Dose dependent effects of injected corticosterone on food intake and locomotor activity of rats in relation with dopamine levels in brain regions

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Abstract: Studies in rat models show that stress has a dual effect on food intake as mild to moderate stress enhances appetite leads to obesity, while severe stress has been shown to suppress appetite leading to anorexia nervosa. It has also been reported that glucocorticoids act directly on CNS and influence behavior while their effects depend upon dose as well as duration of treatment. Present study was designed to monitor the dose dependent effects of injected corticosterone on food intake and locomotor activity of rats in relation with dopamine levels in brain regions. Results suggests that higher doses of corticosterone (25mg/kg and 50mg/kg) decrease cumulative food intake and enhance locomotor activity as monitored in familiar environment by increasing the levels of dopamine in the striatum and midbrain and decreasing the levels of dopamine in the hippocampus of rat brain. Findings would be helpful for extending therapeutics in movement and anxiety related disorders.

Key words: Corticosterone, anorexia nervosa, dopamine, stress, anxiety.
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INTRODUCTION

One of the attributes mediating stress response, is the release of corticosteroid hormones. Neurobiological and behavioral changes are produced by the factors affecting function and regulation of hypothalamic pituitary adrenal (HPA) axis1. In threatening situations induced by stress, appropriate coping behavior is facilitated by increased activity of HPA axis along with associated increase in the levels of serum glucocorticoids2. It has also been reported that caloric intake is significantly increased if corticosteroids are secreted in response to stress stimuli3. This regulation of energy intake and body weight is done by the different neuronal pathways in the hypothalamus and is reported to be effected by corticosteroids. In this context, alteration in the effects of corticosterone are reported to be influenced by both duration and doses of corticosterone treatment4. Since glucocorticoids regulate the neurotransmission of dopamine, their role in affective disorders has been associated to alterations in dopaminergic system. This is further supported by the finding that post-synaptic neurotransmission of dopamine is decreased in rats with adrenalectomy 5, 6, 7. Present study was conducted to monitor dose-dependant effects of corticosterone on locomotor activity and feeding behavior in rats, in relation with the dopamine level in brain regions.

MATERIALS AND METHODS

Animals:
Male Albino wistar rats (180±20 gm) were housed individually in a quiet room with free access to standard rodent diet and tap water, a week before starting the experiment.

Drugs and chemicals:
Subcutaneous (s.c.) injections of corticosterone dissolved in saline (0.9% NaCl) were given at the doses of 10, 25 & 50mg/ml/kg. HPLC grade chemicals were purchased from Sigma (USA), and BDH Chemical pool (England). Control animals were injected with 1ml/kg of saline.

Experimental Protocol:
24 rats were divided into four groups; each containing six animals: (i) saline (ii) low (10 mg/kg)-, (iii) moderate (25 mg/kg)- and (iv) high (50 mg/kg) corticosterone injected rats. To get familiarized with the environment, rats were placed in the familiar environment of Skinner’s box 10min before injection. 5min post injection, activities in Skinner’s box were monitored for 10min. On third day, animals were decapitated 1hr post drug administration, after repeated corticosterone administration for three days. Samples were stored at -70⁰C until neurochemical analysis by HPLC-EC.

Cumulative food intake was determined by weighing the food palettes in the hopper of cages. Locomotive activities in Skinner’s box were recorded as described earlier8. Within 30min of decapitation, brain samples were collected from the rats. Striatum, mid brain and hippocampus were
isolated from rat brains. Procedure was same as described earlier\(^9\). Neurochemical analysis was done using HPLC-EC with standardized conditions\(^10\). Results are given as mean±SD. One-way ANOVA followed by Post hoc Newman-Keuls test was used for the statistical analysis. Values of p<0.05 were considered statistically significant.

**RESULTS**

**Cumulative food intake**

Figure 1 shows the dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on cumulative food intake of rats. One-way ANOVA showed significant effect of corticosterone administration on cumulative food intake (F=3.79, df=3,20; p<0.05). Post hoc analysis by Newman-Keuls test showed that moderate and high doses (25 & 50 mg/kg respectively) of corticosterone decreased (p<0.01) food intake as compared to low dose (10 mg/kg).

**Home cage activity**

Figure 2 shows dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on locomotor activity of rats monitored in familiar environment of home cage. One-way ANOVA showed that effects of corticosterone administration on locomotor activity were significant (F=11.38, df=3, 20; p<0.01) and striatum (df=3, 20; F=10.75; p<0.01) but not in midbrain (df=3, 20; F=2.42). Post hoc analysis by Newman-keuls test showed decreased (p<0.01) dopamine levels in the hippocampus of rats injected with corticosterone moderate and high dose (25 mg/kg & 50 mg/kg) as compared to saline injected and corticosterone low dose (10 mg/kg) injected animals. An increased DA (p<0.05) level was found in striatum of corticosterone high dose (50 mg/kg) injected animals as compared to saline injected animals.

**Brain dopamine**

Figure 3 shows dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on DA levels in striatum, midbrain and hippocampus. One-way ANOVA showed that effects of corticosterone administration on DA levels were significant in hippocampus (df=3, 20; F=94.75; p<0.01) and striatum (df=3, 20; F=10.75; p<0.01) but not in midbrain (df=3, 20; F=2.42). Post hoc analysis by Newman-keuls test showed decreased (p<0.01) dopamine levels in the hippocampus of rats injected with corticosterone moderate and high dose (25 mg/kg & 50 mg/kg) as compared to saline injected and corticosterone low dose (10 mg/kg) injected animals. An increased DA (p<0.01) level was found in striatum of corticosterone high dose (50 mg/kg) injected animals as compared to saline injected animals.
Figure 3: Dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on dopamine levels in striatum, mid brain and hippocampus. Values are means ± SD (n=6). Significant differences by Newman-Keuls test: *p<0.05, **p<0.01 from saline injected controls; +p<0.01 corticosterone (10 mg/kg) injected animals following one-way ANOVA.

Serum corticosterone

Figure 4 shows dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on serum corticosterone levels. One-way ANOVA showed significant (F=3.2, df=3, 20, p<0.05) effects of injected corticosterone on plasma corticosterone level. Post hoc analysis by Newman-Keuls test showed that low, moderate and high doses of corticosterone (10, 25 & 50 mg/kg) increased plasma corticosterone level as compared to saline injected controls; *p<0.01 corticosterone (10 mg/kg) injected animals following one-way ANOVA.

Serum glucose

Figure 5 Shows dose dependent effects of injected corticosterone (10, 25 & 50 mg/kg) on serum glucose level. One-way ANOVA showed significant (F=7.6, df=3, 20, p<0.01) effects of corticosterone on plasma glucose level. Post hoc analysis by Newman-Keuls test showed that low dose (10 mg/kg) of corticosterone increased (p<0.05) plasma glucose level as compared to saline injected controls, while moderate dose decreased plasma glucose level as compared to saline (p<0.05) and low dose (p<0.01) injected animals respectively. High dose injected (50 mg/kg) animals showed increased (p<0.01) glucose level as compared to moderate (25 mg/kg) dose injected ones.
DISCUSSION

Considerable decease in food intake following adrenalectomy in rats suggested that glucocorticoids greatly affect the amount of food intake. Present study showed that corticosterone decreased food intake at 25 & 50 mg/kg and this decrease in food intake was not found at 10 mg/kg of corticosterone. Previous studies have shown that among all brain regions, hippocampus has major role in memory as well as feeding. The expression of CB1 receptors, glucocorticoids, insulin and ghrelin suggest hippocampus as appetite controlling center via non-mnemonic processes.

Dopamine has an established role in the feeding behavior. It has been reported that dopamine in the hippocampus have a positive influence on feeding behavior in rats. Results of the present study showed that moderate and high doses of corticosterone decreased food intake (fig 1) by decreasing the levels of dopamine in hippocampus (fig 3). Present research showed that low dose (10 mg/kg) of injected corticosterone increased the levels of corticosterone and glucose in serum but higher doses i.e. 25 & 50 mg/kg of injected corticosterone failed to produce further increase in plasma corticosterone and glucose levels (fig 4 & 5). It is suggested that corticosterone at 25 & 50 mg/kg suppressed HPA axis through negative feedback regulation which stopped further raise in plasma corticosterone level. Corticosterone has been proposed as a major antagonistic hormone to the actions of insulin. Increase in concentration of corticosterone also increases blood glucose level. So the increase in plasma glucose level at 10 mg/kg of corticosterone can be justified with increased plasma corticosterone level at this dose. The effect of corticosterone on animal’s behaviors has been reported to be biphasic. Scientific studies in the past years have suggested that depressive behaviors are affected differently by short and long term administration of corticosterone. In the present study corticosterone at the doses of 10 and 25 mg/kg did not alter locomotor activity however 50mg/kg of corticosterone has been found to increase locomotor activity in familiar environment of Skinner’s box (fig 2) which could be due to increased concentration of dopamine in striatum (fig 3). It has been reported that chronic high-dose of corticosterone increases dopaminergic function. Current findings suggest that high dose of corticosterone is effective for enhancement of locomotor activity and produces hypophagic effect by decreasing the dopamine levels in the hippocampus of the rat brain.

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REFERENCES


