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The influence of Hatha yoga as an add-on treatment in major depression on hypothalamic–pituitary–adrenal-axis activity: A randomized trial

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ABSTRACT

Objectives: The impact of Hatha yoga as add-on treatment to quetiapine fumarate extended release (QXR) or escitalopram (ESC) in depressed patients on hypothalamic–pituitary–adrenal (HPA) axis activity was assessed.
Methods: 60 inpatients suffering from major depressive disorder (MDD) according to DSM-IV were randomized for a 5 week treatment with Yoga or not (control group) and with either QXR (300 mg/day) or ESC (10 mg/day). Serial dexamethasone/corticotropin releasing hormone (DEX/CRH) tests were performed to assess HPA axis function. The Hamilton Depression Rating Scale (21-HAMD) was used weekly.
Results: A more pronounced down regulation of the HPA axis activity due to yoga could not be detected. The stepwise long term cortisol reduction was seen in both medication groups, irrespectively of yoga add-on treatment. In addition, cortisol improvers in week 1 of therapy (reduction in cortisol peak value within the DEX/CRH test) reached significant greater amelioration of depressive symptoms after 5 weeks.
Conclusions: Our results suggest that antidepressant agents down regulate HPA axis function to a greater extent than additional Hatha yoga treatment. Moreover, an early reduction of HPA system hyperactivity after one week of pharmacological treatment seems to raise the possibility of a favorable treatment response.

1. Introduction

Yoga combines breathing techniques, meditation, muscle relaxation and physical workout (Pilkington et al., 2005; Granath et al., 2006). The aim of the holistic yoga practice is to enhance the development of individual's self-awareness and control of the body and mind, the ultimate goal is a so called "nirvana like state" (Ross and Thomas, 2010; Patel et al., 2012; Mehta and Sharma, 2013) equivalent to deep relaxation which may be useful also as an add-on to antidepressant treatment. In our study the word yoga is used to tag Hatha yoga, which is one of the most commonly practiced types of yoga (Birdee et al., 2008). Yoga increases health-related quality of life in general while reducing perceived stress of the participants (West et al., 2004; Kjellgren et al., 2007; Vera et al., 2009; Patel et al., 2012). With respect to psychological and physiological benefits, Yoga improves a wide range of symptoms such as anxiety, stress and depressive mood, heart rate, blood pressure (Li and Goldsmith, 2012), memory performance (Ross and Thomas, 2010), insomnia (Vera et al., 2009), and reduction of emotional tension (Andrade and Pedrao, 2005). Congruent with these reports and due to a growing number of patients with mood disorders using complementary or alternative therapy interventions (Ernst, 2003), recent reviews indicate that yoga is used in clinical context as an effective therapeutic intervention in unipolar

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depression (Pilkington et al., 2005; Uebelacker et al., 2010; D'Silva et al., 2012; Kinser et al., 2012; Mehta and Sharma, 2013) and bipolar disorders (Andreescu et al., 2008) regarding reduction in depressive symptoms. Practicing yoga is associated with several biochemical effects such as influence on blood pressure, heart rate, urinary catecholamines (Granath et al., 2006) and cortisol levels in healthy subjects (Vera et al., 2009; Rocha et al., 2012). The effects of yoga seem to be mediated via multiple paths such as reduction in sympathetic tone, activation of antagonistic neuromuscular systems, relaxation in the neuromuscular system and stimulation of the limbic system (Riley, 2004) which yield to the restoration of the homeostasis of the stress response systems (Streeter et al., 2012).

Due to a lack of randomized controlled trials (RCT) measuring plasma cortisol levels via DEX/CRH tests in representative study populations, the current studies report inconsistent results regarding the directions of change of potential biomarkers which are associated with depressive symptoms (Pilkington et al., 2005; Mehta and Sharma, 2013). Although the underlying mechanisms concerning neurobiological and emotional changes during yoga exercise in depressed patients are yet unknown (Kinser et al., 2012; Streeter et al., 2012), one of the discussed hypothesis are changes in stress hormone systems, which can be measured via cortisol-secretion (Vedamurthachar et al., 2006; Vadiraja et al., 2009; Ross and Thomas, 2010; Streeter et al., 2012; Woolery et al., 2004). The corticosteroid receptor hypothesis (neuroendocrinological hypothesis) is a prominent approach concerning the etiology of major depression and considers a dysregulation of the HPA axis function as a possible mechanism (Holsboer, 2000, 2001). Since depressive symptoms have been linked to HPA axis hyperactivity in a part of depressed patients, a gradual normalization of the HPA system dysregulation as measured by serial combined DEX/CRH tests precedes or coincides with the response to antidepressant treatment and is according to some authors a necessary prerequisite for clinical remission to become manifest (Ising et al., 2007). Dampening on HPA axis system results in decreased cortisol levels, this is partly mediated or moderated via restored signaling of corticosteroid-activated mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Pariante and Miller, 2001). Moreover, the HPA axis seems to be a promising target regarding new treatment strategies in depression (Schüle et al., 2009b).

To date there is no randomized controlled study investigating the effects of yoga in patients with diagnosed MDD involving a refined measurement of the HPA axis activity using cortisol levels or DEX/CRH-tests (Li and Goldsmith, 2012; Mehta and Sharma, 2013). Therefore, the impact of yoga on cortisol levels in depressed patients seems ambiguous. Only a few RCT's measuring depressive "symptoms" (major depression was not diagnosed) and cortisol levels are available (Woolery et al., 2004; Vedamurthachar et al., 2006; Vadiraja et al., 2009). These studies indicate that two weeks daily yoga sessions of 45 min (Vedamurthachar et al., 2006) and six weeks with three yoga session for one hour each week lead to a significant decrease in plasma cortisol and salivary morning cortisol (Vedamurthachar et al., 2006; Vadiraja et al., 2009) compared to brief supportive therapy (Vadiraja et al., 2009) and continued inpatient care (Vedamurthachar et al., 2006). Moreover, reductions in plasma cortisol were correlated significantly with a decreased sum score in the Beck Depression Inventory (Vedamurthachar et al., 2006; Vadiraja et al., 2009). One randomized study investigated salivary cortisol levels in the morning in young adults with mild depressive symptoms (no diagnosed MDD), which had lower BDI-scores and higher morning cortisol levels after five weeks (two 1-hour yoga classes each week) of yoga compared to wait-list group (Woolery et al., 2004). Another study (non-randomized and without control group) yielded similar results (Curtis et al., 2011): salivary cortisol levels of patients with fibromyalgia and depressive symptoms were increased after 8 weeks of yoga class (75 min twice a week). With respect to the corticosteroid receptor hypothesis, serial DEX/CRH tests are the gold standard concerning the measurement of HPA axis system in depressed patients (Schüle et al., 2009a).

Despite this clearly limited scientific research regarding HPA axis in the frame of yoga and major depression, yoga is already recommended as a second-line adjunctive treatment in mild to moderate major depression (Ravindran et al., 2009).

Given that a direct relationship between yoga, cortisol levels and declines in major depression are not yet finally supported, the purpose of this study was to determine whether yogic practices as a useful supplement to pharmacologic therapy in major depression contribute to a possible reduction of HPA axis activity. We assumed that – independent of the yoga sessions – those patients who would observe a decrease in cortisol levels within the first week (improvement) also would be more likely to show a reduction in symptoms of depression. Due to the unclear direction of possible changes in cortisol levels in DEX/CRH tests caused by yoga training, no predictions were made in this regard. The aim regarding the yoga training was exploratory and not confirmatory: we investigated whether additional yoga treatment would have both endocrine effects on cortisol levels and clinical effects on depressive symptoms regarding response and non-response in the context of conventional treatments (medication) in clinically depressed inpatients. It is widely unexplored up to now whether yoga increases or decreases the probability of a pharmacologic treatment response in depressed patients.

In the present study, the influence of 5-week treatment with the atypical antipsychotic drug with antidepressant properties quetiapine fumarate extended release (QXR) and of the selective serotonin-reuptake inhibitor (SSRI) escitalopram (ESC) in combination with yoga (60 min/week) or control group (no yoga intervention) on the time course of HPA axis activity was investigated in depressed inpatients.

- Are the endocrinological effects of yoga/no yoga treatment and QXR/ESC on HPA system related to the antidepressant efficacy of these drugs after 5 weeks of treatment?
- Is the onset of antidepressant action of QXR/ESC related to yoga?

2. Method

The intention-to-treat sample comprised 60 unrelated patients who were aged 18–65 years and suffering from a major depressive episode according to DSM-IV criteria (296.2 or 296.3). Patients were recruited from August 2009 up to February 2012. The allocation of the patients to the treatment groups was done according to the pre-defined randomization plan and occurred in a randomized order. Patients were treated for 5 weeks with either QXR (300 mg/day; group 1) or ESC (10 mg/day; group 2) and yoga therapy (Hatha yoga 60 min/week) or no yoga (control group). The yoga training group was supervised by a physical therapist and consisted of maximum 15 patients. Due to different side effect patterns of ESC and QUE as well as different administration times in clinical practice (ESC is given preferably in the morning whereas QXR is usually administered in the evening) no blinding concerning the medication was conducted. See Table 1 for details of clinical and demographical characteristics of depressed patients at admission. Details concerning the administration of QXR, ESC and the process of the DEX/CRH-test and laboratory methods see Supplemental Information.

The DEX/CRH was performed before treatment, after 1 and after 5 weeks of treatment calculating cortisol (COR) area under the