SYNERGISM BETWEEN MINERALO- AND GLUCOCORTICOIDS IN THE PRODUCTION OF THE "PHOSPHATE-STEROID-CARDIOPATHY"

By

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In the preceding paper we have already briefly described the mechanism that leads to the formation of the infarct-like cardiac changes that characterize the "phosphate-steroid-cardiopathy" (Selye, 1958). A more detailed survey of this field, with special reference to its clinical implications, has been presented elsewhere (Selye, 1957 a). Let us merely point out here that, among 34 steroids that have been tested so far, 2α-methyl-9α-chlorocortisol (Me-Cl-COL) proved to be most effective in conditioning the cardiac muscle for the production of infarct-like necroses by an excess of dietary phosphate. However, 2α-methyl-9α-fluorocortisol (Me-F-COL) and the corresponding two non-methylated steroids (9α-chlorocortisol and 9α-fluorocortisol) are likewise very effective in this respect. Among those examined, the only halogenated corticoid devoid of this activity is triamcinolone (Δ1-9α-fluoro-16-hydroxycortisol), a highly active glucocorticoid which possesses little or no mineralocorticoid potency. On the other hand, cortisol, a glucocorticoid with little mineralocorticoid activity, is at least as effectice in producing phosphate-steroid-cardiopathy as is desoxycorticosterone (DOC), although the latter is much more mineralocorticoid than the former (Selye, 1957 b; Selye et al., 1957). It is especially noteworthy that, when given in combination with NaH₂PO₄, even cortisol, the principal natural glucocorticoid of man, can produce such cardiac changes (Selye & de Salcedo, 1957; Selye et al., 1957); the same is true of the natural corticoid mixture that is secreted by the adrenals of animals treated with large amounts of ACTH (Selye et al., 1957).

In any case, all the steroid hormones that were found to be highly effective in producing the phosphate-steroid-cardiopathy are potent corticoids. However, from the experiments mentioned so far, it was not possible to ascertain whether
the cardiotoxic effect is more closely related to the mineralcorticoid or to the glucocorticoid action. The experiments just described suggested that perhaps both types of activity are important.

It is the object of this communication to report upon experiments in which triamcinolone (a pure glucocorticoid) and desoxycorticosterone (a pure mineralcorticoid), given singly, did not produce any marked degree of cardiopathy in NaH₂PO₄-sensitized rats, but combined treatment with both these steroids sufficed to induce pronounced and excessive cardiac necroses.

MATERIALS AND METHODS

One hundred-twenty female Sprague-Dawley rats, with an average initial body-weight of 95 gm. (range: 90–105 gm.), were subdivided into six equal groups and treated as indicated in Table 1.

Monobasic sodium phosphate (NaH₂PO₄·H₂O) was given at the dose of 300 mg. in 4 ml. of water, twice daily, by stomach tube. Triamcinolone (Δ¹-9α-fluoro-16-hydroxy-cortisol) at the dose of 500 μg. and DOC-Ac (11-desoxycorticosterone acetate) at the dose of 2.5 mg. were given as microcrystals, subcutaneously, in 0.2 ml. of water, once daily.

The animals were kept exclusively on»Purina Fox Chow« ad libitum, and the experiment was terminated on the 8th day by killing all surviving rats with chloroform. Immediately after autopsy, the heart and kidneys were fixed in neutral formalin for subsequent staining with hematoxylin-phloxine (to determine the general histologic structure) and with von Kossa’s silver nitrate technique (for the histochemical demonstration of calcium). The incidence (% positive) and grade (in terms of an arbitrary scale of 0 to 3) of the cardiac necroses (with standard error) are listed in the table, together with the mortality rate.

Triamcinolone tended to diminish, while DOC-Ac distinctly aggravated the nephrocalcinosis, which is normally produced by treatment with excess NaH₂PO₄. However, this incidental finding is not listed in the table, because it merely confirms previous observations concerning the effect of gluco- and mineralcorticoids upon nephrocalcinosis, and because, in this short-term experiment, the renal changes were too mild and irregular for statistical evaluation.

RESULTS

It is evident, from perusal of Table 1, that, when given alone, NaH₂PO₄ (Group I), triamcinolone (Group II) and DOC-Ac (Group III), produced no detectable cardiac changes. Even when they were given in combination with NaH₂PO₄, neither triamcinolone (Group IV) nor DOC-Ac (Group V) proved to be effective in this respect. By contrast, the rats that received NaH₂PO₄ during conditioning with both triamcinolone and DOC-Ac (Group VI) developed severe cardiac necroses in 80% of the cases.

Although a few animals treated with NaH₂PO₄ plus one of the steroids, succumbed in the course of the experiment, they exhibited no myocardial lesions:
Table 1.
Synergism Between Mineralo- and Glucocorticoids in the Production of the »Phosphate-Steroid Cardiopathy«.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Cardiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incidence</td>
</tr>
<tr>
<td>I</td>
<td>NaH₂PO₄</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Triamcinolone</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>DOC-Ac</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>Triamcinolone + NaH₂PO₄</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>DOC-Ac + NaH₂PO₄</td>
<td>0</td>
</tr>
<tr>
<td>VI</td>
<td>Triamcinolone + DOC-Ac + NaH₂PO₄</td>
<td>80</td>
</tr>
</tbody>
</table>

it is probable that their death was caused by renal insufficiency secondary to the nephrocalcinosis or to other incidental reasons. On the other hand 80 °/o of the rats given phosphate during conditioning with both steroids succumbed with obvious clinical and morphologic signs of cardiac insufficiency.

It would appear, therefore, that the concurrent action of mineralo- and glucocorticoids is particularly effective in conditioning the cardiac muscle for the necrotizing action of phosphates.

It must be kept in mind in this connection that, according to our earlier studies, certain steroids of the vitamin-D group (for example, dihydrotachysterol) also produce severe cardiac lesions, when given in combination with phosphates. However, the change so produced is a suppuring myocarditis, essentially distinct from the infarctoid cardiopathy elicited by steroid hormones under similar conditions (Selye, 1957 c; Selye & Renaud, 1958). Further experiments will be necessary to elucidate the possible relationship between the purulent myocarditis induced by vitamin-D derivatives plus phosphates and the infarctoid cardiopathy elicited by certain steroid hormones when they are given in combination with phosphates. It is evident, however, that the latter change is more readily induced by combined treatment with mineralo- and glucocorticoids than with either type of steroid alone.

SUMMARY

Experiments on rats indicate that high doses of triamcinolone (a pure glucocorticoid) or desoxycorticosterone (a pure mineralocorticoid) do not produce any marked degree of infarctoid cardiopathy in animals sensitized by the concurrent administration of an excess of NaH₂PO₄. On the other hand, combined
treatment with small doses of both these steroids suffices to produce pronounced and extensive cardiac necroses.

It is concluded that the concurrent effect of mineralo- and glucocorticoids is especially effective in conditioning the cardiac muscle for the necrotizing action of phosphate. This is particularly noteworthy because in so many other respects these two types of corticoids are antagonists.

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REFERENCES