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Interactive report

Chronic corticosterone enhances the rewarding effect of hypothalamic self-stimulation in rats¹

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Abstract

Excessive levels of glucocorticoids have been implicated in the etiology of affective disorders in humans, and in a range of behavioral deficits in animals. In the present study, we used an established regimen of corticosterone administration (40 mg/kg, for 21 days) to determine its effects upon responding for rewarding brain stimulation in rats. After chronic treatment, subjects exhibited an unexpected but significantly increased sensitivity to the rewarding effects of brain stimulation. These results suggest that chronic, high levels of corticosterone are unlikely to cause anhedonia in rodents. © 2000 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behavior

Topic: Motivation and emotion

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1. Introduction

In addition to its role in stress-mediated responses, the glucocorticoid hormone corticosterone (cortisol in humans) has been shown repeatedly to play an important role in appetitively motivated behavior. Studies utilizing rodents have demonstrated that exposure to various rewarding stimuli, including food, sexual partners, drugs of abuse and rewarding brain stimulation [5,11,26,35] all increase plasma levels of corticosterone. Indeed, the rewarding properties of corticosterone are sufficient to support its direct self-administration by trained animals [30]. Human studies have verified that cortisol can also have reinforcing effects when administered acutely [13,31].

In contrast to the rewarding effects of acutely administered cortisol in humans, exposure to chronic, high levels of cortisol, as occurs in clinical disorders such as Cushing's disease and Major Depressive Disorder (MDD), is associated with depressive symptomatology [28,29,39]. Animal studies have corroborated these findings, by dem-

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onstrating that when rats are chronically administered medium-to-high doses of exogenous corticosterone, they develop behavioral abnormalities that resemble several of the diagnostic symptoms of MDD in humans. These impairments include decreased sexual performance [14], reduced locomotor activity [9] and cognitive deficits [3,4]: this latter class of symptoms is most commonly manifested as deficits in memory-related tasks and other hippocampal-dependent activities.

Although the detrimental effects of high levels of corticosterone on cognitive function in animals are well established, surprisingly little is known about the effect of chronically high levels of this hormone on affective processes. Given that MDD is primarily an affective disorder, and that persistently high levels of cortisol are hypothesized to contribute etiologically to the dysphoria and anhedonia that are associated with this disorder [8], it may be predicted that sustained and excessive levels of corticosterone in animals could produce behavioral manifestations that parallel the affective dysregulation in humans. In addition, the work of McEwen and his colleagues has demonstrated that high levels (40 mg/kg) of exogenous corticosterone, when administered for a 3-week period [22,32,37], produce a mild atrophy in the rat hippocampus — a brain region that has attracted recent

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interest as an important area for reward-related behavior [18,40].

The present study was therefore designed to test the hypothesis that chronic administration of a high dose (40 mg/kg) of corticosterone in rats would disrupt hedonic processes in a manner similar to those of hypercortisolemic humans. This hypothesis was tested by training rats to respond for intracranial self-stimulation (ICSS) of rewarding electrical current in the lateral hypothalamus. The use of reinforcing brain stimulation is a well-validated technique that provides an operational measure of the responsiveness of the limbic system to rewarding stimuli [19,24,27].

Male Long-Evans rats, 300–350 g at the beginning of the experiment, were housed individually in hanging, wire-mesh cages, and allowed ad libitum access to food and water. The animals were maintained in a light (lights on 07:00, lights off 19:00) and temperature (21°C) controlled colony. Rats were anesthetized with xylazine (7 mg/kg, i.p.) and ketamine hydrochloride (100 mg/kg, i.p.), and implanted with stainless steel bipolar electrodes. Electrodes were directed at a site in the medial forebrain bundle corresponding to the level of the posterior lateral hypothalamus (anteroposterior, -0.5 mm from bregma; mediolateral, +1.7 mm; dorsoventral, -8.3 mm from dura; tooth bar, 5.0 mm above the interaural line).

Training and testing were conducted in 4 Plexiglas boxes (30×30×24 cm), housed within sound attenuating chambers. Depression of a lever delivered sine wave current (60 Hz) of a fixed duration (200 ms), via a flexible lead connected to the chronically implanted cranial electrode assembly. During the initial training period, the current was set at 16 µA, and only those animals that maintained consistent lever pressing were used for the second stage of training. This stage consisted of training subjects on an ascending-series rate-intensity protocol, whereby current intensities were preset by a computer (Nova-3; Manx software) and incremented in 2 μA steps, from an initial value of 8 to 28 µA. Five priming pulses of stimulation were delivered to each animal at the beginning of the first minute of testing at a given current level. The number of bar presses was recorded for the subsequent 4-min period, after which the current intensity was set at the next level. Data collection was controlled by the computer and individual rate-intensity curves were plotted daily for each subject, from which three measures were calculated; the current at which responding was half maximal (M_{50}) , the minimum current required to maintain a threshold level of responding of 40 presses/min [10], and the asymptotic level of responding. The half-maximal and threshold currents provide an accurate measurement of the individual's sensitivity to reward, while the asymptotic level of responding provides a measure of the animal's capacity to perform motor tasks, hence allowing the influence of performance-altering effects of drugs to be determined [20,25].

After stable levels of ICSS responding had been achieved by subjects ($M_{50} < \pm 10\%$, for 3 consecutive days), animals were rank ordered based upon their level of responding over the previous 3 baseline sessions. The rats were then assigned sequentially to 2 groups, from the highest to the lowest M_{50} values. One group of rats (n=7) was subsequently given daily injections of corticosterone (40 mg/kg, s.c.) for 3 weeks, while the other group (n=7) received vehicle injections. Corticosterone-21-acetate (Sigma, St. Louis, MO) was suspended in propylene glycol (1 ml/kg), and injections took place between 09:00–09:30 daily. All animals were weighed every 7 days.

Animals were subsequently tested on the ascending-series rate-intensity protocol every second day, following the commencement of corticosterone/vehicle injections. Test sessions took place between three and six h after the injections, and testing continued until the termination of the injection schedule. Upon completion of this schedule, subjects remained undisturbed for an additional 2 weeks, at which time they were retested to determine if the effects of the corticosterone injections had produced a lasting effect upon ICSS responding. Upon termination of all behavioral testing, subjects were deeply anaesthetized and perfused transcardially with a 4% paraformaldehyde solution. The brains were removed and cut into 40 μm sections and mounted onto slides, which were then stained with cresyl violet to verify the placement of the electrodes.

The data obtained from the individual rate-intensity curves were subjected to a 2-factor repeated-measures ANOVA, with drug condition and test session as between and within subjects factors, respectively. Animal weights were also subjected to a 2-factor repeated-measures ANOVA. Post-hoc tests were used when appropriate, and consisted of tests of simple main effects. Independent samples *t*-tests were used to compare ICSS data between the two groups when animals were tested 2 weeks after the final corticosterone injection.

As can be seen in Fig. 1, the two groups of animals exhibited very similar levels of ICSS responding prior to the daily injections of corticosterone. However, with repeated injections of this drug, the rats that were administered corticosterone began to exhibit a leftward shift in their responding for the reinforcing brain stimulation. This was most clearly evidenced as a decrease in the current required to attain threshold responding, as well as the current necessary to maintain half-maximal responding. Statistical analysis indicated that there was a significant main effect of corticosterone on M_{50} ($F_{(1,12)}$ =4.77; P= 0.05) and a significant main effect of test session $(F_{(11,132)}=3.00; P<0.001)$, as well as a significant interaction between drug condition and test session $(F_{(11,132)} =$ 3.04; P<0.001). Further analysis with post-hoc tests revealed that there was a significant difference between the corticosterone and vehicle groups by the fourth ICSS session, which corresponds to the eighth day of injections, and this difference was maintained until the conclusion of

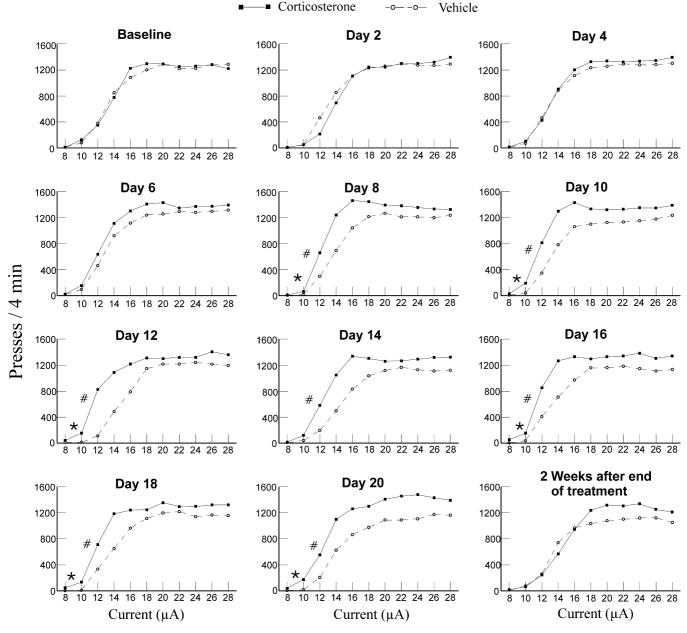


Fig. 1. Effect of daily administration of corticosterone (40 mg/kg) or vehicle for 21 days on self-stimulation of the lateral hypothalamus in male rats, using a current-intensity paradigm. Animals were tested for ICSS responding every alternate day, starting on the second day of drug administration and continuing until its completion; an additional test was conducted 2 weeks after the final injection of corticosterone. $^{\#}P$ <0.05 difference between groups for M_{50} ; *P<0.05 difference between groups for threshold current (40 presses/min).

the injections. The facilitatory role of corticosterone on ICSS was determined by its capacity to reduce the current required for M_{50} compared to both the vehicle-treated group, as well as the corticosterone-treated group's own pre-drug baseline responding (for example, the current required for the M_{50} after 12 days of corticosterone=11.91 μ A, compared to the vehicle-treated group's value of 14.65 μ A, or a baseline value of 14.21 μ A). Hence, there was no effect of acute corticosterone on this measure of ICSS responding, but after at least 1 week of exposure to

high levels of exogenous corticosterone, a prohedonic effect of corticosterone on ICSS was observed.

The effect of corticosterone on threshold currents revealed a similar pattern, whereby it had a marginally significant effect on the current required to maintain threshold responding ($F_{(1,12)}=3.75$; P=0.07) and a significant main effect of test session ($F_{(11,132)}=2.94$; P<0.005); a significant interaction between drug and test session ($F_{(11,132)}=2.94$; P<0.005) indicated that threshold currents were decreased by the fourth ICSS session, and remained

lower (excepting the seventh ICSS test session) until the final injection. In contrast to the effect of corticosterone on M₅₀ and threshold currents, there was no significant effect of the drug on the asymptotic level of responding $(F_{(1,12)} =$ 0.76; NS) or interactive effect with test session $(F_{(11.132)} =$ 1.43; NS), implying that corticosterone had no effect on performance measures. Casual observation of the asymtotic levels of responding of vehicle-treated animals in Fig. 1 appears to show a slight decline in the values across the test sessions. The asymptotic values of responding were compared for vehicle-treated rats between the final day of baseline responding and on the twentieth day of drug treatment, and indicated no significant change in values ($t_{(12)}$ =0.07, NS). When subjects were tested again 2 weeks after the final injection, the M_{50} and threshold currents had returned to levels similar to the vehicleinjected group $(t_{(12)} = 0.41; t_{(12)} = 0.38, NS \text{ for both, respec-}$

The weights of the animals are shown in Fig. 2, and it can be seen clearly that chronically administered corticosterone produced a moderate decrease in the weight of these subjects. An ANOVA indicated that the main effect of drug treatment was significant ($F_{(1,12)}$ =5.61; P<0.05), and there was also a highly significant main effect of week

 $(F_{(4,48)} = 228.6; P < 0.001)$, with a significant interaction between drug and week of testing $(F_{(4.48)}=19.46; P <$ 0.001). Post-hoc analysis of the data revealed that the weights of corticosterone-treated rats were significantly lower by the end of the first week of injections. From this time until the end of drug administration, these rats failed to increase their weight, while the rats that received vehicle injections exhibited a weekly gain in weight. However, 2 weeks after the final injection, there was no longer a significant difference in weight between the groups, as the corticosterone-treated animals exhibited a rapid weight gain to match their vehicle-treated counterparts. As food consumption was not measured in the present study, it is possible that the decreased weight of corticosterone-treated rats could reflect changes in either feeding behavior or metabolic activity [20].

The results of this experiment therefore provide the unexpected finding that the chronic (3-week) administration of a high dose of exogenous corticosterone produces a prohedonic effect in rats, as determined by an ICSS protocol. The capacity of corticosterone to alter two important indices of sensitivity to ICSS reward in the present manner strongly suggests that chronic corticosterone may have rewarding properties. This finding would

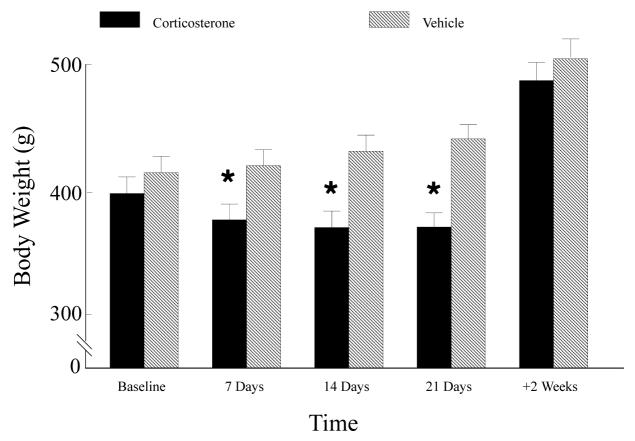


Fig. 2. Effect of daily administration of corticosterone (40 mg/kg) or vehicle on body weights of male rats. Subjects were weighed at the end of every week, from the beginning of corticosterone treatment until its conclusion. Animals were also weighed 2 weeks after the final injection of corticosterone. *P<0.05 compared with controls.

appear to stand in contrast to the wealth of evidence showing that chronic, high levels of corticosterone or cortisol are associated with depressive-like symptoms in animals and humans.

A closer examination of previous studies reveals that the most commonly observed effects of treatment with high doses of corticosterone are changes predominantly of a cognitive or psychomotor nature, rather than affective in type. Hence, the findings from the present study provide evidence that there may be a dissociation in the ability of high levels of this hormone to alter cognitive/psychomotor and hedonic processes. Although few studies have examined the effect of high levels of corticosterone on reward-related behaviors, several articles have shown that drug self-administration in rats is affected potently by the levels of circulating adrenal steroids [7,12]. In particular, one recent experiment showed that administration of a lower dose (2 mg/kg) of exogenous corticosterone for 2 weeks prior to cocaine self-administration subsequently facilitated the self-administration of lower doses of cocaine [23], similar to the manner in which corticosterone increased responding for lower levels of rewarding current in the present study. These combined results indicate that chronic corticosterone may actually enhance the rewarding value of stimuli such as drugs and brain stimulation.

The mechanism by which corticosterone facilitates ICSS responding remains to be determined, and is beyond the scope of the present study. However, it is of interest to note that food-restricted rats exhibit a "sensitization" of ICSS responding, which is of a similar magnitude to that exhibited by the rats in this study [6]. The reward-enhancing effects of corticosterone appeared at a time coincident with weight loss, thus raising the possibility that the prohedonic consequences of corticosterone are secondary to metabolic alterations. Alternatively, the schedule of corticosterone used in the present study was based on previous reports that induced dendritic atrophy of neurons in the rodent hippocampus [32,37]. Several recent studies have reported that damage to similar regions of the hippocampus causes an increased responding for ICSS [18,40], indicating an inhibitory role for this region in reward-related behavior. As both the weight-reducing and atrophying effect of corticosterone are reversible after a 2-week respite from the drug, it is indeterminable which of these two factors plays a more important role in the present findings, and further studies will seek to resolve this issue.

The ability of chronic corticosterone to enhance the reinforcing properties of drugs of abuse and rewarding brain stimulation in rats creates a paradox, as hypercortisolemic humans tend to exhibit opposing affective symptoms, notably anhedonia and dysphoria. This may reflect a unique property of stimuli such as rewarding brain stimulation and drugs of abuse [38], which would be in accordance with the observation that patients with endogenous depression tend to engage in more frequent drug-taking behavior [25]. The effect of chronic corticosterone on the motivation to attain and consume other primary and

secondary reinforcers should thus be determined. Another possible explanation for the discrepancy between the affective consequences of chronically high levels of hormones of the Hypothalamic-Pituitary Adrenal (HPA) axis in the human literature and the present study may lie in the hormonal basis of the results. Sub-groups of depressed humans, in addition to having elevated levels of cortisol, may also exhibit hypersecretion of corticotrophin-releasing factor (CRF) [1]. It is unlikely that the corticosteronetreated animals in the present study would secrete higher levels of CRF (although this remains to be determined empirically), as corticosterone normally provides a negative feedback signal to reduce the transcription of CRF and its receptors [2,15,36]. Previous experiments have demonstrated that high levels of CRF in rodents produce a host of behavioural deficits that may reflect an increased reactivity to stress [17,34], while a recent study demonstrated that intracerebroventricular infusions of CRF potently reduced responding for ICSS in rats [21]. These results suggest that high levels of CRF may have adverse affective consequences, and excessive levels CRF may thus be more likely to act as a neuroendocrine factor in the development and expression of depressive symptoms than high levels of cortisol/corticosterone.

A further difference between the human literature and the present study lies in the duration of exposure to the glucocorticoids. Although 3 weeks of exposure to a high dose of corticosterone was sufficient to generate a hedonic shift in rats, humans are often exposed to excessive levels of hormones of the HPA axis for a much longer period [8,16]. It is entirely possible that if rats had been exposed to corticosterone for a longer duration, opponent-processes would have prevailed [33], and caused a hedonic shift in the other direction. In addition, the use of a single, high dose of corticosterone represents an important limitation of the present study, and future studies should examine the effects of a range of different doses of this hormone on ICSS responding.

In conclusion, the present study found evidence that the treatment of rats with a chronic, high-dose regimen of exogenous corticosterone produced an increased sensitivity to the rewarding effects of brain stimulation. At present, the physiological basis for this phenomenon remains unknown, but may be related to changes in body weight or hippocampal cell morphology.

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