the cyclic ($p = 0.69$) and non-cyclic (postmenopausal) patients ($p = 0.69$) with the corresponding controls or when comparing the different phases in the same way.

Comparing the oxytocin levels between the patients who scored low (0–5) on the adverse symptoms, with those who scored high (6–10) also did not result in any

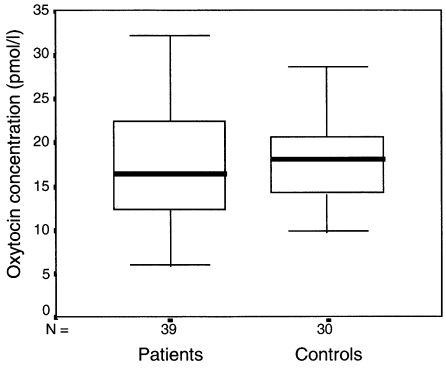

Fig. 1 The figure shows box-plots (median and quartiles)(Tukey 1977) with plasma oxytocin levels in female fibromyalgia syndrome patients (n = 39) and in sex- and age-matched healthy controls (n = 30). There is no significant difference in oxytocin levels between the patients and controls; however, the distribution is larger in the patients than in the controls. Mann Whitney U-test

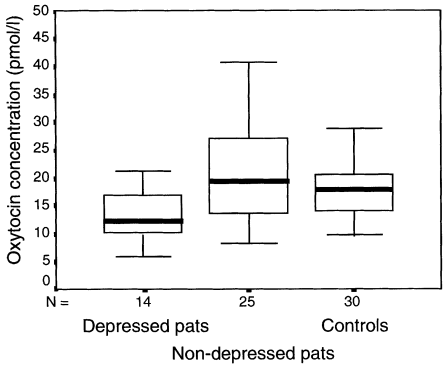

Fig. 2 The figure shows box-plots (median and quartiles) (Tukey 1977) with plasma oxytocin levels in depressed and non-depressed female fibromyalgia syndrome patients (n = 39) and in sex- and age-matched healthy controls (n=30). Depression is determined according to the self-rating instrument Beck Depression Inventory (Williams 1984). The oxytocin levels of the depressed patients (n = 14) were significantly decreased compared to the non-depressed patients (n = 25) ($p = 0.01$) and to the controls (n = 30) ($p = 0.05$). Kruskal Wallis one way ANOVA

difference of significance. However, when investigating the oxytocin levels of the patients who scored very high in these symptoms (8–10) with those of the patients who scored low (0–4), significant differences in the oxytocin levels were found with low levels in the patients who scored high in pain ($p = 0.03$), stress ($p = 0.03$) and depression $p = 0.05$. However, these patient subgroups were small ($n = 5$, 3 and 4, respectively).

Low levels of oxytocin were also found in the depressed FMS patients according to the BDI, compared to the non-depressed ($p < 0.01$) and controls ($p < 0.05$) (Fig. 2).

Correlation between oxytocin levels and symptom scores

When the oxytocin levels were correlated with the scores of pain, depression, anxiety, stress and happiness, a negative correlation was found to depression ($r_s = -0.41$, $p = 0.008$) (Fig. 3) and anxiety ($r_s = -0.46$, $p = 0.003$) (Fig. 4) in all FMS patients.

A positive correlation was seen between the happiness scores and the oxytocin concentration of all patients ($r_s = 0.35$, $p = 0.03$) (Fig. 5). There was no correlation between any of the symptoms and the oxytocin levels of the controls.

BDI scores

The mean (±SEM) of BDI in the total FMS patient group was 14.3 (1.45). The mean (±SEM) for the depressed subgroup of the patients was 23.0 (1.64) and for the non-depressed subgroup of patients 8.5 (0.77). For the control subjects the mean of the BDI was 3.7 (1.1).

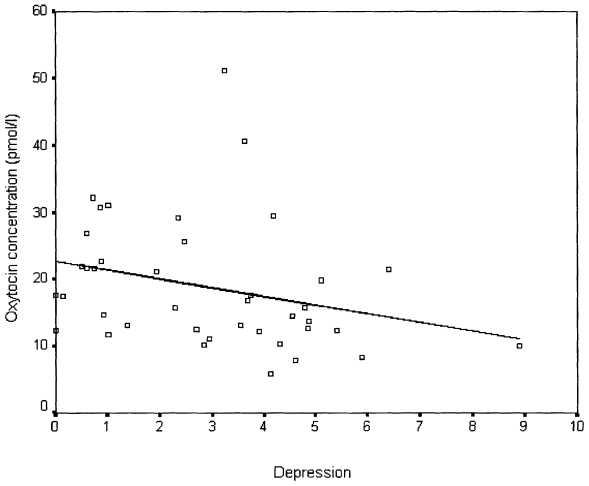

Fig. 3 A negative correlation ($r = -0.41$, $p = 0.008$) is shown between plasma oxytocin concentration and the symptom depression according to the mean of 28 days of daily ratings in female fibromyalgia syndrome patients (n=39). Spearman's correlation test

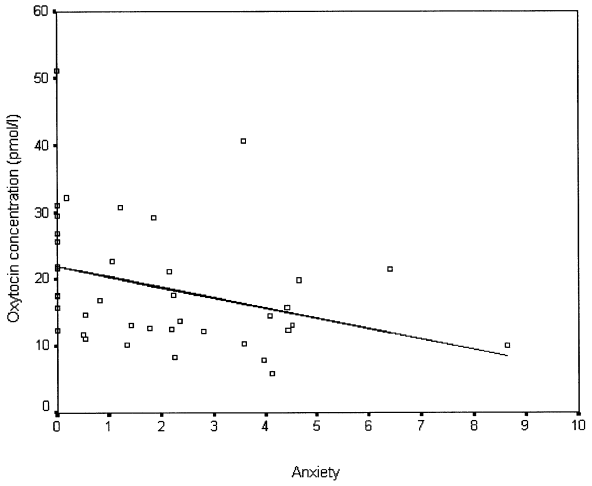

Fig. 4 A negative correlation ($r = -0.46$, $p = 0.003$) is shown between plasma oxytocin concentration and the symptom anxiety according to the mean of 28 days of daily ratings in female fibromyalgia syndrome patients ($n = 39$). Spearman's correlation test

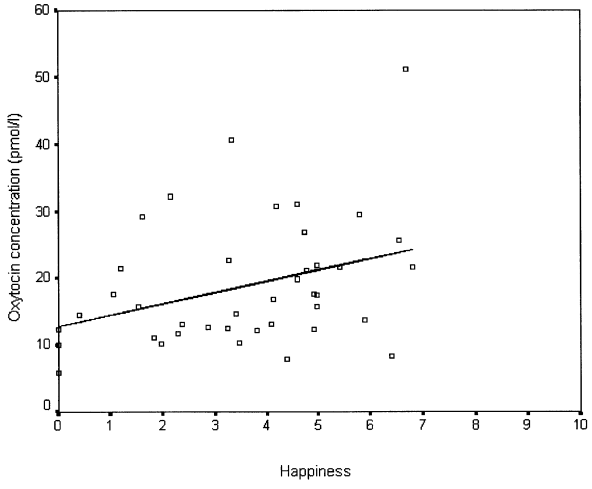

Fig. 5 A positive correlation ($r = 0.35$, $p = 0.03$) is shown between plasma oxytocin concentration and the item happiness according to the mean of 28 days of daily ratings in female fibromyalgia syndrome patients ($n = 39$). Note that this item is positive! Spearman's correlation test

The daily symptom ratings

As expected due to the illness, the patients scored significantly higher in the single symptoms and lower at the positive item "happiness" compared to the control subjects (Table 1).

Table 1 Mean (±SEM) of the daily symptom ratings during 28 days in fibromyalgia syndrome patients (n = 39) and in healthy controls (n = 30)

	Patients		Controls		
	Mean	±SEM	Mean	± SEM	p
Pain	5.9	0.2	0.3	0.1	< 0.001
Depression	2.9	0.3	0.6	0.2	< 0.001
Anxiety	1.9	0.3	0.2	0.1	< 0.001
Stress	2.8	0.3	5.1	0.4	< 0.001
Happiness	3.6	0.3	5.1	0.4	< 0.01

Discussion

New and interesting findings emerge in the present study: 1) Subgroups of FMS patients with perception of severe pain, depression and stress had low levels of oxytocin, and oxytocin levels were higher in those patients who experienced low pain, depression and stress. Although these patient subgroups were small, and firm conclusions therefore are hard to draw, this finding may be of importance. 2) The finding of the low oxytocin levels of the patients who scored high in the daily ratings is supported by the results of the patients who were depressed according to the BDI, who had significantly lower levels of oxytocin than the non-depressed patients and the controls. 3) There was a negative correlation between the levels of oxytocin and the symptom scores of anxiety and depression. In addition, a positive correlation was found between the levels of oxytocin and the item happiness in all patients.

Several animal studies have demonstrated short-term anti-nociceptive and analgesic effects of oxytocin (4, 8, 16, 17, 30, 35, 41). In addition, administration of oxytocin has been found to increase the nociceptive pain threshold in a long-term perspective (weeks) study in female and male rats (17). In patients, one study has demonstrated that intrathecally administered oxytocin relieved pain in patients with low back pain (39). The lowered pain threshold in the FMS patients who had decreased oxytocin levels in the current study may therefore in part be due to the perturbed oxytocin levels.

It is a clinical observation that many FMS patients perceive more pain at increased stress. Perturbations in the stress axes of FMS patients have also been previously demonstrated (9,10,12,13). In the current study, the patients who scored high on the symptom stress had low oxytocin levels. Although this patient group was small, this finding must be noted and is supported by the fact that there was also a negative correlation between oxytocin levels and anxiety. Many patients with FMS have reported difficulties relaxing and perceive decreased pain, increased well-being and relaxation with massage and warm water baths. The decreased perception of pain these patients experience may therefore be due to increased oxytocin effects.

Only one study has to our knowledge already assessed oxytocin concentration in FMS patients (25). In that study there was no difference between the oxytocin concentration of the FMS patients as compared to the healthy controls. Nor did the present study show differences in oxytocin concentration in FMS and controls as whole groups; however, when the patients were divided into depressed and non-depressed subgroups, there was a difference with decreased levels in the depressed patients.

The depressed FMS patients in this study also had lower oxytocin levels than the non-depressed FMS patients and the controls. There was also a negative correlation between oxytocin levels and depression and a positive correlation in all patients between the scored item happiness and oxytocin levels. In rats, oxytocin has been found to have a strong anti-depressant effect similar to that of imipramine (3). The oxytocin and serotonin (5-hydroxytryptophan (5-HT)) systems are interconnected. Oxytocin fibers project to the raphe nuclei and oxytocin may influence the secretion of 5-HT and the release of oxytocin is enhanced in response to administration of 5-HT1a and 5-HT2 receptor agonists. Recent studies have demonstrated that oxytocin is released in response to treatment with selective serotonin reuptake inhibitors (SSRI), opening up the possibility that oxytocin also may mediate further effects caused by 5-HT (34). This is of special interest as it has been demonstrated that FMS patients have low serum concentrations of tryptophan, which is a precursor to serotonin, and 5-HT as well as CSF 5-HIAA (15, 22–24, 40).

In a study by Purba et al. (20), high numbers of arginine-vasopressin and oxytocin neurons in depressed post mortem patients were found. In major depression there is an upregulation in the HPA axis, which in turn down-regulates the 5-HT1A receptors and the activity of serotonin. The increased number of oxytocin neurons may be a compensatory physiological mechanism to balance and increase the serotoninergic activity in order to accomplish better mood and well-being.

The results of this study suggests that the neuropeptide oxytocin may play an important role in the integration of the stress axes, monoaminergic systems and the pain processing peptides. However, further studies to clarify the inter-relationship between the neurobiological changes and the symptoms FMS patients perceive are required to draw firm conclusions.

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