Journal of Affective Disorders 152-154 (2014) 468–473

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

# Prolactin response to buspirone is not impaired in drug-naïve first episode patients with major depressive disorder

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ARTICLE INFO

*Article history:*
Received 18 April 2013
Received in revised form
1 August 2013
Accepted 1 August 2013
Available online 22 August 2013

*Keywords:*
Major depressive disorder
Drug-naïve
First episode
Prolactin
5-$HT_{1A}$ receptor
Buspirone

ABSTRACT

*Background:* An altered postsynaptic 5-$HT_{1A}$ receptor function along with hypercortisolemia has been associated with major depressive disorder (MDD). However, several methodological considerations related to data interpretation arise when subjects previously exposed to psychotropic medication are included in the study population. To address those issues we designed a study in a well defined cohort of first-episode, treatment-naïve MDD patients.

*Methods:* This cross-sectional case–control pharmacologic challenge study was designed to investigate the prolactin (PRL) response to buspirone in 21 non-late-life adult, treatment-naïve MDD patients with the first affective episode and in 20 age- and sex-matched healthy controls. Depressed patients showed a basal score in the Hamilton Rating Scale for Depression (HAMD-17) higher than 20.

*Results:* No significant difference in PRL response to buspirone between first-episode, treatment-naïve patients with MDD and controls, was observed. The correlation between basal cortisol levels and PRL response was not observed in MDD group while significant negative correlation was found in healthy controls. The significantly higher PRL response to buspirone was observed in melancholic patients as compared to non-melancholic subjects.

*Limitations:* The current study is limited by its cross-sectional design, small sample size, factors related to neuroendocrine challenge methodology, and no placebo control.

*Conclusion:* These results indicate no consistent changes in the hormonal response to the 5-$HT_{1A}$ agonist buspirone in major depression. Taken into account the interpretation of the buspirone test the present study does not support the hypothesis of an altered functional activity with down-regulation of the postsynaptic 5-$HT_{1A}$ receptor and/or in the postsynaptic receptor signal transduction in the hypothalamus in the pathogenesis of MDD.



## 1. Introduction

Major depressive disorder (MDD) is a common illness associated with significant disability, morbidity, and mortality. The pathogenetic cause of MDD is unknown. However, the neurobiological observations associated with the MDD implicate hypofunction of the serotonin (5-HT) system and more specifically postsynaptic serotonin-1A (5-$HT_{1A}$) receptors along with hypothalamic–pituitary–adrenal (HPA) axis dysfunction. The interaction between 5-$HT_{1A}$ receptor system and endocrine system may play a role in the pathogenesis of MDD (Porter et al., 2004; Ruhé et al., 2007; Savitz et al., 2009).

The administration of azapirones, selective 5-$HT_{1A}$ receptor agonists, such as buspirone, ipsapirone, and gepirone, induces an increased secretion of several hormones including adrenocorticotropin (ACTH), cortisol, growth hormone (GH), and prolactin (PRL) that result from the stimulation of postsynaptic 5-$HT_{1A}$ receptors in the hypothalamic paraventricular nucleus (PVN). The magnitude of the hormonal response to the 5-$HT_{1A}$ agonists is a suitable indirect measure of the postsynaptic 5-$HT_{1A}$ receptor function in the hypothalamus in humans using non-invasive physiological approach (Cowen et al., 1994; Cowen, 2000; Navinés et al., 2007).

Neuroendocrine challenge studies in depression generally replicate finding on the impaired postsynaptic 5-$HT_{1A}$ receptor function with decreased hormonal response to azapirones in depressed patients compared with the normal controls. However, recent studies of neuroendocrine responses to 5-$HT_{1A}$ receptor agonists in MDD have been inconsistent (Navinés et al., 2007; Savitz et al., 2009) and the postsynaptic 5-$HT_{1A}$ receptor desensitization in depression has been questioned. The divergent findings may be partly related to methodological differences including sample sizes, selection criteria for illness chronicity, unmatched groups, sex, age, time of challenge, hormonal procedures, suicidality, pharmacotherapy, wash-out procedure, etc. As HPA axis

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http://dx.doi.org/10.1016/j.jad.2013.08.005

dysregulation with chronic hypercortisolemia seems to attenuate 5-$HT_{1A}$ receptor function it shall be taken into consideration in study design and data interpretation (Navinés et al., 2007). Several trait phenomena in biological abnormalities in MDD persist during episode remission and may be the predisposing factor to the recurrent course of the disorder or its chronicity while state-related deregulated homeostatic mechanisms occur only during acute illness (Ruhé et al., 2007; Bhagwagar and Cowen, 2008). Other confounding factors include the use of concomitant medications and previous psychotropic medication along with wash-out or discontinuation procedures and variable drug-free period definition. Thus, the observed postsynaptic 5-$HT_{1A}$ receptor neurotransmission shall be controlled for the course and treatment of the MDD related factors affecting neuroendocrine challenge interpretation. Examining first-episode, treatment naïve patients with depression, might help disentangle the effects of some of these potential confounders and may be important in elucidating the core pathogenesis of this illness.

To address these factors, a case–control study in a well defined cohort of first-episode, treatment-naïve MDD patients and healthy subjects was designed to assess the sensitivity of postsynaptic 5-$HT_{1A}$ receptors by measuring plasma concentrations of PRL after the administration of buspirone. Buspirone is a complete agonist of the 5-$HT_{1A}$ autoreceptors and a partial postsynaptic 5-$HT_{1A}$ receptors agonist. It does not bind to other 5-HT receptors in physiologic concentrations as it is an antagonist for the dopamine $D_2$ autoreceptors with its 15-fold weaker affinity than for the 5-$HT_{1A}$ receptors. The enhanced PRL response is likely to reflect facilitation in 5-$HT_{1A}$ neurotransmission along with some reduction in central dopaminergic inhibition of PRL release contributing to the observed hormonal response. Thus, buspirone is a common challenge test used in humans to investigate 5-$HT_{1A}$ receptors (Cowen et al., 1994; Moeller et al., 1994; Navinés et al., 2007; Loane and Politis, 2012). Factors which we considered important for results' interpretation were baseline cortisol levels (Mitchell and Smythe, 1990) and melancholia. According to the literature we established the hypothesis that the depressed patients would show blunted PRL secretion compared to healthy subjects indicating decreased sensitivity of postsynaptic 5-$HT_{1A}$ receptors.

## 2. Methods

### 2.1. Subjects

Twenty-one, first-episode, treatment-naïve MDD patients were recruited from the outpatient clinic of a university-affiliated hospital in the city of Gdańsk, Poland. Patients were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). The severity of depression was evaluated using 17-item Hamilton Rating Scale for Depression (HAMD-17) (Hamilton, 1960). Only those with HAMD-17 score of $\geq 20$ were eligible for the study. Only subjects being drug-naïve for any psychotropic medicine were included to the study. All patients underwent routine physical examination. Exclusion criteria were as follows: any other Axis I disorder, any unstable medical condition, any history of endocrine or neurological disease, pregnancy or lactation, alcohol or drug abuse in the past 12 month, tobacco smoking exceeding 25 cigarettes a day, BMI $\leq 18$ and $\geq 30$. Patients of age younger than 18 years or older than 55 years old were also excluded. Women had not received hormonal contraception for at least 12 month prior to neuroendocrine challenge.

The control group consisted of 20 healthy subjects recruited from the community. They were also interviewed by the same psychiatrists using the Structured Clinical Interview for DSM-IV, non-patient edition (First et al., 1997). All control subjects underwent routine physical examination. None of them had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives, and all were well matched with the patients in terms of age, gender, menopausal status, and metabolic parameters. To be included in the control group, a score $\leq 5$ in the HRSD-17 was required. Exclusion criteria were as follows: positive history of any exposure to psychotropic medication, any unstable medical condition, pregnancy or lactation, alcohol or drug abuse in the past 12 month, BMI of 30 or greater. Women were not allowed to be taken oral contraceptives. Neuroendocrine tests were performed between days 3 and 10 of the menstrual cycle in premenopausal women.

The study was carried out in accordance with the latest version of the Declaration of Helsinki. For each study participant, written consent was obtained after the procedures had been fully explained. The study and recruitment procedures were approved by the Ethic Research Committee of the Institution.

### 2.2. Buspirone protocol

The study followed a cross-sectional, case–control design. Three days prior to endocrine challenge all subjects refrained from alcohol, cheese, oxo, marmite, bovril or other substances likely to alter the endocrine test and fasted from midnight before the experimental day. On the test day, subjects arrived at the laboratory at 07:30 h and had an indwelling catheter inserted in a forearm vein. Subjects were tested seated. After a minimum 30-min rest period to minimize stress factors, three blood samples (08:20 h, 08:40 h, and 09:00 h) were taken for baseline determinations of plasma cortisol. Then 30 mg of buspirone (Spamilan®, Anpharm, PL) was administered orally at 09:00 h. Blood samples for PRL were taken at 09:00 h, 09:20 h, 09:40 h, 10:00 h, 10:20 h, 10:40 h, 11:00 h post challenge. Samples for cortisol and PRL were immediately centrifuged. Plasma was separated and stored at $-80$ °C for later batch analysis. In women, tests were performed in the first phase of the menstrual cycle.

### 2.3. Hormone assays

Plasma cortisol was determined by standard chemiluminescence microparticle Immunoassay (CMIA) using a commercially available kit (Architect® Cortisol, Abbott Diagnostics, USA). The intra-assay coefficient of variation (CV) ranged from 2.1 to 5.5% and the total CV values ranged from 2.5 to 7.7%. The sensitivity was 0.8 μg/dl.

Plasma PRL was determined by standard CIMA using a commercially available kit (Architect® Prolactin, Abbott Diagnostics, USA). The intra-assay coefficient of variation (CV) ranged from 2.3 to 3.8% and the total CV values ranged from 3.3 to 4.7%. The sensitivity was 0.6 ng/ml.

### 2.4. Statistical analysis

Statistical procedures were performed using StatsDirect v2.7.9 (http://www.statsdirect.com). The PRL response to buspirone was calculated as the maximum peak response, that is, the peak response minus baseline (maxPRL) and the area under the curve (AUC) with respect to increase (AUCI) (Pruessner et al., 2003) from baseline. Differences between groups for discrete variables were assessed using the chi-square test. Shapiro–Wilk test was used to assess normal distribution of continuous data. Normally distributed variables were compared using Student's *t*-test, all other continuous data were compared with non-parametric Mann–Whitney *U*-test. All tests were two-tailed. Differences were regarded as significant when $p < 0.05$.