Role of Pituitary Adrenal Discharge in Antipyretic Action of Hydroxyphenyl Cinchoninic Acid (HPCA).* (19630)

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Adrenocorticotrophic hormone (ACTH), certain biologically active adrenocortico steroids and the common analgesic-antipyretic drugs possess certain similar pharmacologic actions(1), and it has been suggested that many actions of these latter agents may be mediated by pituitary adrenal discharge(2,3).

Recently, a derivative of cinchophen, 3-hydroxy-2-phenyl-cinchoninic acid (HPCA), has been shown to be a potent antipyretic and to cause pituitary adrenal stimulation(4,5). Since it has been reported that ACTH and cortisone possess antipyretic properties(6-9), it seemed of interest to know if HPCA is antipyretic by virtue of its ability to cause pituitary adrenal discharge. If HPCA reduces fever indirectly by causing adrenal hormone release, the time-course and intensity of the antipyresis observed following administration of the pituitary adrenal hormones and the antipyretic drug should be analogous, and a single dose of ACTH or cortisone might be expected to produce an immediate reduction in fever, similar to that reported for HPCA.

Methods. The effect of single doses of ACTH, cortisone and HPCA on the febrile response of dogs to purified bacterial pyrogen has been studied. The pyrogen,† a purified extract of *Pseudomonas aeruginosa,* was given intravenously in a dose of 40 μg/kg. The ACTH‡ was given intravenously in a dose equivalent to 50 mg/animal of the La-1-A standard. Cortisone acetate was given intramuscularly, 25 mg/animal. The HPCA‡ was dissolved in 2.7% Na_2CO_3 and given intravenously in a dose of 40 mg/kg. Twelve healthy adult 8-15 kg dogs were used in each experiment. On the first day 6 dogs were given the antipyretic drug 20 minutes prior to injection of pyrogen; the other 6 dogs were given pyrogen alone and served as controls. One week later the procedure was reversed and the 6 dogs previously pretreated now served as controls and vice versa. Such a cross-over technic was used in an effort to randomize the effects of tolerance that are known to occur to the febrile response to pyrogen(10). Two such experiments were performed using ACTH, and one each using cortisone and HPCA. One dog failed to receive the pyrogen in one ACTH experiment and there are only 11 dogs represented in that experiment. Rectal temperatures were determined every 45 minutes for 90 minutes prior to, and 360 minutes following injection of pyrogen. All temperatures are recorded in Fahrenheit degrees, and are increments from the mean of the prepyrogen temperature determinations.

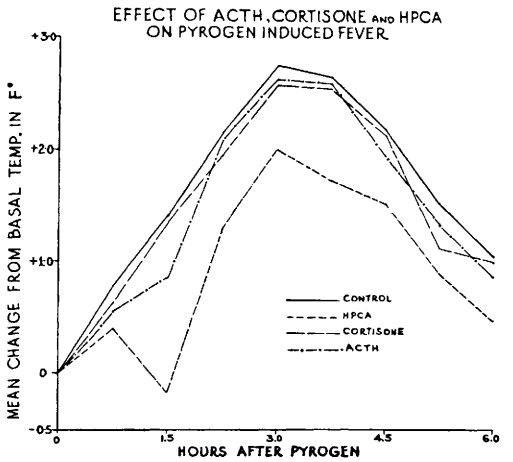

FIG. 1.

Results. Fig. 1 presents the mean febrile responses for the pooled controls, and following each of the drugs tested. As may be seen, only HPCA caused appreciable reduction in the febrile response. The mean increments during the 6-hour period, and the maximum increments have been analyzed statistically. Each dog served as its own control in each

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† Kindly supplied by Dr. L. G. Ginger of Baxter Laboratories. This preparation is marketed under the name of "Pyromen."

‡ Kindly supplied by Dr. John Litchfield, American Cyanamid Co., Stamford, Conn.

TABLE I. Effect of ACTH, Cortisone and HPCA on Pyrogen-Induced Fever.

	ACTH (23 dogs)		Cortisone (12 dogs)		HPCA (12 dogs)	
	Control	Pretreat	Control	Pretreat	Control	Pretreat
Prepyrogen temp.	101.80±.13	101.81±.15	101.83±.21	101.82±.21	101.73±.18	101.63±.17
Mean increment	2.04±.20	1.70±.16	1.67±.22	1.77±.22	1.85±.20	1.03±.14
Mean diff.	−.336±.21		+.099±.07		−.828±.21	
Significance	0		0		High	
Max increment	3.10±.18	3.85±.22	2.75±.29	2.83±.26	2.87±.24	2.02±.20
Mean diff.	−.248±.23		+.083±.15		−.842±.31	
Significance	0		0		High	

All values are in Fahrenheit degrees and are followed by their stand. errors.

experiment and paired comparisons were used to calculate the t ratios. These data are presented in Table I. It is apparent that ACTH and cortisone, in contrast to HPCA, failed to reduce either the maximum increment or the mean 6-hour increment following pyrogen. Since neither the average nor the maximum fever was affected by ACTH or cortisone, it seems unlikely that pituitary adrenal discharge caused by HPCA is an important factor in the antipyretic action of this drug.

The failure, in these experiments, of ACTH and cortisone to reduce fever prompted reexamination of the evidence presented to show that these agents are antipyretic. In most studies, in which an antipyretic action was demonstrated, ACTH or cortisone was given in multiple doses bginning about 24-36 hours before testing the animals' response to a standard pyrogen(6-8). In only one study (9) was there reported an immediate antipyretic action; graphs were presented showing a delayed and diminished pyrogen-induced fever in 3 rabbits immediately after a single injection of 2-3 units of ACTH. Defervescence also appeared to be accelerated in 4 rabbits when ACTH was given at the peak of the fever. However, clinical reports indicate that there is, in febrile patients, a time delay of about 24 hours between the inception of ACTH or cortisone therapy and the resultant antipyresis(11,12). It has been suggested, in fact, that small doses of ACTH or cortisone administered only 24 hours prior to pyrogen may result in augmentation of the febrile response(8). It appears, therefore, that ACTH or cortisone therapy must be initiated about 24 hours before the antipyretic action of these agents becomes manifest and, further, that the prompt antipyresis subsequent to the administration of HPCA is not to be attributed to intermediation of the pituitary adrenal system.

Conclusions. ACTH and cortisone, under the conditions of this experiment, were without significant effect on the febrile response of dogs to pyrogen. In contrast, hydroxyphenylcinchoninic acid produced a significant reduction in the pyrogen-induced fever. It is concluded that HPCA, and perhaps similar common antipyretic drugs, do not cause a reduction in fever by virtue of their ability to cause pituitary adrenal stimulation.

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