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Research article

Basal prolactin levels in rat plasma correlates with response to antidepressant treatment in animal model of depression

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HIGHLIGHTS

- Negative correlation between basal PRL level and response to IMI administration in the animal model of depression – chronic mild stress.
- Lack of correlation between basal PRL level and stress response.
- Basal level of PRL may have a potential effect in the successfully treatment of depression.

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ABSTRACT

Prolactin (PRL) has been shown to be altered by psychotropic drugs, including antidepressant drugs (ADs). Many studies have focused on the response to antidepressant treatment (especially related to the serotonergic system) using the fenfluramine test (PRF), however some data suggest lack of correlation between PRF and prediction of clinical response to ADs.

In our study we have investigated the hypothesis that basal plasma level of prolactin is a better predictor of antidepressant treatment. We have used Chronic Mild Stress (CMS) – the animal model of depression. Rats are exposed to CMS in combination with imipramine (IMI) treatment for 5 consecutive weeks. Blood samples were collected from the rat tail vein three times: before the CMS procedure, after 2 weeks of stress and after the complete CMS procedure (after 5 weeks of stress and IMI treatment). The PRL level in plasma was determined using the commercially available ELISA kit.

In CMS, anhedonia in rats is manifested by reduced consumption of sucrose solution while administration of antidepressant drugs reverses anhedonia. Some animals (ca.30%) did not respond to antidepressant therapy and were considered treatment-resistant. There was no correlation between basal PRL levels and stress response, however, from the results obtained by Spearman Rank Correlation analysis we have observed a significant negative correlation between basal PRL levels before the CMS procedure and behavioral response to IMI administration. The obtained results indicate that the basal PRL level in rat plasma correlates with a good response to treatment in the animal model of depression.

1. Introduction

Hyperprolactinemia, usually defined as increased levels of prolactin (PRL), is one of the most common endocrine dysfunctions of the HPA axis. One of the clinical manifestation of hyperprolactinemia is a tendency to anxiety and depression. It has been shown – using different stressfull conditions – that stress, which is major depression risk factor, has a biphasic effect on PRL secretion. PRL response to acute stress appears to be sensitive to the intensity of the experienced stress. When the animals were repeatedly exposed to the same stressor, some behavioral and physiological consequences of stress were reduced suggesting that the animals become adapted to the stimulus [1,2]. Serum prolactin levels are controlled by tonic inhibitory or stimulatory factors which act by direct impact on the lactotroph cells or by indirect pathways [3]. Antipsychotic drugs have a dopamine D2 receptor blocking effect and can therefore increase the secretion of PRL and drug–induced hyperprolactinemia after antipsychotic treatment is well documented. The impact of antidepressant drug (ADs) treatment on this phenomenon is less well known, although it has occasionally been reported with several classes of drugs [4,5]. Particularly ADs with serotonergic activity, including selective serotonin reuptake inhibitors (SSRI), may cause hyperprolactinemia through the

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enhancement of serotonin activity by inhibiting neuronal serotonin reuptake. Also, monoamine oxidase inhibitors (MAO-I) and some tricyclics may raise PRL levels by reducing catecholamines in the hypothalamus. The relationship between the response to ADs and PRL levels has been studied by Malone et al. [6]. All of the examined groups, i.e. patients with major depression after electroconvulsive therapy, pharmacotherapy and psychotherapy with a high indicator PRF (prolactin response to fenfluramine) predicted good response to ADs treatment. These data suggest indirectly that PRL may predict the response to different forms of treatment. However, other data suggest lack of correlation between PRF and prediction of clinical response to ADs [7–9].

Taking into account the above reports we have aimed to verify whether the response to antidepressant treatment depends on the endogenous PRL level in the plasma. In our study we used the animal model of depression, chronic unpredictable mild stress, CMS, and we tested the impact of basal PRL levels on the response to imipramine (IMI). In this model, rats are exposed to the CMS procedure according to the stress paradigm [10–12] for 2 weeks and subsequently to CMS in combination with IMI treatment for 5 consecutive weeks. Behavioral results obtained in the CMS experiments showed that after 2 weeks of mild stress, anhedonia in rats was manifested by reduced consumption of sucrose solution. In the 5 consecutive weeks of stressful stimuli this effect was maintained while the administration of ADs reversed anhedonia. This indicates that the CMS model is a very good animal model to monitor the action of ADs. It has also been proposed to model some of the environmental factors that contribute to the induction of depressive disorders in humans [11–14]. Furthermore, the use of this model allowed us to identify a group of animals which did not respond to stress. In these studies, we also obtained a group of anhedonic animals (corresponding to a reduced sucrose consumption during stress), which did or did not respond to treatment with IMI. Based on the CMS model, we aimed to verify whether the response to antidepressant treatment depends on the endogenous PRL level in the plasma. The factor which was correlated with the basal PRL level was the difference in the behavioral response (difference in the sucrose intake).

2. Material and methods

2.1. Animals

Male Wistar Han rats were purchased from Charles River, Germany. The animal weight was close to 300 g when adaptation to sucrose consumption was initiated and approximately 350 g at the start of stress procedure. Except when grouping was applied as a stress parameter, they were singly housed in plastic cages ($40 \times 25 \times 15$ cm) with food and water provided *ad libitum*, except when food or/and water deprivation was applied as a stress parameter. The standard 12-h light/dark cycle was only changed in the course of the stress regime. The study has been approved by the Bioethical Committee at the Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.

2.2. Sucrose consumption test

The animals were first trained to consume a palatable sucrose solution (1%). The training procedure lasted 6 weeks and consisted of 1-h testing sessions every week (at 10:00 AM on Tuesdays) in which the sucrose solution was presented to the rats in their home cages after 14 h of food and water deprivation. Sucrose intake was measured after each drinking test as the difference in bottle weight. During the stress period the sucrose consumption test was performed once a week.

2.3. Chronic Mild Stress protocol

CMS experiments were performed according to the method described previously [2,10,12]. Each week of the stress regime consisted of: two periods of food or water deprivation; two periods of 450 cage tilt; two periods of intermittent illumination (lights on and off every 2 h); two periods of soiled cage (250 ml water in sawdust bedding); two periods of paired housing; two periods of low intensity stroboscopic illumination (150 flashes/min); and two periods of no stress. All stressors were of 10–14 h duration and were applied individually and continuously, day and night. The animals were deprived of food and water for 14 h preceding each sucrose test, but otherwise food and water were freely available in the home cage. The control animals remained undisturbed in a separate room with free access to food and water, except for a period of overnight deprivation for the sucrose consumption test once per week. On the basis of sucrose intake in the final baseline test, animals which drank stable sucrose solution were subjected to the chronic mild stress procedure for 7 weeks of stress in combination with imipramine (IMI) treatment for the 5 last weeks. All the stressors were of 10–14 h duration and were applied individually and continuously, day and night. the animals from the control group were housed in separate rooms and had no contact with the stressed animals. The operational cut-off point between the control and stress-reactive group was based on arbitrary retrospective observations with regard to the median split and was set at 7.5 g of sucrose consumption. Anhedonic animals (stress-reactive, SR) displayed decreased sucrose consumption to below 7.5 g when compared with the final baseline test. Animals resilient to stress and animals not responding to IMI administration (stress-non-reactive, SNR and SINR) typically displayed increased sucrose intake to above 7.5 g. In animals responding to the IMI administration, sucrose intake above 8 g was observed.

2.4. Drug administration

Drug and vehicle were administrated daily in the morning. Imipramine (Sigma Aldrich, Germany) was dissolved in saline and was given at 10 mg/kg, i.p. once a day.

2.5. Prolactin concentration in plasma

Before blood collection, the animals were habituated to tail holding and the whole procedure of blood sampling lasted about 2 min. The blood of animals responding (R) and not responding (NR) to stress and/or IMI administration was collected from the tail vein of the same rats using butterfly needles at three time points: before starting the CMS procedure, after two weeks of stress (before the IMI treatment) and after seven weeks of the stress procedure including five weeks of IMI administration. The blood was collected in tubes containing 6% EDTA and kept on ice for a minimum of 30 min. The final volume of the collected blood was 300 μl. Plasma was separated via centrifugation ($1500 \times g$ for 15 min at 4 °C) and stored in −80° C for further analyses. Peptide concentration in the plasma was determined in duplicates using the commercially available kit for rat prolactin (SPIbio, Germany). The inter-assay coefficient of variation was less than 15% for rat plasma samples in the concentration range of 8–1000 ng/mL. The limit of detection was 0.2 ng/mL [15].

2.6. Statistical and correlation analysis

The results were presented as means ± SEM. The sucrose intake values from the CMS behavioral tests were analysed with two-way repeated ANOVA measures. The data from the ELISA tests were analysed using one-way ANOVA (GraphPad Prism 5.0, USA).