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An open-label trial of L-5-hydroxytryptophan in subjects with romantic stress

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Abstract

This open-label trial assessed the clinical efficacy of L-5-hydroxytryptophan (5-HTP), a natural serotonin precursor, in nondepressed young subjects with high levels of romantic stress. Since both neurotrophins and serotonin have been linked to human romantic attachment, we sought to investigate the changes in serum brain-derived neurotrophic factor (BDNF) levels and platelet serotonin content in relation to the changes in romantic stress throughout the study.

A total of 15 healthy subjects (11 females and 4 males, mean age: 23.3 ± 2.1 years) who experienced a recent romantic break-up or reported recent romantic problems took part in the study. The participants were treated openly for 6 weeks with L-5-hydroxytryptophan (60 mg Griffonia simplicifolia extract containing 12.8 mg 5-HTP b.i.d., Amorex, Coropharm, Villach, Austria). The subjects were evaluated at baseline, at 3 weeks and at the end of the 6-week trial using an adapted version of the Seiffge-Krenke's Problem Questionnaire. BDNF and platelet serotonin content were determined at baseline, at 3 weeks, and after the completion of the 6-week trial.

We observed significant improvements in romantic stress scores from weeks 0 through 3 (p=0.007) but no further significant improvement was evident from weeks 3 through 6 (p=0.19). At 6 weeks, subjects had a significant increase from baseline in both BDNF and platelet serotonin values.

Our data suggest that direct modulation of the serotonergic system may have use for the treatment of psychological suffering associated with unreciprocated romantic love.

ORIGINAL ARTICLE

INTRODUCTION

Love is one of the most overwhelming of all affective states and represents a human cross-cultural universal (Esch & Stefano 2005a; Stein & Vythilingum 2009). Recent years have witnessed an increased interest in the empirical study of human romantic relationships (Emanuele *et al.* 2006; Emanuele *et al.* 2007; Marazziti *et al.* 2009). Reciprocated love promotes a stable emotional environment, arise pleasant and safe feelings of sex arousal, and has been even suggested to promote health (Esch & Stefano 2005b). While reciprocated love can be conceptualized as the catalyst behind the spread of the human life, unrequited love and high levels of romantic stress represent a frustrating experience and may be clinically associated with negative mood states such as depres-

sion, anxiety, and obsessionality (Fisher *et al.* 2010). Of much importance, an unhappy love life is frequently mentioned in suicide notes (Lester *et al.* 2004). Altogether, there is evidence suggesting a link between unrequited love affairs, suicidal thoughts and suicidal behaviour (Emanuele 2009). Unfortunately, little work has been devoted to evaluating evidence-based treatment options for subjects suffering from disappointed romantic love and high levels of romantic stress. To our knowledge, the current evidence is limited to one anedoctal report suggesting the efficacy of the homeopathic remedy aurum muriaticum natronatum in two cases of depression accompanied by suicidal ideation after disappointed romantic love (Sevar 2007). Recent imaging and genetic studies have led to the appreciation of the role played by the monoaminergic systems, and particular the serotonergic system, in human mating and romantic bonding (Stein & Vythilingum 2009; Stárka 2007; Marazziti *et al.* 1999). Of interest, a polymorphism (C516T) in the gene encoding the serotonin receptor 5HT2A has been linked to a possessive and dependent love style, which in turn represents a risk factors for high levels of romantic stress (Emanuele *et al.* 2007). It can be therefore hypothesized that serotonergic dysfunction may play a relevant role in the neurobiology of romantic stress.

This open-label trial assessed the clinical efficacy of L-5-hydroxytryptophan (5-HTP), a natural serotonin precursor, in nondepressed young subjects with high levels of romantic stress. Since both neurotrophins (Marazziti *et al.* 2009) and serotonin (Marazziti *et al.* 1999; Emanuele *et al.* 2007) have been linked to human romantic attachment, we sought to investigate the changes in serum brain-derived neurotrophic factor (BDNF) levels and platelet serotonin content in relation to the changes in romantic stress throughout the study.

METHODS

Study design

A total of 15 healthy subjects (11 females and 4 males, mean age: 23.3 ± 2.1 years) who experienced a recent romantic break-up or reported recent romantic problems took part in the study. All subjects expressed disturbing high levels of acute romantic stress. All participants were free of any current and lifetime axis I and axis II disorder diagnoses, free of acute medical illness, and judged clinically not to be at suicidal risk. Written informed consent was obtained from all subjects after the procedures had been fully explained.

The participants were treated openly for 6 weeks with L-5-hydroxytryptophan (60 mg *Griffonia simplicifolia* extract containing 12.8 mg 5-HTP b.i.d., Amorex, Coropharm, Villach, Austria). The subjects were evaluated at baseline, at 3 weeks and at the end of the 6-week trial using an adapted version of the Seiffge-Krenke's Problem Questionnaire (see below). All biochemical assessments were performed at baseline, at 3 weeks, and after the completion of the 6-week trial. No individual or group psychotherapy was permitted during the trial.

Romantic stress

Romantic stress was assessed as previously described by Nieder and Seiffge-Krenke (2001). The instrument is derived from the Problem Questionnaire (Seiffge-Krenke 1995) and consists of 7 items in the domain of romantic/interpersonal relationships (1. I don't have a boyfriend/girlfriend; 2. I feel insecure in dealing with the opposite sex; 3. I'm afraid of losing contact with my other friends if I pair up with a boyfriend/girlfriend; 4. I sometimes have to make pretenses just to please others; 5. I'm afraid of hurting others because I'm unsure of their feelings; 6. It's difficult for me to develop a truly equal and balanced relationship; 7. I'm afraid that my jealousy could ruin my friendships). The study participants were asked to indicate the stressfulness of each specific romantic/interpersonal problem, ranging from 1 (not stressful at all) to 5 (highly stressful). The total score can therefore range from 7 to 35.

Quantification of platelet 5-HT content

Blood samples were drawn by venipuncture after an overnight fast and were collected in 10-ml Vacutainer tubes (Becton-Dickinson, Meylan Cedex, France) containing 0.12 ml (0.34 mol/l) EDTA solution. Ten milliliters of blood was divided into two portions. One portion was centrifuged for 5 min at 1000×g and the supernatant was kept as plasma. The next portion was centrifuged for 5 min at 10,000×g and 4 °C, to obtain platelet-rich plasma. After a platelet count was obtained, platelet serotonin concentration was determined according to a previous method (Brondino *et al.* 2008) using an HPLC system. Concentrations of 5-HT were expressed as nmol/10^9 platelets. Platelet serotonin was determined in a quality control sample with within-series and between-series coefficients of variation of 2.9% and 4.1%, respectively.

Quantification of plasma BDNF levels

Plasma levels of BDNF were determined using a commercially available sandwich enzyme-linked immunosorbent assay (Promega, Madison, WI, USA) as described previously (Brondino *et al.* 2008). All measures were done in duplicate and the results were averaged. The intra- and interassay coefficients of variation were <6% and <8%, respectively. Since laboratory personnel were blinded to the participants' status, any possible measurement error was likely to be nondifferential.

Data analysis

The Kolmogorov-Smirnov test was used to check for normal distribution. Baseline characteristics are given as mean ± standard deviation. Correlations were tested using Pearson correlation coefficient. A repeated measures ANOVA was performed for within-group comparisons between baseline and posttreatment values.

Table 1. Romantic stress ratings and biochemical parameters at baseline, 3 weeks and 6 weeks of 15 patients with high levels of romantic stress following a romantic breakup.

Parameter	Baseline	3 weeks	6 weeks	*p*-value
Problem Questionnaire, Romantic stress	26.1 ± 3.9	17.4 ± 3.3	15.3 ± 2.6	0.001
Platelet 5-HT (nmol/10^9 platelets)	3.4 ± 1.0	4.2 ± 0.8	4.7 ± 0.7	0.001
Plasma BDNF (ng/mL)	9.6 ± 0.8	11.0 ± 1.3	12.8 ± 1.1	0.001

Linear mixed models were used to detect potential interactions, which might influence the relation between treatment and change in the study variables (including age and sex). Data analysis was performed using the Statistical Package for Social Sciences software, version 11.0 (SPSS, Chicago, IL). A two-tailed P < 0.05 was considered statistically significant.

RESULTS

All subjects had high baseline levels of romantic stress at baseline. No participants dropped out from the study. We observed significant improvements in romantic stress scores from weeks 0 through 3 (p=0.007) but no further significant improvement was evident from weeks 3 through 6 (p=0.19) (Table 1). Age and gender had no effect on change in scores on the romantic stress scale. At 6 weeks, subjects had a significant increase from baseline in both BDNF and platelet serotonin values (Table 1). Of note, the correlation between changes in platelet serotonin content and scores of romantic stress was significant in patients receiving L-5-hydroxytryptophan (n=15, r=–0.51, $p<0.05$). In addition, a similar relationship was found between BDNF and romantic stress scores (n=15, r=–0.43, $p<0.05$).

DISCUSSION

The results from this pilot open-label trial suggest that L-5-hydroxytryptophan may be beneficial for young subjects with high levels of acute romantic stress. The finding that subjects responded well to L-5-hydroxytryptophan supplementation seems to suggest that this approach alone could be an effective alternative treatment for patients who prefer a pharmacological approach to psychotherapy. Our study also reveals that patients with romantic stress display alterations in the serotonergic function and plasma levels of NTs and that supplementation with L-5-hydroxytryptophan reversed these biochemical changes. Specifically, we have found that changes in platelet serotonin content and BDNF correlate well with the changes in romantic stress. Our results are in keeping with other research showing that the serotonin system may play a significant role in the psychobiology of love and social bonding (Marazziti *et al*. 1999; Emanuele *et al*. 2007). Of note, BDNF has been recently suggested to play a role in romantic attachment (Marazziti *et al*. 2009). In addition, evidence has clearly shown that negative mood states are associated with a reduced expression of this molecule (Castrén & Rantamäki 2010). Previous studies have also shown that BDNF might serve as a peripheral marker for the mechanism of action of psychopharmacological agents in humans (Wang *et al*. 2008), and these results were confirmed in the current study.

It is clear that our preliminary results need to be interpreted with caution given the small group size and the open-label nature of the study. Nevertheless, the significant response seen in our subjects suggests that direct modulation of the serotonergic system may be useful for subjects with high levels of romantic stress. Larger studies are needed to confirm these preliminary findings. These limitations notwithstanding, we believe that these data have at least two important implications. First, these findings expand previous observations implying a potential serotonergic dysfunction in human romantic stress. Second, they suggest that direct modulation of the serotonergic system may have use for the treatment of psychological suffering associated with unreciprocated romantic love. Hopefully, in the future the scientific community should not shy away from studying the psychological impact of unrequited romantic love and romantic stress (Fisher *et al*. 2010).

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