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RESEARCH ARTICLE

Serum cortisol and BDNF in patients with major depression—effect of yoga

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ABSTRACT

Depression is associated with low serum Brain Derived Neurotrophic Factor (BDNF) and elevated levels of serum cortisol. Yoga practices have been associated with antidepressant effects, increase in serum BDNF, and reduction in serum cortisol. This study examined the association between serum BDNF and cortisol levels in drug-naïve patients with depression treated with antidepressants, yoga therapy, and both. Fifty-four drug-naïve consenting adult outpatients with Major Depression (32 males) received antidepressants only ($n = 16$), yoga therapy only ($n = 19$), or yoga with antidepressants ($n = 19$). Serum BDNF andcortisol levels were obtained before and after 3 months using a sandwich ELISA method. One-way ANOVA, Chi-square test, and Pearson's correlation tests were used for analysis. The groups were comparable at baseline on most parameters. Significant improvement in depression scores and serum BDNF levels, and reduction in serum cortisol in the yoga groups, have been described in previous reports. A significant negative correlation was observed between change in BDNF (pre–post) and cortisol (pre–post) levels in the yoga-only group ($r = -0.59$, $p = 0.008$). In conclusion, yoga may facilitate neuroplasticity through stress reduction in depressed patients. Further studies are needed to confirm the findings and delineate the pathways for these effects.

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Introduction

Depression is a highly prevalent mental disorder. As per the World Health Organization (2001), depression is expected to be the 2nd leading illness in the world by 2020. Although the mono amine hypothesis is the leading explanation for the pathophysiological basis of depression (Leonard, 2000; Ruhe, Mason, & Schene, 2007), decreased neuroplasticity in the hippocampus and hypothalamic–Pituitary–adrenal axis dysfunction are equally important (Duman & Monteggia, 2006). This may explain the relationship between stress, neuroplasticity, and depression.

Depression is known to be associated with low serum Brain-Derived Neurotrophic Factor (BDNF) (Karege et al., 2002) and elevated levels of cortisol (Gillespie & Nemeroff, 2005). Yoga has been shown to be an effective intervention in both stress and depression (Janakiramaiah, Gangadhar, Naga Venkatesha Murthy, Harish, Subbakrishna, & Vedamurthachar, 2000). Previous reports from the same data set have reported that patients in all three groups obtained reductions in depression scores, and those in the yoga groups had more benefit (Gangadhar, Naveen, Rao, Thirthalli, & Varambally, 2013). Serum BDNF levels were low in patients, and had an inverse correlation with the severity of depression (Varambally et al., 2013). There was a positive correlation between fall in depression scores and rise in serum BDNF in the yoga-only group (Naveen et al., 2013), and more patients in the yoga groups had a reduction in serum cortisol as compared to the antidepressant-only group (Thirthalli et al., 2013).

In order to test the correlation between decrease in the stress marker (cortisol) and improvement in neuroplasticity marker (BDNF), we have examined the association between serum cortisol and BDNF levels in patients with depression who were on treatment with antidepressants, yoga therapy, and both in combination. Since yoga-based interventions have been demonstrated to be effective in relieving stress, we hypothesized that the subjects in the yoga groups

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would show a better correlation between these parameters.

Materials and methods

Subjects

The data for this study came from a study comparing the clinical and laboratory outcome of patients with depression who were treated with antidepressants only, yoga therapy only, and both in combination (Naveen et al., 2013). Consenting out patients with major depression who scored 11 or more on Hamilton Depression Rating Scale (HDRS) and scored 2 or less on the suicidal item of HDRS (Hamilton, 1960) were recruited after screening by a psychiatry resident from the out-patient services of NIMHANS, Bangalore. Diagnosis was made based on DSM IV criteria and Mini International Neuropsychiatric Interview (Sheehan et al., 1998). The diagnosis was confirmed by a consultant psychiatrist. Patients were aged between 18–55 years. Patients with mental retardation, substance abuse disorders (except nicotine and caffeine), organic disorders such as dementia, epilepsy or cerebrovascular accidents, history suggestive of psychosis or bipolar disorder, or having suicidal risk or catatonia were excluded from the study. None of them had received yoga as treatment before. The patients did not have any indications for ECT (i.e. catatonia/severe depression). The study was approved by the Institutional Ethics Committee.

Fifty-four drug-naïve outpatients (32 males) were offered the option of Yoga therapy alone ($n = 19$), in combination with antidepressant medication ($n = 19$), or antidepressants alone ($n = 16$). The choice of treatment group was non-randomized and made by the subjects themselves. The consenting subjects had serum cortisol values assessed at baseline and follow-up. Duration of follow-up was 12 weeks.

Treatments

Yoga therapy

Subjects in the yoga groups practiced a specific developed and validated yoga module (Naveen et al., 2013) for 3 months. The participants of the two yoga groups were requested to come daily for a period of 10 days to NIMHANS Yoga centre, where a yoga professional with a graduate medical degree in Yoga and Naturopathy of 5 years duration taught them the yoga practices. Each session of practice lasted for 1 h. The participants were then asked to come for sessions once a week for the next 2 weeks and instructed to continue the yoga practices at home thereafter. There was also a booster training session in the yoga centre in the first weeks of the 2nd and 3rd months of the study. Home practices were monitored by a family member. The subjects were instructed to maintain a register of each day's yoga practice at home, and to report any adverse effect during the study period.

Antidepressant medication

Anti-depressants were prescribed by the treating psychiatrist for the period of study. This treatment remained unchanged in nearly all patients. Antidepressants administered were escitalopram (10–15 mg/day), fluoxetine (20–40 mg/day), duloxetine (60 mg/day), sertraline (50–100 mg/day), amitriptyline (25–100 mg/day) and mirtazapine (7.5–15 mg/day). The first author had a telephonic conversation with all the subjects at different time points during the 3 months of treatment to encourage compliance to medication.

Assessments

A trained rater who was blind to the group status of the patients (psychiatry resident) assessed severity of depression using the Hamilton Depression Rating Scale (HDRS). Serum BDNF & cortisol levels were assessed by a biochemist who was also blind to the group status, using sandwich ELISA method. Assessments were done before starting the treatment and after 3 months.

Assessment of serum BDNF and cortisol levels

Venous blood was sampled between 8.30 and 11 AM before breakfast at baseline and 12 weeks thereafter. The sample was allowed to clot and the serum was separated within 30 min. Coded serum samples were stored at −80 °C. The BDNF and cortisol assay was performed in batches within a period of 3 months from the beginning of the sample collections. Analysis was done with the help of the biochemist using enzyme-linked immunosorbent assay (ELISA) with commercial kits (Ray Biotech Inc, UK, & Globe diagnostics SRL, Milan Italy) according to the manufacturer's instructions. The intra and inter assay coefficient of variations were 1.34% and 4.34%, respectively.

Statistical analysis

Baseline differences were analyzed using one-way ANOVA and Chi-square test. The number of subjects in whom cortisol levels dropped or increased was

compared across groups using Chi-square test. Correlations between Serum BDNF (pre–post) and cortisol levels (pre–post) were analyzed using Pearson's correlation. For significance, alpha was fixed at $p < 0.05$.

Results

Patients in the three groups were not different with respect to baseline socio-demographic details and other clinical parameters except education, where patients in the yoga group had higher educational status, and baseline BDNF, where patients in the yoga + antidepressant group had lower BDNF levels (Table 1). However, years of education and baseline BDNF levels did not correlate significantly with change in BDNF or cortisol levels.

Overall among the 54 subjects, cortisol level dropped in 31 subjects and increased in 23 subjects. The majority of subjects in the two yoga groups had reductions in cortisol, whereas more subjects in the antidepressant-only group had increase in cortisol. This effect of yoga was statistically significant (Table 2).

Pre- and post-intervention BDNF levels were available in 46 patients (Antidepressant only, $n = 11$; yoga + antidepressant, $n = 16$; yoga-only, $n = 19$). There was a significant negative correlation between the change in cortisol (Pre–Post) and the change in BDNF (Pre–Post) in the 46 subjects ($r = -0.307$, $p = 0.038$) (Figure 1). When the changes were analyzed in individual groups, the correlation was significant only in the Yoga-only group ($r = -0.59$, $p = 0.008$), whereas it was not significant in the other two groups—Yoga + antidepressant ($r = -0.14$, $p = 0.6$); antidepressant-only ($r = -0.21$, $p = 0.54$).

Discussion

In this study, we found a significant negative correlation between change in serum BDNF and serum cortisol levels in patients with depression treated with yoga alone. This is the first study to report this finding. The findings suggest that levels of serum BDNF and cortisol are reciprocal in nature in patients with depression.

In this study, rise in BDNF levels was observed in the Yoga group, which is consistent with the previous antidepressant related studies on serum BDNF levels (Aydemir, Deveci, & Taneli, 2005; Aydemir, Deveci, Taskin, Taneli, & Esen-Danaci, 2007; Gervasoni et al., 2005; Shimizu et al., 2003). Patients getting yoga therapy, either with drugs or solely, had better reductions in cortisol levels. This is in keeping with yoga reducing cortisol in healthy and alcohol-dependent subjects undergoing detoxification when yoga was added (Vedamurthachar et al., 2006).

Negative correlation was observed between change in BDNF and cortisol level in the Yoga-only group. It is possible that the finding of such a correlation in the Yoga-only group could be related to absence of the medication confound. Yoga may have different biological mechanisms that operate on antidepressive, BDNF elevation, and cortisol reduction pathways. Stress reduction mechanisms, by way of quieting the HPA axis, may be particularly relevant to the effect of Yoga in reducing depression. Demonstrating the correlation between reduction in cortisol and increase in BDNF levels helps to understand the link between

Table 1. Demographic and clinical characteristics of patients in the three groups.

Parameter	Medication ($n = 16$) Mean ± SD	Yoga with medication ($n = 19$) Mean ± SD	Yoga only ($n = 19$) Mean ± SD	One-way ANOVA/χ^2	
				F	p
Age	33.19 ± 7.11	34.11 ± 10.75	35.89 ± 7.85	0.435	0.649
Education (in years)	7.38 ± 4.65	11.53 ± 4.58	12.79 ± 3.41	7.65	0.001*
Male	9 (56.3%)	11 (57.9%)	12 (63.2%)	0.194	0.907
Duration of Illness (months)	22.44 ± 19.02	18.47 ± 15.37	22.37 ± 26.26	0.219	0.804
Age of onset (years)	30.88 ± 7.81	32.71 ± 11.16	34.42 ± 7.33	0.676	0.513
HDRS baseline score	18.12 ± 3.86	18.47 ± 5.43	16.84 ± 4.10	0.669	0.516
Baseline serum Cortisol	95.73 ± 62.09	110.27 ± 56.57	113.61 ± 61.67	0.425	0.656
Baseline serum BDNF^	21.48 ± 7.46 ($n = 11$)	15.71 ± 5.28 ($n = 16$)	20.27 ± 6.60 ($n = 19$)	3.32	0.046*

*$p < 0.05$.
^BDNF baseline ($n = 46$).

Table 2. Changes in cortisol across the three groups.

Category	Medication-only ($n = 16$)	Yoga + medication ($n = 19$)	Yoga-only ($n = 19$)	Chi-square
Patients with reduction in Cortisol (percentage)	5 (31.3%)	13 (68.4%)	13 (68.4%)	0.042*
Patients with increase in Cortisol (percentage)	11 (68.7%)	6 (31.6%)	6 (31.6%)	

*$p < 0.05$.

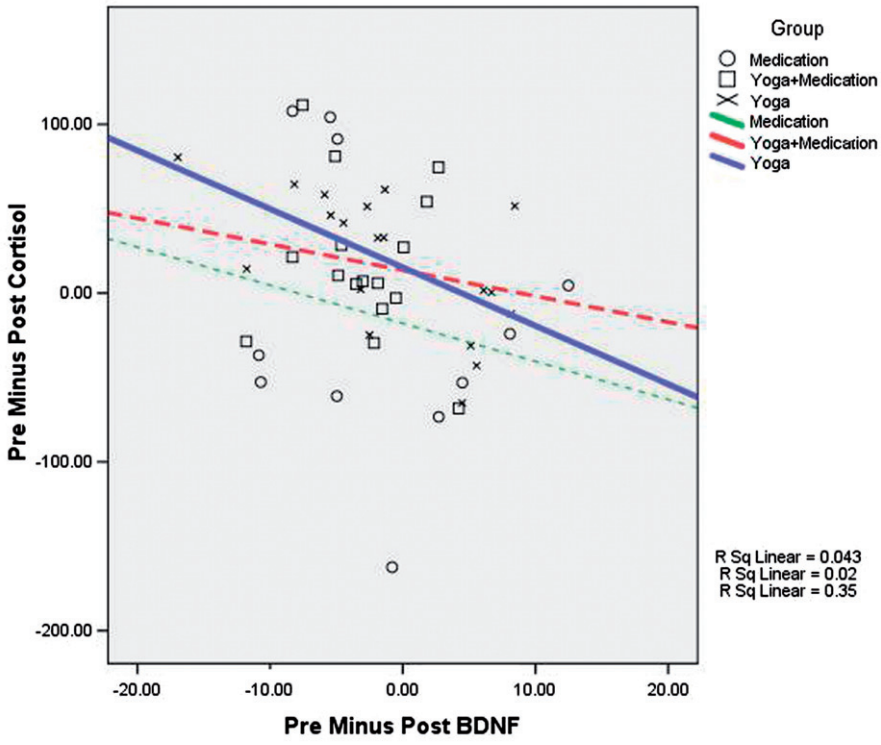

Figure 1. Correlation between change in serum cortisol and BDNF levels.

stress reduction and facilitation of neuroplasticity, which is now thought to be the mechanism of antidepressant effects (Andrade & Rao, 2010). It is of great importance in relapse prevention, as it suggests that control of stress by continued yoga practice may help prevent relapse.

It is also evident that we had little control over the medication sub-types or their doses in this study. It is possible that the drug effects may have confounded BDNF and cortisol responses. Low BDNF level and hypercortisolemia are the result of decreased neuroplasticity in the hippocampus and hyper functioning of the hypothalamic–pituitary–adrenal axis (Christensen & Kessing, 2001; Duman & Monteggia, 2006; Gillespie & Nemeroff, 2005).

We used a Yoga-therapy module rigorously validated for use in patients with depression. Patients with suicidal risk were not recruited due to ethical reasons. The raters being blind to the allocation status of the patients avoided any possible bias in the assessments. We used a standardized diagnostic tool, the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) to diagnose depressive disorder. Further, antidepressant drugs and dosages used in this study are according to the standard treatment algorithms (Anderson, Nutt, & Deakin, 2000). Assessment of serum BDNF and cortisol level was done by a biochemist blinded to the treatment status of the patients. Standard procedure was followed to collect and store the serum samples. Non-random allocation to treatment groups is a major limitation of this study. The three groups were not different in most of the socio demographic details, illness, and other parameters at baseline, except serum BDNF being lower in the yoga + antidepressant group and years of education being higher in the yoga-only group. Years of education and baseline BDNF did not correlate significantly with change in BDNF or cortisol levels. Therefore, the possibility of bias due to baseline differences is small. However, one cannot rule out the possibility of differences in unmeasured variables influencing the outcome measures. The sample size in each group being small is another limitation of this study.

The interactions of BDNF with serotonergic systems, HPA axis, and other biological markers have been extensively studied (Manji et al., 2003; Ren-Patterson et al., 2005). Reduction in stress may be expected to lower the cortisol levels. There is evidence to suggest a reciprocal role for stress and cortisol on BDNF (Bravo et al., 2009; Schaaf, de Jong, de Kloet, & Vreugdenhil, 1998; Smith, Makino, Kvetnansky, & Post, 1995). Further, impaired hypothalamo-pituitary-adrenal axis has been associated with reduced hippocampal volumes, suggesting its interference with neuroplasticity (Gold, et al., 2010; Knoops, Gerritsen, van der Graaf, Mali, & Geerlings, 2010; Lupien et al., 1998). It is, hence, likely

that lowered cortisol levels facilitate neurotropism. Relation between BDNF and cortisol levels has been well addressed in this study, which could explain these observations. Increased BDNF levels related to antidepressant drugs have been interpreted as neuroplastic mechanisms in the relief of depressive symptoms. Alternatively, it is known that 'de-stressing' effects of some treatments, including yoga, reduce cortisol.

An important issue is whether serum BDNF levels are related to brain BDNF levels. It may be noted that BDNF crosses the blood–brain barrier (BBB) and, hence, serum BDNF reliably reflects brain BDNF concentrations (Pan, Banks, Fasold, Bluth, & Kastin, 1998). Pre-clinical studies in rats have shown a positive correlation between serum and cortical levels (Karege et al., 2002). Future studies could look to explore the relation between serum BDNF levels and cerebrospinal fluid (CSF) in patients with depression. Association between BDNF levels and volumetric changes in the hippocampus may be worth exploring as there are reports that patients with depression have decreased hippocampus volume (Videbech & Ravnkilde, 2004). As BDNF may be a marker for neuroplasticity and cortisol may be a marker for stress, this finding has a significant implication in the pathophysiology of depression and mechanisms of antidepressant treatment.

In summary, there was a significant correlation between change (increase) in serum BDNF and change (decrease) in serum cortisol levels in patients with depression treated with yoga intervention alone. This suggests that yoga may have stress reduction and neuroplastic effects in depressed patients, which is an important finding for explaining the effects of yoga in this population. However, these findings need to be replicated and confirmed in randomized controlled studies.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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