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METABOLIC EFFECTS OF CYPROTERONE ACETATE AND CORTICOSTERONE IN THE CHICKEN
GALLUS DOMESTICUS

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Key words : Corticosterone, cyproterone acetate, chickens, metabolism.

ABSTRACT
The metabolic effects of corticosterone were compared with those of cyproterone acetate, a steroidogenic inhibitor with suggested corticoid-like effects. Corticosterone significantly increased serum levels of glucose, triglycerides, globulins and uric acid. No significant changes were observed in serum total cholesterol, LDL, HDL and albumin with corticosterone treatment.
Cyproterone acetate did not alter any of the studied parameters. It is concluded from this study that as cyproterone acetate is devoid of any glucocorticoid-like activity, it can be used as a reliable adrenal suppressor in chickens.

INTRODUCTION
The relationship of plasma levels of glucocorticoids to modifying the response to chronic stressors and their effects on the immune system have been reported in mammals (Del Rey et al., 1984; Smith et al., 1988) and birds (Davison et al., 1988). Glucocorticoids are known to induce deep metabolic effects to prepare the animal to sustain stress. In mammals, they increase blood glucose, mobilize tissue fats and speed up the breakdown of proteins in the process of gluconeogenesis (Liddle, 1974; Martin, 1978). Similar effects have also been observed in birds following glucocorticoid or ACTH administration. Davison et al. (1983, 1985) reported that the administration of corticosterone or ACTH, either in the diet or by implanting subcutaneous pellets, caused a dose-related increase in plasma concentration of glucose, triglycerides, cholesterol and uric acid in chickens.

The study of the responses of chickens to stressors and their effects on the immune system, would require producing sustained increases and decreases in the levels of circulating glucocorticoids to understand their role in the process of stress adaptation. The sustained increase has been successfully achieved by many authors using ACTH or exogenous glucocorticoids.
administered through different routes (Freeman et al., 1979; Ambler et al., 1982; Davison et al., 1985).

On the other hand, the achievement of a method to induce a consistent decrease in circulating levels of glucocorticoids with reliability in birds has not been completely successful. Many investigators have tried to block or inhibit the adrenal steroidogenesis by different chemical inhibitors such as metyrapone (Culbert and Wells, 1975; Ezzat, 1988), aminoglutethimide (Lang, 1984), and spironolactone (Aupetit et al., 1979), but the results were conflicting.

Cyproterone acetate; (1,2-methylene-6-chloro-17-acetoxy 4,6-pregna-diene-3,20-dione:CA) has been used as a potent inhibitor of adrenal and gonadal steroidogenesis in mammals (Gooren, 1984; Lambert et al., 1985). A previous work by Davison et al., (1989) has shown that CA was useful in lowering circulating levels of corticosterone in chickens with different doses and over prolonged periods. This CA-steroidogenic blocking effect was also found to be related to histological changes indicative of adrenal hypofunction (Wahba and Ezzat, 1988). However, Davison et al., (1989) reported that CA did not affect the number of circulating peripheral blood lymphocytes or their ability to proliferate in the presence of mitogens. Consequently, they suggested that CA, although being effective in suppressing the adrenocortical activity, might have some corticoid-like action on lymphocytes and the immune system which in turn could alter the effects of decreased endogenous glucocorticoids. If this assumption was true, there might be some drawbacks to its use in chickens especially in immunological studies.

The aim of the present study is to examine the feasibility of using CA in chickens by investigating its possible effects on some metabolic parameters known to be affected by glucocorticoids and to assess its corticoid-like activity. A comparison will also be made of the metabolic effects of CA with those of corticosterone.

MATERIALS AND METHODS

Broiler chickens Gallus domesticus were obtained from a commercial hatchery and maintained with food and water ad libitum as described by Ezzat (1987). At eight weeks of age, twenty four males were randomly allocate to three groups of eight birds. The treatment included the propylene glycol vehicle, corticosterone (10mg Kg⁻¹, Sigma), and cyproterone acetate (10mg Kg⁻¹, Abdacur, Schering). All injections were administered in a volume of 0.2 ml into the pectoralis major muscle. Each bird received a daily injection of either one of the treatments for five consecutive days. On the sixth day, all birds were bled by brachial vein puncture. Serum was separated and stored deep frozen at −20°C pending analysis for glucose, (Trinder, 1969a), cholesterol.

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Table 1
Effects of corticosterone and cyproterone acetate on the levels of some serum constituents of the chicken *Gallus domesticus* 6 days following treatment.

<table>
<thead>
<tr>
<th>Serum Constituent</th>
<th>Control</th>
<th>Corticosterone</th>
<th>Cyproterone acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/100ml)</td>
<td>257.50 ± 9.65</td>
<td>349.50 ± 14.89***</td>
<td>268.67 ± 22.15</td>
</tr>
<tr>
<td>Total cholesterol (mg/100ml)</td>
<td>170.50 ± 15.44</td>
<td>198.50 ± 11.15</td>
<td>169.33 ± 7.22</td>
</tr>
<tr>
<td>HDL (mg/100ml)</td>
<td>99.68 ± 4.77</td>
<td>115.35 ± 6.16</td>
<td>99.40 ± 5.87</td>
</tr>
<tr>
<td>LDL (mg/100ml)</td>
<td>53.12 ± 5.76</td>
<td>56.50 ± 3.54</td>
<td>56.12 ± 3.08</td>
</tr>
<tr>
<td>Triglycerides (mg/100ml)</td>
<td>88.40 ± 5.40</td>
<td>124.17 ± 6.51***</td>
<td>68.30 ± 10.01</td>
</tr>
<tr>
<td>Total Protein (g/100ml)</td>
<td>4.46 ± 0.24</td>
<td>5.11 ± 0.29</td>
<td>4.73 ± 0.22</td>
</tr>
<tr>
<td>Albumin (g/100ml)</td>
<td>1.07 ± 0.06</td>
<td>1.30 ± 0.09</td>
<td>1.11 ± 0.05</td>
</tr>
<tr>
<td>Globulin (g/100ml)</td>
<td>3.22 ± 0.10</td>
<td>3.81 ± 0.23*</td>
<td>3.62 ± 0.19</td>
</tr>
<tr>
<td>Albumin/Globulin ratio</td>
<td>0.34 ± 0.02</td>
<td>0.37 ± 0.04</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td>Uric Acid (mg/100ml)</td>
<td>3.84 ± 0.40</td>
<td>6.38 ± 0.35***</td>
<td>4.48 ± 0.48</td>
</tr>
</tbody>
</table>

Data are expressed as means ± S.E.  
P < 0.05* ; 0.01** ; 0.001***
(Trinder, 1969b), triglycerides (Wahlefeld, 1974), low density lipoprotein (LDL) (Friedewald et al., 1972), high density lipoprotein (HDL) (Lopes-Virella et al., 1977), total protein (Weichselbaum, 1946), albumin and globulin (Doumas et al., 1971) and uric acid (Steel, 1958). All data were paired and analyzed using the student’s t-test.

RESULTS
Serum glucose level was significantly (P<0.001) increased in response to corticosterone injection. The levels of triglycerides, globulin and uric acid were significantly elevated with corticosterone treatment above the control values (p<0.01, 0.05 and 0.001 respectively). On the other hand, the serum levels of total cholesterol, HDL, LDL, total protein and albumin were not significantly altered. The statistical analysis showed that cyproterone acetate administration did not induce any significant changes in the studied parameters.

DISCUSSION
The results have clearly indicated that corticosterone, the major glucocorticoid in chickens (Kalliecharan, 1981) causes effects on the metabolism of carbohydrates, lipids and proteins comparable with those usually obtained in similar experiments with mammals and birds. Hyperglycaemia was evident and this was also reported by Exton (1972) and Ramey (1975) in mammals, and Davison (1983, 1985) in birds. There is more than one mechanism by which glucocorticoids can raise blood glucose level. They increase gluconeogenesis and inhibit the extra-hepatic utilization of glucose (Exton, 1972; Ramey, 1975; Martin, 1978). Exton (1972) reported that glucocorticoids promote the induction of hepatic gluconeogenic enzymes and enhance the supply of substrate, provided mainly by protein catabolism. In addition, to increased hepatic gluconeogenesis, hyperglycaemia is also mimicked by the glucocorticoid-induced inhibition of glucose uptake by peripheral tissues, mainly the adipose tissue (Beato and Doenecke, 1980). Moreover, it was found that glucocorticoids cause degradation of fats and release of fatty acids into the blood; the elevated levels of fatty acids affect plasma membranes of many cell types and decrease their ability to take up glucose (Deane and Rubin, 1968). The increase in serum triglyceride levels observed herein with corticosterone administration is most likely due to stimulated hepatic lipogenesis which is consistent with the results of Davison et al. (1983). In the present work, corticosterone did not alter the levels of serum LDL, HDL or total cholesterol. It was expected that high levels of circulating serum corticosterone would inhibit the adrenocortical activity through the feedback inhibition on ACTH and thereby reduce cholesterol uptake by the adrenals.
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leading to an increase in its circulating levels (Jones et al., 1974). However, it may be suggested that the administered corticosterone caused elevation in the circulating levels of this hormone enough to induce metabolic effects but not to exert feedback on the hypophyseal-adrenal axis. The fact that exogenous corticosterone has a short half life and is rapidly degraded and eliminated in chickens (Birrenkott and Wiggins, 1984) supports this assumption.

In the present study, corticosterone administration induced a marked increase in serum globulin whereas albumin was not significantly affected. This result is in accordance with the report of Steele (1975) showing that corticosteroid-induced hyperproteinemia is mostly attributed to increased production of non-albumin proteins which are mainly carrier proteins used in lipid transport. Nevertheless, other reports have shown that corticosterone caused an increase in serum total proteins through the promotion of hepatic protein synthesis and increased plasma albumin in mammals (Martin, 1978) and chickens (Davison et al., 1985).

The increase in serum uric acid observed in this study following corticosterone administration reflects an increased protein turnover and that amino acids have been utilized to provide the necessary substrate for hepatic gluconeogenesis. Glucocorticoids enhance amino acid mobilization from peripheral tissues and promote synthesis of enzymes catalyzing deamination reactions (Liddle, 1974) thereby increasing nitrogen excretion.

As for cyproterone acetate, its administration in a dose reported to lower endogenous corticosterone in chickens effectively (Davison et al., 1989) did not change any of the studied parameters known to be sensitive to glucocorticoid-like activity. Consequently, we infer from these data that CA is not effective by itself as a glucocorticoid-like compound, which is unlikely to interfere with the suppressed endogenous glucocorticoids when used in chickens.

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التأثيرات الأيضية لعقار خلات السيبروتيرون
وهرمون الكروتئيكوستيرون في الدجاج «جايس دوميستيكس»

فواد صلاح و أحمد رفعت عزت

تمت مقارنة التأثيرات الأيضية لعقار خلات السيبروتيرون وهو يستخدم كمثبط لنشاط الغدة الكظرية مع هرمون الكروتئيكوستيرون في الدجاج. وقد أدت المعالجة بهرمون الكروتئيكوستيرون إلى زيادة ملحوظة في مستوى المصل من الجلوكوز والجلسريدات الثلاثية والجلوبيولين وحامض البوليك. ولم يكن هناك تغيرات ملحوظة في مستوى المصل من الكوليسترول الكلي والدهون البروتينية عالية الكثافة وخفضة الكثافة والألبومين.

كما لوحظ أن عقار خلات السيبروتيرون لم يكن مؤثراً إطلاقاً على أي من مكونات المصل المدرسة.

ويستنتج من هذا البحث أن عقار خلات السيبروتيرون ليس له أي نشاط مشابه للكروتئيكودات السكرية يمكن استخدامه لتثبيط نشاط الغدة الكظرية في الدجاج بفاعلية بدون إحداث تأثيرات أية أيضية.

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