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ScienceDirect
European Journal of Pharmacology 580 (2008) 135–142
www.elsevier.com/locate/ejphar

An anti-immobility effect of exogenous corticosterone in mice

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Received 2 May 2007; received in revised form 11 October 2007; accepted 16 October 2007
Available online 25 October 2007

Abstract

Although traditionally considered to be etiological factors in depression, corticosteroids have been shown to exert an acute antidepressant action under some conditions. To investigate the mechanism of this effect, the present experiment sought to develop an animal model of it in mice using the repeated forced swim procedure. Corticosterone or desmethylimipramine was administered in the drinking water before, during or after repeated daily forced swims or a tail suspension test. Glucocorticoid and mineralocorticoid receptor involvement were assessed by coadministration of RU486 or spironolactone. Plasma corticosterone and fos expression in the paraventricular nucleus of the hypothalamus and piriform cortex were also measured in the treated animals. Corticosterone, given either before/during or after repeated swim, was found to produce a rapid reduction of immobility that was greater than that produced by desmethylimipramine given by the same route and dose and for the same duration. There was a nonsignificant tendency toward this effect in the tail suspension test. RU486 failed to block the effect but results with spironolactone were ambiguous. Plasma corticosterone was elevated in an inverted U-shaped fashion by the hormone treatment. Fos expression in response to the last swim was blunted in the paraventricular hypothalamus but enhanced in the piriform cortex. It is concluded that short-term treatment with corticosterone has a marked antidepressant effect in the mouse repeated forced swim test and merits further consideration as a short-term therapeutic agent in low doses. The hormone may act by suppression of neural activity in central stress circuits leading to a disinhibition of regions involved in active behavioral coping.

Keywords: Corticosterone; Depression; Antidepressant; Immobility; Forced swim; Tail suspension test

1. Introduction

With depression representing a major disabling illness with a lifetime prevalence of 15% and with antidepressant agents being effective in only 60–70% of patients, it is obligatory that new forms of therapy be explored and developed. New insights into the neurobiological bases of depression may help in this effort. Recent clinical and animal studies have revealed that depression is accompanied by increased neural activity in a number of stress-sensitive brain regions. These areas include the paraventricular nucleus of the hypothalamus (Arborelius et al., 1999; Shumake et al., 2001), amygdala (Siegle et al., 2007; Stone et al., 2007), anterior insula (Kimbrell et al., 2002; Mayberg et al., 2000), subgenual anterior cingulate gyrus (Mayberg et al., 2000), bed nucleus of the stria terminalis (Greenwood et al., 2005; Marvel et al., 2004; Stout et al., 2000), locus coeruleus (Grant and Weiss, 2001), dorsal raphe nucleus (Maier and Watkins, 2005) and periaqueductal gray (Kollack-Walker et al., 1997). As antidepressant agents have been found to reduce stress-area increases (Mayberg et al., 2000; Stone et al., 2007), it has been hypothesized that the latter may be responsible for the negative affective state of the illness and may serve also to inhibit neural activity in brain regions involved in positively motivated behavior, which show hypoactivity and reduced function during this illness (Mayberg et al., 1999; Stone et al., 2007; Baxter et al., 1989; Kimbrell et al., 2002).

An agent that is capable of suppressing the neural activity of the paraventricular nucleus of the hypothalamus is corticosterone. The paraventricular nucleus has a dense concentration of glucocorticoid and membranal receptors that mediate negative feedback effects on the activity of corticotropin releasing factor (CRF)-containing neurons (de Kloet et al., 2005). Corticosterone

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doi:10.1016/j.ejphar.2007.10.045

also acts to inhibit paraventricular activity via the hippocampus (Herman and Mueller, 2006). It might therefore be predicted that the hormone can exert antidepressant actions at some dosages or schedules. Although corticosteroids have traditionally been considered to be causative factors in depression because they are frequently elevated in this condition (Carroll et al., 2007), there is accumulating evidence that they can have acute behaviorally activating (Deroche et al., 1992; Sandi et al., 1996; Tenk et al., 2006), anti-stress (Schelling et al., 2001; Johnson et al., 1996; Het and Wolf, 2007) and antidepressant actions as well (Dinan et al., 1997; DeBattista et al., 2000; Arana et al., 1995). Surprisingly, however, very few studies have systematically examined the effect of the exogenous hormones on animal models of depression with the exception of early studies demonstrating the role of corticosteroids in the consolidation of immobility response acquisition in the forced swim test (Veldhuis et al., 1985). In one study chronic 21 day injections of a high dose of corticosterone (40 mg/kg) led to increased immobility in rats in the forced swim test (Gregus et al., 2005). However, in a second study, a shorter period of injections (10 days) of a lower dose (20 mg/kg) produced a decrease in forced swim immobility in aged female but an increased immobility in aged male rats (Brotto et al., 2001). In the present study to further investigate a possible animal model for these antidepressant effects, we reexamined the action of acute exogenous corticosterone treatment on two models of depression in the mouse, the repeated forced swimming test and the tail suspension test. We also examined the ability of the hormone to reduce swim stress-induced neural activity in the paraventricular hypothalamus and to increase activity in a brain region that has been shown to be involved in sniffing and exploratory behavior, the piriform cortex (Kareken et al., 2004; Stone et al., 2004, 2007). Since we showed in an earlier study that administration of the hormone in the drinking water abolished the depressing effect of repeated stress on the motor activity response to modafinil (Stone et al., 2002), and since repeated intraperitoneal injections of saline are known to produce depressive-like effects in rats (Izumi et al., 1997), in the present study the hormone was administered in the drinking water either before or after the repeated swims or tail suspension test.

2. Materials and methods

2.1. Subjects

Swiss Webster male mice, 8–10 weeks old, were subjects. To preclude disturbing grouped animals during behavioral testing, all mice were housed singly for 3 days prior to the start and throughout all procedures (total period of single housing was 6 days). Standard mouse cages with nesting material were maintained at a room temperature of 22±1 °C under a 12 h light/dark cycle (lights on 0500 h). Food and water were available *ad libitum*. All experiments were conducted in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals (1996) and were approved by the New York University School of Medicine IUCAC.

2.2. Behavioral procedures

Independent groups of mice were given either repeated forced swim stress, a single tail suspension test or a single open field test. Two forms of the forced swim test were used. The primary test was the open space swim modification of the original Porsolt test described by Sun and Alkon (2003). This involved swimming mice for 15 min/day (0700–0800 h) in a 25×46×22 cm clear Plexiglas tank (rat shoebox cage) of 13 cm high 29–31 °C water for a total of 3–4 d. Although these conditions are somewhat different than those used in the classical forced swim test in that they use more and longer swims and a larger tank of tepid water (to avoid hypothermia), the open space test is easier to score objectively in terms of both active swimming (distance swum) and floating time because of the greater space utilized. Furthermore, we and others have shown that this modified test produces marked decreases in swimming activity and increases in floating over repeated swims that are comparable to the classical test and that both changes are reversed by effective antidepressant drugs given chronically and not acutely (Stone et al., 2007; Sun and Alkon, 2003; Strekalova et al., 2005). Moreover the longer duration swim provides for a greater sampling of behavior and enhances the expression of brain fos making it possible to study brain activation patterns in the tested animals. To confirm results with the open space swim test, other animals were subjected to the standard forced swim utilizing a once repeated 6 min swim in a 21.5×34.5 clear Plexiglas cylindrical tank filled to 15 cm with 24 °C water. The tail suspension test involved taping by the tail 72 cm above a platform for 6 min. For the open field test, a square clear plexiglass open field of dimensions 46×46×35 ($w \times l \times h$) cm whose floor ruled into 4 quadrants was used. All behavioral tests were videotaped. In the swim stress experiments videotapes were rated for distance swum (quadrants of the tank entered) and time floating (drifting with no observable movement of the limbs or tail) and in the tail suspension experiments for time immobile in the last 4 min of the test. All ratings were made by an observer unaware of the animals' treatments. In the open field test, distance moved was automatically recorded as number of quadrants entered with a commercial videotracking system (Smart Video Tracking System).

2.3. Hormone and drug administration

Corticosterone was administered in the drinking water at concentrations ranging from 0–50 μg/ml in a vehicle of 0.8% ethanol in the absence or presence of RU486 or spironolactone (both at 50 μg/ml). Preliminary experiments indicated that the 0.8% ethanol vehicle had no effect on the swimming behaviors discussed below. In the forced swim experiments, hormone treatment was begun either 24 h prior to the first swim (pretreatment) and continued throughout the 2–4 day experiment or was administered following the 3rd swim (posttreatment) 24 h prior to the 4th swim. For the tail suspension and open field tests, the hormone was administered for 3 days prior to the test. In antidepressant experiments, the animals received