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EFFECT OF ALDOSTERONE AND CORTISOL ON LEPTAZOL-INDUCED SEIZURES IN RATS

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Leptazol *B.P.* (0.2 ml./kg) produced convulsions in 65% of normal adult rats with no fatalities. The same dose of leptazol in animals which had previously been given 0.125 mg/kg aldosterone resulted in fits in 70.2% with 7.7% deaths. Cortisol pretreatment (25 mg/kg) resulted in fits in 82.9%, and 12.2% of the animals died in convulsions. The incidence of convulsions in the animals treated with aldosterone and leptazol was not significantly increased above the animals treated with leptazol. The cortisol-leptazol group did exhibit a significantly raised incidence of fits.

Although adrenal cortical steroids have been found to aggravate certain cases of epilepsy, and even induce convulsions in non-epileptic subjects (Ruzicka, 1956), reports have recently been published describing the use of these drugs in several varieties of seizures (Stamps, Gibbs, Rosenthal & Gibbs, 1959 ; Branco, 1960 ; Pauli, O'Neill, Ybanez & Livingstone, 1960 ; and Scheffner & Doose, 1961). The present communication describes experiments on rats in which the effect of aldosterone and cortisol on leptazol-induced seizures is investigated.

METHODS

Female Norwegian rats, weighing 190 to 210 g, were used.

Control groups. Intraperitoneal injections of 0.2 ml./kg of leptazol *B.P.* were given to 40 rats. Three other groups of 19, 32 and 30 rats were given 0.125 mg/kg aldosterone, 25 mg/kg cortisol (each in 0.2 ml. saline) and 0.2 ml./kg isotonic saline, respectively. The animals were observed in a quiet room, in daylight, for 3.5 hr.

Test groups. 26 rats were given 0.125 mg/kg aldosterone, and another group of 41 animals were each given 25 mg/kg of cortisol. Both drugs were administered intraperitoneally. After 1.5 hr each animal was injected with 0.2 ml./kg of leptazol *B.P.* and was observed for a further 3.5 hr.

RESULTS

No change in behaviour was observed in the animals given cortisol, aldosterone or saline only.

The results in the other groups are summarized in Table 1. Fits occurred in 65% (26/40) of the leptazol-treated animals and no deaths occurred in these. Of the remaining 14 rats in this group, two showed no abnormality of behaviour and the rest exhibited shivering, localized twitching and tachypnoea.

TABLE 1

EFFECT OF PRETREATMENT WITH 0·125 MG/KG ALDOSTERONE AND 25 MG/KG CORTISOL ON SEIZURES INDUCED BY 0·2 ML./KG LEPTAZOL *B.P.*

(Significance (*P*) calculated from χ^2 test compared with leptazol-treated animals)

Drugs administered	Number of animals	Generalized fits %	Death %
Leptazol	40	65	0
Aldosterone and leptazol	26	70·2 ($P>0·7$)	7·7 ($P<0·01$)
Cortisol and leptazol	41	82·9 ($P=0·05$)	12·2 ($P<0·01$)

70.2% (18/26) of the aldosterone-leptazol animals had fits, of which 7.7% died following continuous convulsions. Although the appearance of the fatalities was significant, the increased incidence of convulsions compared with the leptazol group was not statistically significant.

The rats treated with cortisol and leptazol showed a higher incidence of convulsions (82.9%, 34/41), and 12.2% of the group died during severe seizures. The increased occurrence of seizures, compared with the leptazol-treated animals, was statistically significant.

No animals in the aldosterone-leptazol or cortisol-leptazol groups failed to show any effect at all from the drugs, and the rats which did not have generalized convulsions exhibited localized twitching and shivering.

DISCUSSION

The mechanism by which corticotrophin and adrenal cortical steroids induce epilepsy in susceptible subjects is not known. Ruzicka (1956) studied three children with severe prolonged tonic-clonic convulsions following therapy with adrenocorticotrophic hormone. Although there was hypertension on some occasions, this was not constant. The electroencephalogram was abnormal before the fits commenced, but the serum and cerebrospinal fluid electrolytes were unchanged. However, this does not exclude an intracellular electrolyte disturbance. Woodbury (1952), for example, has demonstrated that cortisone and cortisol lower the electrospasm threshold in mice, and Woodbury & Koch (1957) have shown that adrenal cortical steroids can alter the intracellular sodium concentration and the ratio of intracellular/extracellular potassium concentration in mice.

Cerebral overhydration lowers the seizure threshold in man (Rowntree, 1926), and this is another possible consequence of steroid administration. In the rat, however, cortisol and aldosterone do not affect the water content of the brain (Seller & Spector, 1962).

A further possibility is that the aggravation of leptazol seizures produced by cortisol and aldosterone is due to a specific action on the excitability of the neurone, and is independent of changes induced in other systems of the body. A mechanism of this nature might explain electroencephalographic and personality abnormalities in hypo- and hyper-adrenal states in the absence of chemical or circulatory disturbances.

REFERENCES

BRANCO, F. G. (1960). Corticosteroid therapy in emergency states. *Rev. Bras. Med.*, **17**, 910–911.

PAULI, I., O'NEILL, R., YBANEZ, N. & LIVINGSTONE, S. (1960). Minor motor epilepsy. Treatment with corticotrophin (A.C.T.H.) and steroid therapy. *J. Amer. med. Ass.*, **174**, 1408–1412.

ROWNTREE, L. G. (1926). Effects on mammals of administration of excessive quantities of water. *J. Pharmacol. exp. Ther.*, **29**, 135.

RUZICKA, O. (1956). Krampfzustände bei Kindern unter A.C.T.H. und Cortison-Behandlung. *Z. Kinderhlk.*, **77**, 526.

SCHEFFNER, D. & DOOSE, A. (1961). On the hormonal treatment of malignant forms of petit mal. *Med. Welt.*, **37**, 1872–1876.

SELLER, M. J. & SPECTOR, R. G. (1962). Influence of cortisol, aldosterone and 2-methyl-1, 2-di-3′ pyridyl propan-1-one on cerebral water content. *J. Endocrinol.* (In press.)

STAMPS, F. W., GIBBS, E. L., ROSENTHAL, I. M. & GIBBS, F. A. (1959). Treatment of hypsarrhythmia with A.C.T.H. *J. Amer. med. Ass.*, **171**, 408.

WOODBURY, D. M. (1952). Effect of adrenocortical steroids and adrenocorticotrophic hormone on electroshock seizure threshold. *J. Pharmacol. exp. Ther.*, **105**, 27.

WOODBURY, D. M. & KOCH, A. (1957). Effects of aldosterone and desoxycorticosterone on tissue electrolytes. *Proc. Soc. exp. Biol. & Med.*, **94**, 720.