ON THE EFFECT OF VARIOUS STEROIDS UPON THE EXTRA-ADRENAL THYMOLYTIC ACTION OF ACTH

BY

HANS SELYE and BERNARD JACOT*)

A short time ago we noticed that, even in the absence of adrenals, ACTH increases the thymolytic action of cortisone (Selye, 1951). Furthermore, ACTH causes hypertrophy of the preputial glands of the adrenalectomized rat (Jacot & Selye, 1951). We therefore wished to explore the possibility of a synergism between other steroids (desoxycorticosterone acetate and oestradiol benzoate) and ACTH in the adrenalectomized rat.

Since in a previous experiment we had seen that the thymolysis induced by ACTH and cortisone was unusually marked in one animal which had a spontaneous abscess, we also investigated the influence of a turpentine abscess upon this thymolysis.

EXPERIMENTAL PROCEDURE

This experiment was performed on a total of 135 male piebald rats. We used nine groups of 15 rats which were respectively treated as follows; I hypertensinogen, II ACTH, III hypertensinogen and cortisone, IV ACTH and cortisone, V

*) Fellow of the Swiss Academy of Biology and Medicine.

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ACTH, cortisone and turpentine, VI hypertensinogen and desoxycorticosterone acetate (DCA), VII ACTH and DCA, VIII hypertensinogen and estradiol benzoate, IX ACTH and estradiol benzoate. Each treatment lasted four days.

Hypertensinogen was administered in order to determine the possible effect of a non-hormonal foreign protein. It was given at a daily dose level of 6 mg. in the form of 6 subcutaneous injections of 1.0 mg. in 0.1 ml. saline solution, every four hours.

ACTH (Connaught Laboratories, Toronto, Lots Nos. 4—1, 3—1) was given at the same dose level and in the same manner as the hypertensinogen. It will be recalled that in order to obtain maximal adrenocorticotrophic effects from ACTH, it is essential to give it at short intervals. For this reason the injections were made every four hours during the day and night.

Cortisone was administered in a single subcutaneous injection of 0.5 mg. per day, in the form of a microcrystalline suspension (as distributed by Merck and Co. Limited, Montreal, Canada) containing 5 mg. of cortisone acetate per ml.

Turpentine was given in the form of 0.1 ml. per day injected subcutaneously.

DCA was administered by one subcutaneous injection of 2.5 mg. per day in the form of microcrystalline suspension which we prepared from desoxycorticosterone acetate (Schering Corporation, Bloomfield, N. J.) in a concentration of 25 mg. per ml.

Oestradiol benzoate was administered in one subcutaneous injection of 100 γ per day, in the form of a solution of 2 mg. per ml. in sesame oil.

All the experimental animals were bilaterally adrenalectomized and castrated, 48 hours before the initiation of the injections. Immediately after this, they were given 1 per cent NaCl, instead of tap water, as a drinking fluid. The removal of the testes and the adrenals was necessary in order to eliminate both of the known endogenous sources of steroid hormones.
At the end of the experiment the animals were killed by exsanguination and their thymus removed for weighing and histologic study.

EXPERIMENTAL RESULTS AND CONCLUSION

The details of the experimental arrangement, the initial and final body weights as well as the thymus weight expressed in mg. and in mg. per 100 gm. of body weight (the latter with its standard error) are given in Table 1.

Table 1.
Effect of the various four-day treatments on thymus weight.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>TREATMENT</th>
<th>No. of ANIMALS</th>
<th>BODY WEIGHT IN GM.</th>
<th>THYMUS WEIGHT in mg./100 gm. body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>INITIAL</td>
<td>FINAL</td>
</tr>
<tr>
<td>I</td>
<td>Hypertensinogen</td>
<td>14</td>
<td>103</td>
<td>105</td>
</tr>
<tr>
<td>II</td>
<td>ACTH</td>
<td>13</td>
<td>101</td>
<td>91</td>
</tr>
<tr>
<td>III</td>
<td>Hypertensinogen + Cortisone</td>
<td>11</td>
<td>101</td>
<td>107</td>
</tr>
<tr>
<td>IV</td>
<td>ACTH+Cortisone</td>
<td>15</td>
<td>102</td>
<td>93</td>
</tr>
<tr>
<td>V</td>
<td>ACTH+Cortisone + Turpentine</td>
<td>14</td>
<td>103</td>
<td>92</td>
</tr>
<tr>
<td>VI</td>
<td>Hypertensinogen + DCA</td>
<td>12</td>
<td>102</td>
<td>117</td>
</tr>
<tr>
<td>VII</td>
<td>ACTH+DCA</td>
<td>12</td>
<td>104</td>
<td>109</td>
</tr>
<tr>
<td>VIII</td>
<td>Hypertensinogen + Oestradiol</td>
<td>13</td>
<td>102</td>
<td>95</td>
</tr>
<tr>
<td>IX</td>
<td>ACTH+Oestradiol benzoate</td>
<td>11</td>
<td>104</td>
<td>89</td>
</tr>
</tbody>
</table>

The slight variations in body weight not conclusive in our short-term experiment. At this dose-level, cortisone, when
given in conjunction with hypertensinogen, induced only a moderate degree of thymolysis. However, marked thymus involution was noted in the animals given ACTH and cortisone. The simultaneous administration of turpentine did not change this effect. DCA induced no thymolysis when administered with hypertensinogen or ACTH. Oestradiol benzoate administered in conjunction with ACTH produced the same involution of the thymus as when given with hypertensinogen ("P" between Groups VIII and IX is > 0.2).

Histologic study essentially confirmed the observations made by mere weighing of the thymus in that maximal thymolytic phenomena were noted in groups IV and V.

The above mentioned findings confirmed on male, adrenalectomized and castrated rats, the first observations concerning the peripheral synergism between ACTH and cortisone on the thymus, which had been made on female, adrenalectomized and ovariectomized rats (Selye, 1951).

An inflammatory reaction to turpentine did not change the thymolytic effect of combined treatment with ACTH and cortisone. Under the same conditions prevailing in this study, ACTH did not modify the action upon the thymus, of desoxycorticosterone acetate or oestradiol benzoate.

SUMMARY

Experiments on male, adrenalectomized and castrated rats, confirm that the thymolytic effect of cortisone is greatly enhanced by simultaneous treatment with ACTH.

Turpentine inflammation does not modify this effect.

ACTH has no action on the thymus in the presence of desoxycorticosterone acetate or oestradiol benzoate.

ACKNOWLEDGEMENTS

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REFERENCES