THE MECHANISM OF CORTISONE'S EFFECT OF HYPERTHERMIA IN RABBITS INDUCED BY 2,4-DINITROPHENOL

V. I. Pytskii

From the Laboratory of Experimental Pathology (Head – Docent M. I. Undritsov) of the State Institute for Scientific Research in Rheumatism (Dir. – Active Member AMN SSSR A. I. Nesterov)
(Presented by Active Member AMN SSSR A. I. Nesterov)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 51, No. 3, pp. 49-52, March, 1961
Original article submitted April 29, 1960

Since steroid horomones are widely used to treat collagenoses and many other diseases, detailed study of the mechanism of their effect on the organism is required. This mechanism is still inadequately understood, however, in many respects. For example, the pronounced antipyrogenic effect of cortisone (and ACTH, the adrenocorticotropic hormone) in various febrile affections is well known [14, 16, 17]. This observation is corroborated by experimental investigations demonstrating that both cortisone and ACTH reduce the fever reaction induced by various bacterial antigens [8, 10, 13, 15].

However, the mechanism of the antipyrogenic effect of these hormones is not yet clear. There are hypotheses to the effect that ACTH either directly changes the activity of the thermoregulator centers [13] or acts indirectly by liberating adrenal cortical hormones of the gluco-corticoid series [8], which is borne out by the fact of cortisone's antipyrogenic effect. The latter is either associated with inhibition of the inflammatory reaction which causes the fever or with a direct effect on the central nervous system [15].

This question, however, has not been specifically investigated.

The purpose of this work was to determine whether an inhibitory influence on the thermoregulator centers is part of the mechanism of cortisone's antipyrogenic effect.

EXPERIMENTAL METHODS

All the experiments were performed on rabbits weighing 2.2-2.8 kg each. We used 2,4-dinitrophenol (DNP) in a dose of 20 mg/kg as the pyrogenic factor. Cortisone (Adreson) was injected intramuscularly in a dose of 25 mg in 1 ml of fluid. The temperature was determined three times before the injection at half hour intervals. The average of these determinations was taken as the original level. Then the injections were administered. Some rabbits were given 1 ml of a physioligical solution free of pyrogenic ingredients, intramuscularly administered, and DNP intravenously administered; others received cortisone and DNP. In all the experiments, the temperature was determined 30, 60 and 90 min and 2, 3, 4, 5 and 6 hrs after the injections. In order to compare the temperature reactions, we determined the hyperthermic index in the plainimetric units. We used a mark PP-2k planimeter to measure the area between the temperature curve and a horizontal line drawn from the original temperature.

EXPERIMENTAL RESULTS

DNP is known to have a peripheral effect which intensifies the oxidizing processes in the tissues considerably and paralyzes the associated phosphorylation [2-5, 7]. This creates a large amount of heat in the tissues,

and the activity of the thermoregulator center is directed towards the liberation of the surplus heat from the organism [1]. Therefore, if cortisone is proposed to have an inhibitory effect on the activity of the thermoregulator centers, the administration of cortisone would increase rather than reduce the hyperthermic reaction.

The ten rabbits used in the first series of experiments were divided into two groups according to weight. The rabbits of the first group were each given 1 ml intramuscularly of a physiological solution and an intravenous injection of a DNP solution in a dose of 20 mg/kg. The hyperthermic reaction developed rapidly. Within an hour, we observed a considerable rise of temperature; the temperature was highest during the first three hours, after which it fell rapidly. The other group of rabbits received cortisone, injected in a dose of 25 mg, before the DNP injection. The hyperthermic reaction developed rapidly in these rabbits also, but it was less intense, and there was not the same sharp, peak-like rise of temperature. Table 1 shows the relative intensity of the hyperthermic reactions in the two groups of rabbits.

TABLE 1

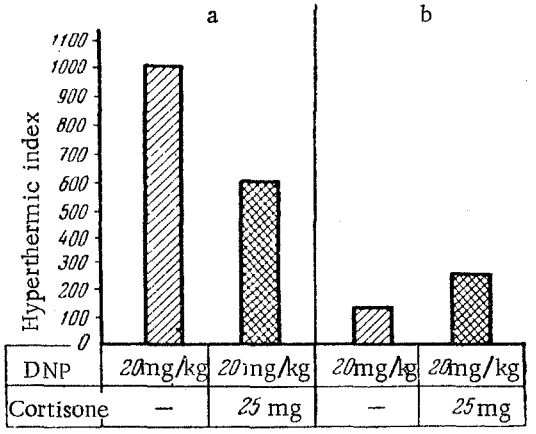
Hyperthermic Index of Rabbits Given DNP Alone and with Cortisone

DNP	Cortisone + DNP
+596	+487
+1,086	+656
+1,468	+771
+970	+745
+1,053	+295

TABLE 2

Hyperthermic Index of Thyroidectomized Rabbits Given DNP Alone and with Cortisone

DNP	Cortisone + DNP
+275	+485
+78	+295
+157	+66
+67	+223
+71	+265



Arithmetic mean intensity of hyperthermic reaction in control (a) and thyroidectomized (b) rabbits.

The figure shows the arithmetic mean intensity of hyperthermic reactions in the two groups of animals. Statistical processing proved the difference in the arithmetic means to be over 95% reliable. It was therefore established that cortisone has a restrictive influence on the development of dinitrophenol hyperthermia.

This fact would seem to contradict out hypothesis. There are literature data, however, which indicate that the effect of DNP is considerably enhanced by thyroxin [6, 9]. Cortisone inhibits the thyroid gland function and reduces the formation of endogenous thyroxin [11, 12], which could in turn decrease the intensity of DNP's effect.

In order to prove this hypothesis, we conducted a second series of experiments on ten thyroidectomized animals 6 and 12 days after the operation. Just as in the preceding series, one group of rabbits was given a physiological solution intramuscularly and then DNP intravenously, and the other group of rabbits received cortisone before the DNP. A mild hyperthermic reaction was observed in both groups. The temperature rise was not pinnacle-like, as in the healthy animals, but was somewhat slower, with considerable up and down fluctuations. However, the hyperthermic reaction was clearly more intense in the group of rabbits which had received the cortisone (Table 2).

The figure shows the arithmetic mean intensity of the hyperthermic reactions in the two groups of thyroidectomized animals. Statistical processing showed the difference in the arithmetic means to be more than 95% reliable. It is therefore clear that, under these experimental conditions, the administration of cortisone inhibited heat emission, so that the hyperthermic reaction was greater in the animals given cortisone than in the thyroidectomized animals given DNP alone.

To prove conclusively our hypothesis that cortisone inhibits the thermoregulator centers, we decided to exclude the possibility that cortisone might itself be, like thyroxin, a condition promoting intensification of DNP's effect by acting on peripheral mechanisms of some kind. For this purpose, we performed a third series of experiments on thyroidectomized animals, using the same method as in the second series except that the DNP dose was increased to 25 mg/kg. If cortisone were, like thyroxin, necessary for the development of the DNP effect, the experimental results should be similar to the picture observed in the second series. If, however, cortisone had an inhibitory effect on the thermoregulator centers, the increased thermogenesis in the tissues should have a stronger stimulating effect on the thermoregulator centers, diminishing the inhibitory effect of cortisone. In the second case, there should not be much difference between the hyperthermic reactions of the rabbits given DNP alone and those of the animals given cortisone and DNP. The actual results of the experiments showed no difference in the intensity of the hyperthermic reactions and therefore confirmed our hypothesis.

The data obtained indicate that cortisone has a direct inhibitory effect on the thermoregulator centers of rabbits with dinitrophenol hyperthermia. This effect is evident when DNP is administered in small doses. With larger doses of DNP, this effect is nullified by the stronger stimulating effect on the thermoregulator centers resulting from the intensified thermogenesis. In healthy animals, these effects are masked by partial inhibition of the thyroid gland function.

SUMMARY

The paper deals with the study of the mechanism of antipyrogenic action exerted by cortisone in dinitrophenol hyperthermia. The author proceeded from the fact that dinitrophenol hyperthermia is connected with a considerable intensification of the oxidative processes in the tissues, while the activity of the thermoregulating centers is directed towards discharge of heat from the body. If cortisone depresses the condition of these centers, hyperthermia would be more pronounced against the background of its action. However, cortison administration in a dose of 25 mg leads to the reduction of the hyperthermia intensity in rabbits in comparison with controls. Since the action of dinitrophenol is intensified by thyrotoxin, whereas cortisone reduces the production of the latter, experiments were staged on thyroidectomized rabbits. Hyperthermia was intensified in these animals by cortisone administration. Hence the antipyrogenic effect of cortisone tends to remove its depressing effect on the thermoregulating centers.

LITERATURE CITED

1. P. N. Veselkin, in: The Physiologic Mechanisms of the Fever Reaction [in Russian] (Moscow, 1957) p. 14.
2. S. M. Dubashinskaya, in: The Effect of Benzene Nitro Derivatives on the Organism [in Russian] (Khar'kov, 1935) p. 19.
3. E. K. Evzerova et al., in: The Effect of Benzene Nitro Derivatives on the Organism [in Russian] (Khar'kov, 1935), p. 86.
4. I. F. Seits, The Coordination of the Aerobic and Anaerobic Metabolisms and Respiratory Phosphorylation in the Cell [in Russian] (Doctorate's dissertation) (Leningrad, 1954).
5. A. I. Cherkes et al., in: The Effect of Benzene Nitro Derivatives on the Organism [in Russian] (Khar'kov, 1935) p. 5.
6. N. Alwall, Fiziol. Zhur. SSSR 21, 5-6, 843 (1936).
7. G. R. Cameron, New Pathways in Cellular Pathology (London, 1956).
8. W. W. Douglas and W. M. Paton, Lancet. 1, 342 (1952).
9. E. Frommel and F. Vallette, Physiol. Rev. 39, 3, 81 (1959).
10. F. G. Germuth, et al., Bull. John Hopk. Hosp. 91, 22 (1952).
11. J. D. Hardy, et al., Am. J. med. Sci. 220, 290 (1950).
12. S. R. Hill, et al., J. Clin Endocr. 10, 1375 (1950).
13. E. H. Kass and M. Finland, New Engl. J. Med. 243, 293 (1950).
14. E. H. Kass, et al., Ann. intern. Med. 33, 1081 (1950).
15. L. Recant, et al., Proc. Soc. exp. Biol. (New York, 1950) Vol. 75, p. 264.
16. J. E. Smadel, et al., Ann. intern. Med. 34, 1 (1951).
17. T. E. Woodward, et al., Ann. intern. Med. 34, 10 (1951).