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Desipramine administered chronically inhibits lipopolysaccharide-stimulated production of IL-1β in the brain and plasma of rats

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ABSTRACT

Nowadays, it is assumed that therapeutic efficacy of antidepressants depends, at least partly, on their anti-inflammatory properties. The present study investigated for the first time the effect of 21-day oral administration of desipramine on the lipopolysaccharide (LPS)-stimulated IL-1β concentration in the olfactory bulb, hypothalamus, frontal cortex, hippocampus and plasma of rats, and on the LPS-induced IL-1β mRNA level in the olfactory bulb. Desipramine (15 mg/kg/day) reduced significantly the LPS (250 μg/kg i.p.)-induced IL-1β concentration in the olfactory bulb, hypothalamus and in plasma, and diminished the LPS effect on IL-1β mRNA in the olfactory bulb. Plasma concentration of desipramine was comparable to its therapeutic range. By using the α1/α2-adrenoceptor antagonist prazosin and the unspecific β-adrenoceptor antagonist propranolol given prior to LPS, we found that the effect of desipramine on LPS-induced IL-1β production was partially mediated by both adrenoceptors in the olfactory bulb and plasma, and that β-adrenoceptors contributed also to its effect on the stimulated IL-1β concentration in the hypothalamus. The effect of LPS on the cerebral IL-1β levels was, in part, mediated by β-adrenoceptors and, in a region-specific manner, by α1/α2-adrenoceptors. The findings provide evidence for central and peripheral anti-inflammatory activity of desipramine and confirm the impact of the noradrenergic system on IL-1β production induced by an immunostimulatory challenge.

1. Introduction

Chronic inflammation characterized by an elevated production of cytokines is implicated in the development and progression of some diseases of the central nervous system (CNS) [1]. Cytokines produced by glial cells in the brain and peripheral cytokines released by immunocompetent cells, the latter mainly indirectly, affect the function of the CNS by influencing metabolism of neurotransmitters (serotonin, noradrenaline, dopamine and glutamate), hypothalamic–pituitary–adrenal axis activity, metabolic activity, synaptic plasticity and neurogenesis [2].

IL-1β is a well-known major pro-inflammatory cytokine which plays a pivotal role in neuroinflammation and neuroprogression [3]. This cytokine is thought to be a key central regulator of the stress response and an important mediator of depressive-like behavior [4,5]. It has been hypothesized that IL-1β is the first step in the pro-inflammatory response to psychological stress leading to the development of a cascade of inflammatory cytokine responses [6]. Ample evidence indicates that immune dysregulation manifested by an activation of the inflammatory system has a role at least in a significant sub-population of depressed patients. The first paper showing an increased IL-1β production in depression was published by Maes [7]. Thereafter, the elevated levels of this cytokine were evidenced by some but not all clinical studies [8–11]. Meta-analysis published by Hannestad [11] reported that antidepressants reduced serum levels of IL-1β and to a lesser extent IL-6, but not TNF-α. Major depression and neurodegenerative diseases characterized also by chronic inflammation are frequently comorbid [12] what suggests that antidepressants with anti-inflammatory properties could be a useful adjunctive therapy [13].

Abbreviations: HPA axis, hypothalamic–pituitary–adrenal axis; IL-1β, interleukin-1β; TNF-α, tumor necrosis α; LPS, lipopolysaccharide; TLR, toll-like receptor.

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IL-1β and TNF-α were proven to contribute to neuropathic pain which has many features of a neuroimmune disorder [14] and is treated with antidepressants, especially tricyclic antidepressants. Experiments conducted in a rat model of neuropathic pain showed that analgesic action of the studied antidepressant was partially mediated through inhibiting cerebral production of pro-inflammatory cytokines including IL-1β [15].

Desipramine, a tricyclic antidepressant, is recommended for the therapy of depression, even a drug-resistant depression, chronic neuropathic pain, anxiety and insomnia [16]. It is principally a selective norepinephrine reuptake inhibitor which also displays a much weaker blocking effects on serotonin reuptake, α1-adrenoceptors, cholinergic M1 and histaminergic H1 receptors [17]. An enhancement of the noradrenergic system activity is thought, at least partly, to account for antidepressant action of desipramine. Data on the role of norepinephrine in controlling inflammatory events in the CNS and periphery indicate that this effect may be of significance for the influence of desipramine on cytokine networks [18,19]. In fact, in a few studies the anti-inflammatory properties of desipramine were demonstrated in the periphery [20–22]. Until now, only one in vivo investigation demonstrated that desipramine given in a single i.p. injection decreased the lipopolysaccharide (LPS)-evoked IL-1β and TNF-α gene expression in the rat cortex [23]. However, the effect of its chronic administration, typical for therapy with this drug, on the cerebral neuroinflammation has not been evaluated. Moreover the influence of the long-term treatment with the other antidepressants on brain cytokines up-regulated by immunostimulators such as LPS or IFN-γ was a subject of only a few studies [24–26].

The present study addressed the question whether desipramine given chronically is able to modulate the LPS-activated IL-1β network in the rat brain structures, such as the hypothalamus, frontal cortex, hippocampus and olfactory bulb. Moreover, we studied the desipramine effect on LPS-stimulated peripheral production of IL-1β by measuring its plasma levels. In anticipation that changes in the noradrenergic system activity may be significant for the influence of desipramine pretreatment on LPS response, the unselective β-adrenergic receptor antagonist propranolol and the α1/α2 adrenoceptor antagonist prazosin were used as pharmacological tools.

LPS injected i.p. induces peripheral as well as central neuroinflammation which is characterized by an excessive production of pro-inflammatory cytokines, oxygen radicals, glucocorticoids and so-called sickness behavior paralleled by neurovegetative features of depression, and anhedonia [27]. However, the LPS-induced inflammation is much more severe than the low-grade inflammatory process considered to contribute to chronic pathological states but estimation of the drug properties in this model allows for a better recognition of its putative mechanism of action in the therapy of neuroimmune disorders.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats, 8–10 weeks old, of initial body weight between 220 and 290 g, from the Center for Experimental Medicine of the Medical University of Silesia were adapted for one week to the new conditions in the animal facility of the Department of Pharmacology. They were kept six–seven per cage (52 cm × 31 cm × 19 cm) under standard conditions (12-h light/dark schedule, lights on at 7:00 AM; ambient temperature of 22 ± 2 °C; humidity 55 ± 10%). Food and water were provided ad libitum. During experiments the rats were housed individually in cages (35 cm × 21 cm × 14 cm). All animal experiments were carried out in accordance with the European Directive (2010/63/EU) and were approved by the Local Ethics Committee for the Care and Use of Laboratory Animals (Katowice, Poland). An every effort was taken to minimize the suffering of the rats.

2.2. Oral desipramine administration

Desipramine hydrochloride (Sigma–Aldrich, St. Louis, MO, USA) was given orally for 21 days in 1% saccharin solution in two different doses either 7.5 or 15 mg/kg/day, similar to doses used by others who administrated desipramine chronically in drinking water [28,29]. The antidepressant was dissolved in a small volume of redistilled water. After dilution with an appropriate volume of tap water saccharin was added to increase palatability. Drug solution was prepared twice a week and was given in light-proof drinking bottles. Body weights and fluid intake were recorded every 3–4 days throughout the experimental period. According to these data, the concentration of desipramine in saccharin solution was adjusted in order to maintain the correct doses.

2.3. Experimental design

2.3.1. Experiment 1. Analysis of desipramine level in plasma and brain of rats

After 21-day treatment with desipramine (15 mg/kg/day) the rats (n = 10) were sacrificed by decapitation with guillotine (8:00–9:00 AM) and then, brains were rapidly removed and frozen on dry ice. Trunk blood was collected into prechilled tubes containing 10% EDTA solution and centrifuged (800 g, 15 min, 4 °C). All samples were kept frozen at −70 °C until assay. Concentration of desipramine was assessed by the HPLC method as described previously [30]. The brains were homogenized in distilled water (1:3 w/v). The homogenates were alkalized with 3 M sodium hydroxide to achieve pH = 12. Desipramine was extracted with hexane containing 1.5% of isoamyl alcohol. To plasma aliquots 25% ammonium hydroxide was added. After alkalization to pH = 12 desipramine was extracted as above. Extraction efficiency of the drug was about 96%. The residue obtained after evaporation of the plasma and tissue extracts was dissolved in a mobile phase and injected into the LaChrom HPLC system (Merck-Hitachi) equipped with an L-7480 fluorescence detector, L-7100 pump and D-7000 System manager. The analytical column (Econosphere C18, 5 μm, 4.6 × 250 mm; Alltech, Carnforth, England) was used. The mobile phase consisted of methanol and acetonitrile (1:1, v/v) containing 1 ml/l of triethylamine. Elution was carried out at an ambient temperature at a flow rate of 1 ml/min. Fluorescence of the samples was measured at an excitation wavelength of 240 nm and 370 nm emission wavelength. All the reagents applied were of HPLC purity and were purchased from Merck (Darmstadt, Germany).

2.3.2. Experiment 2. The effect of desipramine on LPS-induced IL-1β concentration in the brain structures and plasma of rats

The rats (n = 6–10 per group) were given orally desipramine or 1% saccharin solution for 21 days and on day 22 they were injected i.p. with LPS (250 μg/kg) or saline alone in a volume of 2 ml/kg. LPS was dissolved in sterilized, pyrogen-free saline just before injection. Five groups of rats were used:

1% saccharin + saline
desipramine (15 mg/kg/day) + saline
1% saccharin + LPS (250 μg/kg ip.)
desipramine (7.5 mg/kg/day) + LPS (250 μg/kg ip.)
desipramine (15 mg/kg/day) + LPS (250 μg/kg ip.).