EFFECT OF DESOXYCORTICOSTERONE ON INFLAMMATION AFTER LOCAL ADMINISTRATION

By

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Most studies concerning the effect of mineralocorticoids on inflammatory processes have shown that these hormones exert a prophlogistic influence. This conclusion was reached using various techniques to produce inflammation experimentally, e.g., topical irritation arthritis (Selye, 1949), turpentine abscess (Taubenhaus & Amromin, 1950), granuloma pouch (Selye, 1955), tuberculin reaction (Ballabio & Bonomo, 1951). Furthermore, it is known that adrenalectomized rats treated with desoxycorticosterone acetate (DCA) often develop spontaneous arthritis (Selye et al., 1944). Finally, it is also possible, following chronic treatment with mineralocorticoids, to induce a syndrome of malignant hypertension characterized by extensive vascular lesions, inflammatory in nature (Selye, 1942).

All these results were obtained after systemic administration of the hormones. There are very few data on the effect of mineralocorticoids when locally applied in an inflammatory area. Rindani (1953, 1954 a, 1954 b) obtained a prophlogistic response after injecting directly into the cavity of the granuloma pouch either DCA or Reichstein’s compound «S». On the other hand, Meier et al. (1951) and Desaulles et al. (1954), using the implantation of a cotton pellet as an assay, observed an inhibition of granuloma formation after local application of desoxycorticosterone (DOC). Finally, Schneebeli & Dougherty (1951), Taubenhaus et al. (1952) and Sakabe et al. (1954) in various tests did not observe any effect on inflammation of locally applied DOC or DCA. Recently Desaulles et al. (1955) showed that local application of 50 and 100 µg. of aldosterone slightly increased granuloma weight in the cotton pellet implantation test.

It was deemed of interest to investigate further the activity of locally applied mineralocorticoids. It seemed logical a priori to assume that if a
hormone such as DOC exerted any local activity, it should be in the prophlogistic direction, as this is the effect regularly observed after systemic administration.

**Materials and Methods**

One hundred twenty female rats of the Upjohn strain (originally from Sprague-Dawley) weighing from 165–180 gm. were divided into 12 groups of 10 animals each. In all of these a granuloma pouch was formed on the 1st day according to a technique already described (Robert & Nezamis, 1957) and briefly summarized as follows. Under sodium cyclopentenylallylbarbiturate (Cyclopal) anesthesia, each compound, suspended in 0.2 ml. of a mixture of carboxymethylcellulose, polysorbate 80, propylparaben, water and formaldehyde 1/100 (as an antiseptic), was administered on the 1st day subcutaneously in the middle of the back. Immediately after, 25 ml. of air were injected 1–2 cm. behind the first injection. The substance thus remained in the elevated skin throughout the experiment. This was followed by the injection into the air sac of 0.5 ml. of 1% croton oil, diluted in cottonseed oil. The treatment given to each experimental group is detailed in Table 1. Pregnan-3,20-dione, which has been reported to be hormonally inactive, was used as a control substance for DOC. Air was withdrawn from the pouches on the 2nd day, at a time when exudate had just begun to accumulate, and the animals were sacrificed on the 4th day. At autopsy the exudate present in the pouches was accurately measured in a graduated cylinder and the thymuses of the animals of Groups 1, 7, 8, 9, 10, 11 and 12 removed and immediately weighed on a torsion balance.

**Results**

The results are summarized in Table 1 and illustrated in Fig. 1. Pregnanedione exerted no effect on inflammation whereas DOC inhibited markedly the formation of inflammatory exudate, its threshold dose being between 2 mg. and 5 mg. The body weight was not changed by the treatment nor was the thymus weight, although the lower dose of DOC seemed to have exerted a slight thymotrophic effect.

**Discussion**

This unexpected effect of desoxytocicosterone is difficult to explain. Is this local antiphlogistic action a function of the mineralocorticoid property of the compound or is it related to a special structural configuration of the molecule independent of the mineralocorticoid activity? One could partially answer this question by studying the effect of other mineralocorticoids under the same conditions. One can also think that DOC may be converted by inflammatory tissues into a compound possessing antiphlogistic properties. This seems to be a likelier hypothesis. Actually it has been demonstrated that DOC can be
Table 1.
Effect of Increasing Doses of DOC on Inflammation, expressed as ml. of Exudate.

<table>
<thead>
<tr>
<th>Group</th>
<th>1 0 CMC</th>
<th>3 P-one** 100 µg.</th>
<th>4 P-one 2 mg.</th>
<th>5 P-one 5 mg.</th>
<th>6 P-one 10 mg.</th>
<th>7 P-one 15 mg.</th>
<th>8 DOC 100 µg.</th>
<th>9 DOC 2 mg.</th>
<th>10 DOC 5 mg.</th>
<th>11 DOC 10 mg.</th>
<th>12 DOC 15 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight Initial</td>
<td>171</td>
<td>173</td>
<td>170</td>
<td>172</td>
<td>175</td>
<td>178</td>
<td>172</td>
<td>176</td>
<td>181</td>
<td>175</td>
<td>168</td>
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<tr>
<td>Body Weight Final</td>
<td>172</td>
<td>178</td>
<td>175</td>
<td>177</td>
<td>180</td>
<td>182</td>
<td>178</td>
<td>181</td>
<td>184</td>
<td>178</td>
<td>172</td>
</tr>
<tr>
<td>Body Weight Difference</td>
<td>+1</td>
<td>+5</td>
<td>+5</td>
<td>+5</td>
<td>+4</td>
<td>+6</td>
<td>+5</td>
<td>+3</td>
<td>+3</td>
<td>+4</td>
<td>0</td>
</tr>
<tr>
<td>Exudate</td>
<td>5.92</td>
<td>5.79</td>
<td>5.90</td>
<td>6.76</td>
<td>5.83</td>
<td>6.55</td>
<td>6.04</td>
<td>6.26</td>
<td>6.16</td>
<td>2.80</td>
<td>1.05</td>
</tr>
<tr>
<td>± 0.34</td>
<td>± 0.44</td>
<td>± 0.44</td>
<td>± 0.34</td>
<td>± 0.52</td>
<td>± 0.52</td>
<td>± 0.52</td>
<td>± 0.52</td>
<td>± 0.13</td>
<td>± 0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymus</td>
<td>269</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistical analysis showed that the difference in volume of exudate is not significant between Groups 2 and 8 (p > 0.4), Groups 2 and 9 (p > 0.1), but is significant between Groups 2 and either 10, 11 or 12 (p < 0.01).

** P-one: Pregnane-3,20-dione.
converted in vitro into cortisone by adrenal, liver, testis and kidney tissue (Seneca et al., 1950). It is not impossible that other peripheral tissues such as granulation tissue can likewise operate similar transformations. The end product, endowed with antiphlogistic properties, would be expected to exert only a local effect if formed in minute quantities. This would explain why the hormonal depot of DOC in the tissues of the pouch exerted its antiphlogistic effect locally but was ineffective in producing thymolysis as a glucocorticoid would do. It would be of interest to identify such a metabolic compound.

It is noteworthy that in our 4-day test, cortisol is only 4 to 5 times more active than DOC (Robert & Nezamis, 1957). Therefore the local antiphlogistic action of DOC is far from being negligible. Baker (1954) reported an inhibition of connective tissue formation around a pellet of DOC implanted intraorbitally; similarly there was skin atrophy and inhibition of hair growth when a suspension of DOC was applied onto the skin (Baker, 1951). Jasmin (1955) also observed hair loss and atrophy of the skin covering a DCA pellet implanted subcutaneously. These effects on connective tissue are reminiscent of the antiphlogistic activity we report here.

It is difficult to reconcile our data with those obtained by Rindani (1953, 1954 a, 1954 b), who consistently found that mineralocorticoids stimulate inflammation when administered locally in an inflamed area. We have no explanation for the disparity of results.
SUMMARY

Desoxycorticosterone has been injected into the wall of a granuloma pouch in order to study the local effect of this hormone on inflammation. It was found that this compound inhibits inflammation by the local route whereas it is known to stimulate it when injected systemically. It is suggested that this anti-phlogistic effect of desoxycorticosterone could be due to conversion of this hormone within granulation tissue into another substance endowed with anti-phlogistic properties.

REFERENCES