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Effects of imipramine on cytokines panel in the rats serum during the drug treatment and discontinuation

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ABSTRACT

Time dependent sensitization (TDS) - phenomenon described originally by Chiodo and Antelman (1980) in context of dopamine receptors, refers to cascade of events that continue to develop in the organism, after the initiating stimulus is no longer available. Treatment could be recognized as such a initiating stimulus (in case of depression, example of electroconvulsive therapy would be obvious, but some aspects of pharmacotherapy too). The process leads to improvement, but, on the other hand, phenomena of kindling in recurrent depression is well known (more relapses and therapies make heavier and longer lasting subsequent episodes). Hence our interest in delayed effects of treatment. Here we report alterations in rat immune system after Imipramine (IMI) treatment cessation.

Wistar male rats were treated with IMI (10 mg/kg i.p. in 2 ml/kg of saline) repeatedly for 21 days or once - on the last day of drug administration period. Then the 3 weeks discontinuation phase begun, during which, at certain time points (3 h, 72 h, 7days, 21days) the trunk blood was collected. Tissue concentrations of IMI and its metabolite desipramine (DMI), as well as ACTH and various cytokines were measured.

The IMI and DMI was detectable only 3 h after the last i.p. injection of the drug. Ever since the second time point (72 h of discontinuation) the levels of either compound were below detection threshold.There was no significant changes in ACTH levels between rat groups, although IMI seemed to attenuate alterations of the hormone level comparing to control groups. We observed differences between groups regarding certain cytokines at certain time points. Namely: at 72 h of discontinuation IL-2 and IL-4 were elevated in sera of rats treated with IMI acutely; at 7d of discontinuation levels of IL-1α, IL-5, IL-10 and IL-12 were affected in both acutely and chronically treated animals.

Presented data support, regarding some cytokines in serum, the TDS theory. Furthermore they refer to important aspect of antidepressants (ADs) action – antidepressant discontinuation syndrome (ADS). The most frequently, ADS has been described in context of ADs-disrupted monoamine homeostasis. Here, the other principle (i.e. immunomodulation) of the syndrome is proposed.

1. Introduction

The antidepressant discontinuation syndrome (ADS) associated with interruptions in taking antidepressants (ADs), is one of the serious side effects of treatment with ADs. Numerous factors cause patients to discontinue ADs and may include: insufficient education regarding the required extended duration of use, impatience with the delayed onset of action, side effects, that emerge on ADs initiation, such as anxiety and insomnia, or after extended use, such as sexual dysfunction and weight gain, or overall perception of clinical improvement (Ferguson, 2001). Several studies suggest that up to 30% of patients with depression discontinue their drugs within the first month of initiating treatment and 45–60% of patients discontinue ADs by the end of the third month (Hotopf et al.,

Abbreviations: ADS, antidepressant discontinuation syndrome; ADs, antidepressants; DMI, desipramine; ECS, electroconvulsive shock; FST, forced swim test; IMI, imipramine; SNRIs, selective norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; TDS, time dependent sensitization.

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1997; Harvey and Slabbert, 2014). ADS concerns patients who not only prematurely discontinue antidepressant drugs, but also discontinue treatment owing to improvement in their health. Some of the discontinuation symptoms can be very difficult to distinguish from symptoms of recurrent depression. The symptoms of ADS may include flu like symptoms, insomnia, nausea, imbalance, sensory disturbance, and hyperarousal (Warner et al., 2006). Symptoms of ADS present quickly, they appear in the first two days after antidepressant discontinuation (or dose reduction) and then undergo gradual regression. However, rapid antidepressant discontinuation has been shown to remain associated with a shorter time to the next recurrent depressive episode (Viguera et al., 1998; Baldessarini et al., 2010). ADS is most often associated with tricyclic antidepressants (TCA), serotonin reuptake inhibitors (SSRIs), or serotonin and noradrenaline reuptake inhibitors (SNRIs).

Phenomenon of time-dependent sensitization (TDS), which has been described in animal models over the past 30 years by Antelman (Antelman et al., 1983, 1997) can, in some respects, refer to ADS. Several animal studies have shown that the action of various drugs can augment or sensitize with time, following even a single treatment. Long-term or single administration of antidepressants or electroconvulsive shock (ECS) has been shown to alter sensitization of dopamine autoreceptors in the substantia nigra, as observed in an electrophysiological study (Chiodo and Antelman, 1980). Moreover, it has been shown that the effect of short-term treatment, followed by 7–10 days of withdrawal before testing the effects of the treatment, was approximately 30% greater, than that in groups receiving the same treatment every day. These experiments provided the basis of a few small clinical trials to investigate the effect of the mode of administration of ADs on their therapeutic effect. These studies confirmed the possibility of the phenomenon of TDS in the clinical effectiveness of SSRIs and ECS (Antelman and Gershon, 1998). In addition, our previous biochemical studies (binding of [^{3}H]CGP12177 to β-adrenergic receptors) confirmed the phenomenon of TDS observed two weeks after administering a single dose of desipramine in rats subjected to the Forced Swim Test (FST) (Kuśmider et al., 2006).

Depression is considered a syndrome that includes diverse symptoms and mental disorders with various etiologies. Many hypotheses have been postulated to elucidate the etiopathogenesis of depression, most of which are based (retrogradely) on the known mechanism of action of ADs. Among others, there is evidence that ADs influence inflammatory responses and the monocytic and T lymphocytic arms of cell-mediated immunity (Maes, 2011). Studies with animal models and observations during cytokine immune therapy in humans, suggest that pro-inflammatory cytokine production and/or action result in exacerbation of depressive symptoms. In some studies, antidepressant treatments were shown to normalize the initially increased IL-6 plasma levels in patients with depression (Kubera et al., 2000). Furthermore, it has been shown that a tricyclic antidepressant, imipramine (IMI), has anti-inflammatory effects (Kubera et al., 1995). Results obtained in an animal models of depression suggest that ADs decrease the production of pro-inflammatory cytokines such as interferon-γ and tumor necrosis factor-α, and increase anti-inflammatory cytokines, such as interleukin-10 (Maes, 1999).

Mechanisms of action of antidepressant drugs are predominantly studied in context of chronic administration, and/or in animal models of depression. The data from aforementioned studies however speak in favor of experimental design considering short-term treatment followed by withdrawal period. Such a paradigm, in naïve (non-modeled) rats would help elucidate physiological response of rat organism to antidepressant-provoked perturbations, and how this response develops during drug discontinuation. We believe it will help to understand some aspects of treatment with ADs especially regarding ADS. Here we report how chronic treatment of rats with IMI influences state of their immune system during three weeks after last dose of drug. Using the Bio-Rad Bioplex Assay (Bio-Rad, Hercules, CA) the cytokine levels were measured in the rat serum. Furthermore, we aimed to verify the phenomenon of TDS on the cytokine panel. To this aim, from animals which received IMI acutely (1x), serum was taken at the same intervals as from animals treated repeatedly.

2. Materials and methods

2.1. Animals

Male Wistar Han rats were purchased from Charles River, Sulzfeld Germany. The experiments were conducted on rats weighing 220–230 g; after 21 days of drug/saline administration, their weight increased to 280–320 g. The animals (5 rats per cage/group) had ad libitum access to food and water during the experiment and were housed at a constant temperature 22 ± 1 °C, under a 12-h light/dark cycle (lights on at 07:00 AM). Experimental protocols were approved by the local ethics committee and were performed in accordance with guidelines of the Bioethical Committee at the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.

2.2. Drug administration

IMI was dissolved in saline and administered intraperitoneally (i.p.) once daily. All animals were handled in the same manner. Control animals were receiving a vehicle for 21days, whereas repeatedly treated animals were receiving IMI. The animals receiving short-term treatment with a drug (IMI 1x) received saline for 20 days followed by single IMI administration on the 21st day. Using this experimental paradigm, we avoided the effect of the single i.p. injection, which inevitably, as a stressful event for an animal, might have masked or changed the actual effect of acute administration of the studied drug. Moreover, tissue from all groups of animals treated acutely or repeatedly was collected for biochemical analysis simultaneously after 3 h, 72 h, 7days or 21days since the last i.p. injection. Blood was left to clot in separation tubes at ambient temperature for 30min and then centrifuged at 1500 g for 10min (for serum separation), or collected to tubes coated with EDTA and centrifuged the same way but immediately (to separate plasma). Collected serum and plasma were stored in −80 °C until measurements. The experimental paradigm is shown in Fig. 1.

2.3. Serum cytokine assay

The Bio-Plex Pro Rat assay (The Cytokine Rat Magnetic 12-Plex Panel, Bio-Rad, Hercules, CA) was performed in accordance with the manufacturer's instructions. The samples were diluted in buffer (1:5) and incubated with premixed beads for 1 h in ambient temperature. Signal detection was performed by the means of MagPix device, using Bio-Plex Manager software 6.0 (Bio-Rad, Hercules, CA).

2.4. Measurement of adrenocorticotropic hormone in rat serum

Stress related peptide concentration in the serum were determined in duplicates, using the commercially available kit for adrenocorticotropic hormone (ACTH) (Wuhan, China). According to manufacturer the inter-assay coefficient of variation for ACTH is less than 10% for rat serum samples in the concentration range of 15.6–1000 pg/ml.