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EFFECT OF ACTH AND CORTISONE UPON AN "ANAPHYLACTOID REACTION"

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A FEW years ago we observed that an extensive "anaphylactoid" œdema of the nose, tongue and paws can be elicited in rats by the parenteral administration of egg-white. We called the reaction "anaphylactoid" to emphasize its resemblance to true anaphylaxis, yet it is apparently not dependent upon a previous sensitizing exposure to an allergen, since rats appear to be naturally hypersensitive to egg-white, even though they have never been pretreated with it.[1]

Soon after the discovery of this reaction it was observed to be completely inhibited by an alarm-reaction elicited immediately preceding the administration of egg-white. A variety of stress-producing "alarming stimuli" (such as formaldehyde, muscular exercise, exposure to cold, etc.) were found to be effective in this respect.[1, 2, 3] It was assumed that, in all these experiments, the protective effect of the alarm-reaction was due to its ability to produce "non-specific resistance". It was noted that an individual exposed to stress becomes more resistant not only to the particular damaging agent with which the alarm-reaction was elicited, but also to entirely unrelated stimuli. Thus, for instance, an alarm-reaction produced by spinal-cord transection, forced muscular exercise or cold, was found to increase resistance against fatal effects from lung œdema (produced by toxic doses of adrenaline) or true anaphylaxis (produced by foreign proteins). Many other examples of this phenomenon have been given elsewhere.[2] Such manifestations of non-specific resistance are always accompanied by histologic signs of increased adrenocortical activity and never occur in adrenalectomized animals exposed to stress, hence, they had been tentatively ascribed to an increased production of corticoids during the alarm-reaction.[2, 4]

In the present communication we should like to report upon experiments which may help to elucidate the mechanism of this non-specific resistance, by furnishing further evidence of the important rôle played in their development by the corticoid hormones.

METHODS

The *experimental animals* used in this investigation were adult male Wistar albino or piebald rats. Before receiving the eliciting injection of egg-white, they were pretreated with various corticotrophic and corticoid preparations.

Corticotrophin (*ACTH*) was administered subcutaneously in the form of a solution containing 5 mgm. per c.c. of physiological saline. We used a highly purified preparation "Lot 60-61", supplied by Armour and Company of Chicago. This material has a biological potency of 100% Armour Standard La-I-A and contains 0.03 units of oxytocin and 0.06 units of vasopressin per mgm. It is contaminated only by negligible amounts of other known pituitary factors.

Lyophilized anterior pituitary (*LAP*) was injected subcutaneously in the form of a preparation containing 40 mgm. of lyophilized, cattle anterior pituitary powder, suspended in a 10% aqueous alcoholic solution.

Cortisone was given subcutaneously as a saline suspension of cortisone acetate microcrystals, each c.c. containing 25 mgm. The preparation was that distributed by Merck and Co. Inc., Rahway, N.J., in which suspending agents (to keep the microcrystals from settling) and 1.5% benzyl alcohol (as a preservative) are added.

Desoxycorticosterone (*DCA*) was administered subcutaneously as a microcrystal-suspension containing 50 mgm. per c.c. of corn oil, or in the form of pellets weighing 25 mgm. each, as furnished by the Schering Corporation of Bloomfield, N.J.

EXPERIMENTAL

Effect of DCA and cortisone upon the anaphylactoid reaction to egg-white.—Our first experiment was designed to examine the effect of DCA and cortisone (both in themselves and in combination with each other) on the development of the anaphylactoid response to egg-white. For this purpose we used 40 male piebald rats weighing 120 to 150 gm. All animals were bilaterally adrenalectomized on the first day of the experiment in order to eliminate any complicating endogenous corticoid formation. Then they were subdivided into four groups of ten rats each. Group I: no hormone treatment; group II: DCA; group III: DCA and cortisone; group IV: cortisone.

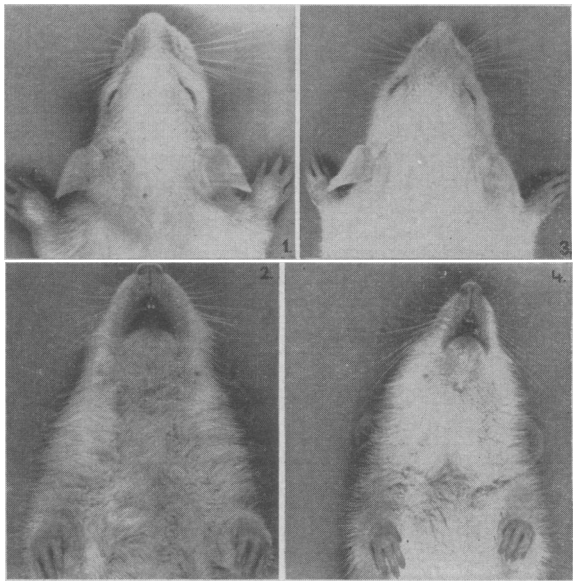
DCA was administered in the form of two 25 mgm. pellets subcutaneously on the day of adrenalectomy. Cortisone was given in two 2.5 mgm. injections daily subcutaneously.

All animals received 1% NaCl as drinking fluid in order to help their survival after adrenalectomy and also because a sodium supplement is known to aggravate DCA intoxication.

On the fourth day after adrenalectomy, 2 c.c. of egg-white was administered intraperitoneally to all animals in the four groups mentioned above. One hour after this, marked cyanotic hyperæmia and œdema developed around the face, tongue, and paws in the rats of groups I and II, that is, those receiving no hormone treatment and those given DCA. In the animals of groups III and IV which received cortisone, with and without DCA respectively, this anaphylactoid response was either absent or extremely mild.

By the third hour after the administration of egg-white, the animals given no hormone treatment had died, after having developed a condition of pronounced hypothermia and shock. All other animals survived, and those in the two groups receiving cortisone were actually in excellent clinical condition. The rats in group II (DCA) showed an even slightly more pronounced anaphylactoid reaction than those in group I, although still surviving. Those in groups III (DCA and cortisone) and IV (cortisone) still showed almost no response but the difference between the latter two groups was not sufficiently obvious to permit any definite conclusion.

Effect of ACTH upon the anaphylactoid reaction to egg-white.—Having thus learned that cortisone inhibits, while DCA tends to aggravate the anaphylactoid reaction to egg-white, we wanted to determine whether ACTH would act like cortisone, because in many other respects, these two hormones exhibit essentially similar properties. For this purpose, twelve male Wistar albino rats, weighing 120 to 180 gm., were subdivided into two groups of six animals each. Group I received no hormone treatment; in group II each animal was given 2.5 mgm., and two hours later an additional 2 mgm., of ACTH subcutaneously. One hour after this second hormone injection, all animals of both groups received 2 c.c. of egg-white intraperitoneally. Three hours later, all the control animals had developed marked anaphylactoid reactions, while only two of the ACTH treated showed a barely noticeable response (see Figs. 1 to 4).



Figs. 1 and 2.—Head and paws of an unpretreated rat injected with egg-white. Note marked œdema and hyperæmia of the paws, lips and nose. **Figs. 3 and 4.**—Corresponding photographs of a rat having received ACTH prior to treatment with egg-white. Note the absence of the anaphylactoid response.

Comparative study of the effect of LAP and ACTH upon the anaphylactoid reaction to egg-white.—In the last experiment of this series, we wanted to study the effect of our two anterior pituitary preparations under comparable experimental conditions. For this purpose, 18 male piebald rats weighing 120 to 150 gm. were subdivided into three groups of six animals

each. Group I received no hormone preparation; group II were given 40 mgm. of LAP daily, divided into five doses; group III received 10 mgm. of ACTH daily, also divided into five doses. On the 5th day of this treatment, all animals were injected intraperitoneally with 2 c.c. of egg-white. The anaphylactoid response became most rapidly obvious in group III (LAP), and a few minutes later, in the untreated controls of group I. The difference in the intensity of the response was not very marked, yet, it appeared to be definitely more pronounced in the LAP-treated than in the untreated controls. By contrast, only two animals pretreated with ACTH showed a transitory slight reaction, which had disappeared almost completely in four hours. By that time the untreated controls of group I, and especially the LAP-treated animals of group III, still exhibited very pronounced œdema of the paws and face.

DISCUSSION

The above mentioned experiments clearly indicate that both ACTH and cortisone are highly effective in inhibiting the anaphylactoid response to egg-white in rats. It is interesting in this connection that antihistaminics exert a similar inhibitory effect upon this reaction.[3, 5] The question arises whether antihistaminics could not also be used in the therapy of those clinical conditions which are known to be beneficially influenced by ACTH or cortisone (*e.g.*, rheumatic fever, rheumatoid arthritis, lupus erythematosus).

It is less obvious from the present experiments that DCA and LAP exert an effect opposite to that of cortisone or ACTH. However, a few years ago we noted that arthritic and other "rheumatic" changes tend to develop in rats chronically treated with DCA; such lesions tend to be particularly severe in animals whose suprarenals had previously been removed. These findings have recently been confirmed by others on extensive experimental material.[6] It has also been shown that Addisonian patients may develop "rheumatic-like" joint swellings under the influence of DCA overdosage[7 to 10] and Addisonians are notoriously hypersensitive to overdosage with DCA. Furthermore, several actions of mineralo-corticoids (such as DCA) are inhibited by gluco-corticoids (such as cortisone).[11] Hence, it was assumed that adrenalectomy sensitizes to the toxic effects of DCA because it removes the source of endogenous gluco-corticoids and thereby predisposes to the development of a particularly unfavourable gluco-corticoid/mineralo-corticoid balance.[2, 4]

Many other observations could be quoted in support of this assumption, but it will suffice to mention a few of them here. Chronic pretreatment with DCA tends to cause thymus hypertrophy,[12, 13] while gluco-corticoids exert an opposite effect.[4] DCA-pretreated rats respond to various alarming stimuli with hypoglycæmia instead of the usual hyperglycæmia characteristic of exposure to stress;[13a] conversely, adrenal cortical extracts (rich in gluco-corticoids) increase the hyperglycæmic response during the alarm-reaction.[14] The development of shock after extensive trauma is aggravated by DCA-pretreatment and mitigated by corticosterone (another gluco-corticoid compound[15]). Quite recently, it has been shown that even the hypertension, elicited in sensitive patients by DCA-overdosage, is abolished by an adrenal extract rich in gluco-corticoids.[16] Perhaps DCA given in toxic doses creates a condition of "partial hypocorticoidism", that is, a state in which manifestations of hypo-gluco-corticoidism, are combined with hyper-mineralo-corticoidism.[2, 17] Since DCA is a close chemical relative of cortisone, it may block the "target organs" so that the latter cannot act upon them. This "blocking" might be due to some mechanism of "competition for the substrate", such as has been demonstrated to exist between adrenaline and certain adrenaline derivatives or vitamins and their corresponding anti-vitamins.

It is especially difficult to understand why LAP, an impure anterior pituitary preparation, acts like DCA, while purified ACTH exerts cortisone-like effects. LAP contains ACTH and, under the conditions of our experiment, it produced an equally pronounced adrenal cortical enlargement; hence, we must consider the possibility that the pituitary contains additional principles which antagonize the ACTH effect or so modify it that a DCA-like action results. This may be important in the pathogenesis of what we called the "disease of adaptation". It will be recalled that under certain conditions, chronic exposure to stress (*e.g.*, infections, intoxications, cold, parenteral protein administration) causes nephrosclerosis, myocarditis, hypertension as well as arteriosclerotic and "rheumatic" changes similar to those produced by DCA or LAP.

In this connection it is interesting that the so-called "formalin-arthritis" (produced in rats by injecting a dilute formaldehyde solution into the vicinity of joints) is also slightly aggravated by pretreatment with DCA or LAP and almost completely inhibited by cortisone or ACTH. Thus here again there appears to exist an antagonistic relationship between DCA or crude anterior pituitary preparations, on the one hand, and cortisone or purified ACTH on the other.[17]

At the time of our first observations in 1944, the assumption of a pathogenetic relationship between the adrenal cortex and the allergic rheumatoid and other collagen diseases, appeared rather far fetched. However, this view received strong support from recent clinical observations showing that adrenal cortical extracts,[18] which are notoriously rich in gluco-corticoids, and especially cortisone,[19] a typical gluco-corticoid compound, produce spectacularly beneficial effects in patients with chronic rheumatoid arthritis. Purified ACTH likewise proved effective in rheumatoid arthritis, as well as in acute rheumatic fever, and allied collagen diseases such as lupus erythematosus.[19, 20]

Various points of view have been expressed concerning the probable relationship between the experimental production of rheumatic and rheumatoid changes with mineralo-corticoids or pituitary extracts on the one hand and their prevention with gluco-corticoids and ACTH on the other.[6, 21, 22] It is remarkable that the lesions particularly amenable to cortisone or ACTH treatment have empirically been found to respond well to the so-called "non-specific therapy", "fever therapy" and "shock therapy". Such drastic measures stimulate defence by eliciting a general-adaptation-syndrome and, more particularly, an increased production of ACTH and gluco-corticoids.[2, 4]

We feel in agreement with the concept of the "diseases of adaptation", first outlined in this Journal,[23] that a number of maladies (*e.g.*, rheumatic and rheumatoid conditions, allergic and anaphylactic phenomena, certain hypertensive diseases, nephrosclerosis) may largely depend upon a derangement of the pituitary-adrenocortical response to stress, a derangement in which the pattern of corticoid secretion is abnormal. The present communication presents a few additional observations illustrating the possible clinical implications of this concept upon the therapy of these "diseases of adaptation".

SUMMARY

Cortisone (a gluco-corticoid compound) and purified ACTH inhibit the anaphylactoid reaction of the rat to the parenteral administration of egg-white. Desoxycorticosterone acetate (a mineralo-corticoid compound) and a highly corticotrophic impure anterior pituitary preparation failed to inhibit, and indeed tended to aggravate this reaction.

These observations are discussed in connection with the probable participation of the adrenal-cortex in the pathogenesis of the allergic and other so-called collagen diseases.

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Genius is not a single power, but a combination of great powers. It reasons, but it is not reasoning; it judges, but it is not judgment; imagines, but it is not imagination; it feels deeply and fiercely, but it is not passion. It is neither, because it is all.—Whipple.