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Paradoxical effects of chronic corticosterone on forced swim behaviours in aged male and female rats

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Abstract

The effects of chronically administered corticosterone on forced swim test and open field test behaviours were explored in aged male and female rats. Though corticosterone has typically been associated with depressive behaviours, recent data have suggested a putative antidepressive effect of corticosterone. The current study used the forced swim test as a model of antidepressant efficacy in order to explore this. Aged male and female rats received either corticosterone (20 mg/kg) or the vehicle for 10 days before testing in the forced swim test, then for an additional 3 days before testing in the open field test. On day 11, each animal was individually tested on the duration of swimming, immobile, and struggling behaviours, and on day 14, for the display of rearing and line crossing behaviours. Results revealed that corticosterone significantly increased swimming and decreased immobility behaviour in females, but failed to do so in males. Additionally, there was a main effect of corticosterone on struggling behaviour such that it decreased it in males. There were no effects of corticosterone or sex on open field test behaviours, suggesting that the present findings are not accounted for by a general effect of corticosterone on motor behaviour. Overall, the data suggest that chronically administered corticosterone possesses effects that are sex-specific, and that it may exert mildly antidepressive effects in females, but the opposite effects in males. These data are consistent with emerging evidence that corticosterone may play a paradoxical antidepressive effect.

Keywords: Corticosterone; Forced swim test; Sex difference; Depression; Hypothalamic–pituitary–adrenal axis

1. Introduction

The adrenal steroid corticosterone serves an adaptive function in protecting the organism against many defense reactions elicited by acute stress. Repeated stress, however, produces chronically elevated corticosterone levels, and is associated with dysregulated emotional and physiological homeostasis, and has been implicated in the etiology of human psychopathology (Dinan, 1996). Corticosterone has also been associated with impairment in cognitive and motor performance, when chronically administered at physiological doses (White-Gbadebo and Hamm, 1993). The mechanism of action of corticosterone has been linked to multiple neurotransmitters, including norepinephrine and serotonin (Dinan, 1996), and in particular, to upregulation of serotonergic type 2A (5-HT_{2A}) receptors (Berendsen et al., 1996; Gorzalka and Hanson, 1998; Gorzalka et al., 1999). It has been speculated that corticosterone-induced alterations in receptor density and affinity may be responsible for these behavioural effects.

The forced swim test has been well validated in paradigms involving the administration of a chronic stressor. Given that similar behavioural and physiological consequences result from chronic corticosterone administration and treatment with chronic stressors, the effects of corticosterone on forced swim test behaviour have more recently been examined. The forced swim test has been most extensively described for its role in defining antidepressant efficacy (Borsini and Meli, 1988). While the forced swim test has been suggested to be of questionable utility in studies utilizing mice, due to the problem of false positives and false negatives, the test appears to be more accurate and useful for studies employing rats (Borsini and Meli, 1988). The forced swim test paradigm involves placing a rat into a cylinder containing water at a predetermined depth, based on its weight, and monitoring its behaviour over a period of time. Responses measured include active behaviour thought to reflect adaptive coping to the inescapable situation and passive behaviour, which

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reflects learned helplessness. Studies demonstrating a chronic stress-induced increase in immobile behaviour in the forced swim test (Molina et al., 1994; Hata et al., 1995) suggest that the hormone corticosterone may be mediating this effect. Furthermore, reductions in the circulating levels of corticosterone via adrenalectomy (Jeffreys et al., 1983), via administration of a glucocorticoid antagonist, RU 38486 (De Kloet et al., 1988) and via treatment with the corticosterone synthesis inhibitor, metyrapone (Baez and Volosin, 1994), all reliably decrease behavioural immobility in the forced swim test. Given this effect of corticosterone blockade, it seems reasonable to predict that corticosterone administration would increase the display of behavioural immobility while decreasing active behaviours in the forced swim test. However, more recent data have demonstrated a paradoxical rewarding effect of chronically administered corticosterone (Barr et al., 2000). Moreover, data demonstrating that chronic restraint stress elicited a positive antidepressive effect on forced swim behaviour (i.e. by reducing immobility) strengthens the notion of a paradoxical rewarding property of corticosterone (Platt and Stone, 1982). These data stand in contrast to numerous studies that implicate a depressive role for corticosterone and cortisol. Data taken from the human literature also provide the suggestion of a curious prohedonic effect of corticosterone as injections of the corticosterone analogue, hydrocortisone, to patients with a diagnosis of major depression produced a marked reduction in depressive symptomotology (DeBattista et al., 2000). On the other hand, elevated levels of corticosterone in rats have been shown to upregulate the density of 5-HT_{2A} receptors (Fernandes et al., 1997), similar to the increased density of 5-HT_{2A} receptors found in the postmortem analyses of the brains of depressed victims of suicide (Arora and Meltzer, 1989). Although these findings would seemingly refute a putative antidepressive role of corticosterone, the human data are correlational and based on a subgroup of depressed patients who later commit suicide, and who may not generalize to the entire population of depressed individuals. Although an examination of the effects of chronic administration of corticosterone on forced swim test behaviours will not resolve the conflicting findings as to the rewarding vs. depressive effects of corticosterone, this investigation will shed some light on whether or not the rewarding properties of corticosterone demonstrated in other behavioural paradigms remain consistent in a validated test of depressive potential.

In addition to its primary role as an antidepressant screen, the forced swim test has also been used as a behavioural stressor, and numerous biochemical sequelae of forced swim test exposure have been documented. It would seem reasonable to predict that prior chronic treatment with corticosterone should amplify behavioural disruption produced by the forced swim test, and that given the demonstrated sex differences in habituation to a stressor (Galea et al., 1997), it may do so differentially between males and females. A blemish in most of the prior research using the forced swim test is the failure to employ female subjects either instead of, or in addition to males. Female rats have been shown to be more vulnerable than males in certain animal models of depression (Kennett et al., 1986), thus highlighting the importance of using both males and females in animal models of pathology such as the forced swim test.

The purpose of this study is to examine the effects of chronically administered corticosterone on behaviours in the forced swim test. Based on documented studies and the similarity of behavioural stressors to corticosterone administration, one would expect that corticosterone administration would lead to changes that parallel those produced after exposure to a chronic stressor. However, given recent evidence of a rewarding property of chronically administered corticosterone, a prohedonic effect of the hormone cannot be ruled out. Robust sex differences which exist in animal models of stress and depression (Kennett et al., 1986), and in human psychopathology (Bracke, 1998), necessitate the testing of behaviours in both males and females. Additionally, the effects of chronic corticosterone on active behaviours in the forced swim test have not previously been examined. Finally, in order to rule out a general effect on locomotor activity as a result of chronic corticosterone administration, the open-field test will be used in the current study to help interpret findings in the forced swim test.

We have chosen to employ animals that are of middle age, in contrast to most of the prior research utilizing the forced swim test. The effects of chronically administered corticosterone have also almost exclusively been examined in relatively young animals (Bisagno et al., 2000; Barr et al., 2000), when the behavioural effects would be at their least efficacious. A large body of evidence suggests that disruptions of the hypothalamic–pituitary–adrenal axis become more pronounced with age (Hatzinger et al., 1996; Hassan et al., 1999), and the behavioural effects of high levels of glucocorticoids are most influential in older animals (Issa et al., 1990). By utilizing older animals, it is presumed that the generalizability of the findings would be increased to possibly account for the observed effects in hypercortisolemic, older humans (Lupien et al., 1999).

2. Materials and methods

2.1. Subjects

Twenty male (520–690 g) and 20 female (350–450 g) Long–Evans rats, originally obtained from Charles River, Quebec, were used in this experiment. Female rats were bilaterally ovariectomized at 3 months of age using standard surgical procedures. Female rats were ovariectomized in order to reduce the demonstrated effects of variable ovarian hormone levels on forced swim test behaviours

(Barros and Ferigolo, 1998). Naïve rats were tested at 10 months of age, and were housed in groups of three to four, by sex in standard triple-wire mesh cages. Colony conditions were temperature-controlled (21 ± 1 °C) and lights were set on a 12-h dark/12-h light reversed cycle with lights off at 0900 h. Animals were provided with Purina Rat Chow and tap water ad libitum.

2.2. Treatment

Animals were randomly assigned to receive either chronic treatment with corticosterone or the vehicle, resulting in equal numbers of animals in each condition ($n = 10$ females and $n = 10$ males per condition). Male and female rats were administered corticosterone and participated concurrently in behavioural testing. Corticosterone was injected daily in a manner previously described and found to decrease sexual behaviour in male rats (Gorzalka and Hanson, 1998) and increase it in female rats (Hanson and Gorzalka, 1999). Animals in the present study were not adrenalectomized in order to make the current methodology comparable to numerous prior studies which have investigated the behavioural effects of chronic corticosterone (Reagan et al., 1999; Barr et al., 2000). Corticosterone was obtained from Sigma (Chicago, USA), was suspended in propylene glycol (20 mg/ml), and was injected daily for 10 days (1 ml/kg) during the middle third of the dark cycle. This paradigm of corticosterone administration was chosen as it simulates that employed by McEwen et al. who demonstrated chronic corticosterone-induced behavioural changes (Stone et al., 1988; Sapolsky et al., 1985). Control animals received propylene glycol (1 ml/kg) for the same duration. Injections were performed s.c., daily, with 26-gauge needles, and continued during the period of behavioural testing. On the day of forced swim testing (Day 11), injections were performed immediately after exposure to the swim chamber, and were continued for an additional 2 days. There was no injection on the day of open field testing (Day 14). All procedures were conducted in accordance with the Canadian Council on Animal Care guidelines for work with laboratory animals.

2.3. Forced swim test procedure

The design of the forced swim test was adapted from Hansen et al. (1997). On Day 11, rats were placed in a cylindrical glass container (45-cm height, 28-cm diameter) which contained tap water (25 ± 1 °C) to a depth of 35 cm. The water was changed after each subject was tested and the cylinder was thoroughly rinsed in order to remove the presence of any potential alarm substances. Animals were tested for 15 min, after which each was individually dried with a towel and returned to its home cage.

All testings were recorded on videotape, and later scored by an observer who was blind to the experimental conditions of the animals. Test behaviours were scored according to the criteria of Armario et al. (1988), which include (1) struggling—characterized behaviourally as when the rat struggles to get out of the container, with its forepaws above the surface of the water, (2) swimming—defined by when the subject makes active swimming motions, and (3) immobility—described as when three paws are immobile and the fourth paw exhibits only minimal movement. The presence of depressive activity is inferred from a significant reduction in the amount of time spent in either of the two types of active behaviour, i.e. either struggling or swimming.

2.4. Open field test procedure

Seventy-two hours after forced swim testing (Day 14), all subjects were tested in the open field apparatus for 5 min. The apparatus consisted of a square arena (120×120 cm), with a 40-cm-high opaque white wall. The floor was marked into 16 equal segments, and three fluorescent lights provided diffuse overhead illumination (20 lx at the level of the arena). The animals were tested in a quiet room, and locomotor activity over a 5-min period was recorded on a ceiling-mounted videocamera (Tracker VP200; HVS Image, Hampton, England). Videotapes were later scored by an experienced observer who was blind to the condition of the animals. Line-crossing behaviour (defined as at least three paws in a quadrant) and rearing behaviour (defined as the animal standing upright on its hindlegs) were tallied and compared between the experimental conditions.

2.5. Statistical analyses

Two-way analyses of variance (ANOVA) were performed on data from the forced swim and open field testing, with drug condition and sex as independent, between-subjects factors. In cases of significant interactions, Fishers least-significant differences test of multiple comparisons was performed. In all cases, a P-level less than 0.05 was considered significant.

3. Results

3.1. Forced swim test

There was no statistically significant interaction between sex and corticosterone for struggling behaviour, $F(1,36) = 2.57$, $P = 0.12$, nor main effect of sex on this measure, $F(1,36) = 2.85$, $P = 0.10$. The main effect of corticosterone, however, was significant, $F(1,36) = 4.01$, $P = 0.05$, with Fishers multiple comparisons test showing that corticosterone significantly decreased struggling in males (Fig. 1).

Statistical analyses revealed a significant interaction between corticosterone and sex for swimming behaviour,

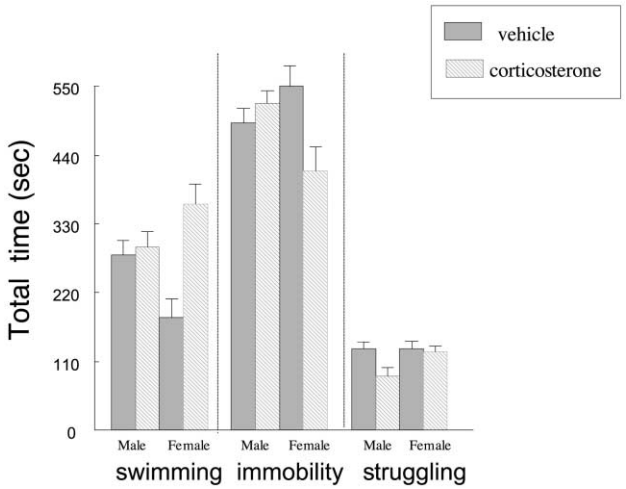

Fig. 1. Effects of chronic corticosterone administration on swimming, immobility, and struggling behaviour(s) in male and female rats after 10 days of administration in the forced swim test. Results demonstrate a significant interaction between corticosterone and sex on swimming ($P = 0.005$) and on immobility ($P = 0.002$), and a significant main effect of corticosterone on struggling ($P = 0.05$). Data represent means ± S.E.M.

$F(1,36) = 9.04$, $P = 0.005$, as well as a significant main effect of corticosterone, $F(1,36) = 11.58$, $P = 0.002$. There was, however, no significant main effect of sex, $F(1,36) = 0.32$, $P = 0.57$. Fishers test for pair-wise comparisons revealed that corticosterone significantly increased swimming behaviour in females, but not males, as shown in Fig. 1.

On behavioural immobility, statistical analyses revealed that the interaction between corticosterone and sex was of statistical significance, $F(1,36) = 10.77$, $P = 0.002$, as was the main effect of corticosterone, $F(1,36) = 5.26$, $P = 0.028$. The main effect of sex, however, was not statistically significant, $F(1,36) = 0.02$, $P = 0.90$. Fishers multiple comparisons test indicated that in vehicle-treated animals, females showed higher levels of immobile behaviour than males; however, with corticosterone pre-treatment, males showed higher levels of immobility than females. Inspection of Fig. 1 shows that compared to control animals, corticosterone-treated females displayed lower levels of immobile behaviour.

3.2. Open field test

Statistical analyses on crossing behaviour revealed no significant main effects of sex, $F(1,36) = 1.47$, $P = 0.23$, of corticosterone, $F(1,36) = 0.01$, $P = 0.92$, or of the interaction between sex and corticosterone, $F(1,36) = 1.47$, $P = 0.23$.

As with crossing behaviour, there were no statistically significant main effects of sex, $F(1,36) = 0.64$, $P = 0.43$, of corticosterone, $F(1,36) = 0.31$, $P = 0.58$, or of the interaction between sex and corticosterone, $F(1,36) = 0.02$, $P = 0.90$ on rearing behaviour.

4. Discussion

The results of the present study demonstrate that chronically administered corticosterone produces differential effects on behaviour in rats in the forced swim test, and that these effects are dependent on the sex of the animal. Daily administration of corticosterone, administered at a dose similar to those used in previous studies to mimic the effects of a chronic stressor (Bardgett et al., 1996; Gorzalka and Hanson, 1998; Reagan et al., 1999), altered the pattern of responding that animals exhibited in the forced swim test in a complex manner. In male rats, this effect was observed as a significant decrease in the amount of time spent struggling during exposure to the forced swim test, although no overall change was noted in the time spent swimming or immobile. Female rats that were chronically treated with corticosterone exhibited a large increase in the amount of time spent swimming in the forced swim test, although no change was observed in struggling behaviour. The overall effect of pretreatment with corticosterone in female rats was to produce a significant decrease in the amount of time spent immobile. While previous data demonstrate that females engage in more active behaviours than males (Alonso et al., 1991), these have employed younger, intact females. In contrast, females in the present study were 10 months of age and had been previously ovariectomized for 7 months. A recent study has shown that ovariectomized female rats display more immobility and less swimming behaviour than intact females (Rachman et al., 1998), suggesting that this may account for the observed sex differences in the current study.

The forced swim test was originally developed as a screen for compounds with putative antidepressant properties (Porsolt et al., 1977). However, it has seen increased recent use as a procedure with which to measure the influence of depressogenic manipulations on rodents. Several established animal models of depression have noted increased levels of immobility in the forced swim test (Heritch et al., 1990; Velazquez-Moctezuma and Diaz Ruiz, 1992; Overstreet et al., 1995; Hansen et al., 1997), hence increasing the validity of the test for detecting the presence of "depressive-like" behaviours. In addition, compounds that are known to induce depressive effects in humans have also been shown to increase levels of immobility in the forced swim test in rodents (Kokkinidis et al., 1986; Noda et al., 1995). Conversely, antidepressant compounds are detected with a remarkably high degree of accuracy by their ability to decrease the amount of time that rodents spend immobile in the forced swim test (Borsini and Meli, 1988; Dalvi and Lucki, 1999). Given these basic findings, the results from the present study suggest that chronically administered corticosterone may have mildly antidepressant properties in female rats. The decreased time that corticosterone-treated females spent immobile, reflecting the increased time that they spent

swimming compared to control rats, indicates that the current dose of corticosterone may have sex-specific antidepressant effects. Male rats that had been treated chronically with corticosterone did not display an overall change in their levels of immobility, which implies that corticosterone did not exhibit antidepressant properties in males.

While more complex types of behaviour than "immobility" vs. "active" have been described previously in the forced swim test (Armario et al., 1988), Lucki (1997) and Reneric and Lucki (1998) have recently emphasized the particular importance of "swimming" and "struggling" behaviours. A substantial body of evidence indicates that these two behavioural strategies may reflect the participation of different neurochemical substrates. The treatment of animals with antidepressant compounds that act primarily on the noradrenergic system, such as the tricyclic compound desipramine, selectively increases struggling behaviour (Detke et al., 1995). In contrast, the serotonergic-mediated antidepressants, such as fluoxetine, selectively increase the amount of time that animals spend swimming (Detke et al., 1995; Page et al., 1999). Therefore, the observation that treatment with chronic corticosterone increases swimming behaviour in female rats in the forced swim test is consistent with prior studies that have noted effects of corticosterone on the serotonergic system (Berendsen et al., 1996; Zahorodna et al., 2000). In our laboratory, we have shown that chronic treatment of female rats with corticosterone increases behaviours that are mediated by the 5-HT_{2A} receptor (Hanson et al., 1998).

The decrease in struggling behaviour that was noted in male rats in the current study represents an interesting novel finding. Several animal models of depression have observed overall decreases in active behaviour in the forced swim test (Heritch et al., 1990; Velazquez-Moctezuma and Diaz Ruiz, 1992; Overstreet et al., 1995; Hansen et al., 1997), but as the total time spent in immobility by corticosterone-treated male rats did not differ from controls, it does not appear that these animals were "depressed". The data from the open field test also support the hypothesis that chronic corticosterone did not simply reduce overall levels of activity, given that corticosterone-treated and control animals did not differ on locomotor measures. It is unlikely that the additional 3 days of corticosterone administration between the forced swim test and open field test would have confounded behaviour seen in the open field test given that recent data from our laboratory demonstrate that the behavioural effects of chronic corticosterone peak at approximately 7 days of administration, and that there do not appear to be further increases in behavioural change with additional injections (Barr et al., 2000). The selective reduction of struggling behaviour may therefore represent a decrease in noradrenergic activity, or a possible shift in the balance between the noradrenergic and serotonergic systems. A previous study by De Villiers et al. (1992) found that chronic corticosterone decreased levels of norepinephrine in the pons-medulla in male rats, while Flugge (1999) observed that cortisol in male tree-shrews induced dynamic changes in the number of frontal α_2-adrenoceptors. We are not aware of any other reports in the literature that have observed a selective reduction in struggling behaviour in male rats in the forced swim test, without an effect on overall levels of immobility. Clearly, further study is required to elaborate the neurochemical mechanisms that underlie these effects. Although the molecular mechanisms by which chronic, high levels of corticosterone produce an antidepressant effect in rats remain unknown and were not addressed in this study, several possibilities are indicated by prior reports in the literature. For instance, elevated levels of glucocorticoids serve to inure animals to the effects of physical stressors, by mobilizing metabolic factors that can help sustain the individual during extended periods of heightened arousal (Sapolsky et al., 2000), such as during swim stress. Alternately, the high dose of corticosterone that was administered to rats was presumably sufficient to stimulate Type II glucocorticoid receptors, which are a common substrate of antidepressant drugs (Budziszewska et al., 2000). Antidepressants decrease the transcription of the glucocorticoid receptors, and it would be consistent with the behavioural findings of this study if elevated levels of corticosterone were shown to act by a similar molecular mechanism.

Chronic, high levels of corticosterone have been demonstrated to produce a host of behavioural and physiological responses in rats. Whereas acute increases in plasma corticosterone are of critical importance to the healthy homeostasis of the animal (Sapolsky et al., 2000), excessive levels of the hormone may lead to detrimental effects. The clinical importance of hypercortisolemia is attested to by animal studies which have shown that chronic and high levels of exogenously administered corticosterone can lead to damage to regions of the brain such as the hippocampus (Lupien et al., 1998; Brown et al., 1999). Behaviourally, high levels of corticosterone have been demonstrated to decrease cognitive performance in memory-related tasks (Bodnoff et al., 1995; Krugers et al., 1997; McLay et al., 1998). These effects resemble several of the symptoms that are observed in Major Depressive Disorder in humans (Kalska et al., 1999), which is consistent with a putative role for excessive levels of glucocorticoids in the etiology of this disorder (Dinan, 1994; Steckler et al., 1999). It is therefore unexpected that the present study found no evidence for a depressogenic effect of chronic corticosterone, given that the forced swim test is sensitive to other rodent models of depression, and it is predicted that if chronic corticosterone had depressive-like effects in rats, this would have been manifested in the current study with increased time spent immobile.

However, it should be noted that behaviour in the forced swim test is hypothesized to reflect affective processes (Nishimura et al., 1988; Liebsch et al., 1998). The majority of animal studies that have examined the effects of chronic corticosterone have focused on the cognitive

consequences of the hormone; the few experiments that have assessed the effects of chronic corticosterone in affective tasks have observed prohedonic effects in behaviours such as increased female sexual responding, and increased male intracranial self-stimulation and drug self-administration (Hanson et al., 1998; Mantsch et al., 1998; Barr et al., 2000). A recent study in humans observed that intravenously administered hydrocortisone (a synthetic glucocorticoid) has powerful antidepressant properties in depressed patients (DeBattista et al., 2000). The results of the present study, wherein chronic corticosterone produced a mild antidepressant effect in female rats, are thus entirely consistent with previous studies that have examined the influence of corticosterone on affect-mediated tasks. Indeed, it has been shown that the capacity to produce high levels of corticosterone prevents increased "learned-helplessness" after rats are exposed to acute stressors (Edwards et al., 1990). The mode of action of corticosterone is likely to be complex, and it has been suggested that corticosterone may act to consolidate the memory of stressful events (Peeters and Broekkamp, 1994; Cahill and McGaugh, 1998). If corticosterone plays such a role, it may be predicted that high levels of the hormone may be useful for responding to acute stressors, as was observed in the present study. However, chronically high levels of corticosterone, only in combination with chronic stress, may lead to the pathological conditions that are observed in certain hypercortisolemic humans. The exposure of animals to multiple episodes of the forced swim test, in combination with exogenous corticosterone, would therefore be more likely to provide a valid model of human disorders.

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