Effect of Pitressin on Adrenocortical Activity in Man. (22399)

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Vasopressin has been postulated to be the neurohormone responsible for enhanced ACTH release in acute stress situations (1-3). Sobel, *et al.*(4), have shown that the guinea pig excretes an increased quantity of neutral reducing lipids following parenteral administration of either posterior pituitary extract or commercial vasopressin (Pitressin). Intravenous administration of Pitressin in rats has been shown to result in ACTH discharge as evidenced by depletion of adrenal ascorbic acid(3). Using an *in vitro* method for the study of ACTH release by culture of the rat anterior pituitary gland, Guillemin and Hearn(5) have shown that incubation of the gland with Pitressin results in a significantly increased release of ACTH.

The present study was undertaken to determine the effect of an intravenous infusion of Pitressin on the release of ACTH as evidenced by increased 17-hydroxycorticosteroid production in human subjects.

Methods. Three male and 4 female normal subjects, ranging from 18 to 21 years of age, were studied. The test procedure consisted of determining free 17-hydroxycorticosteroid concentrations in plasma of blood samples drawn immediately before, and at intervals during and after, a 2-hour infusion of commercially prepared Pitressin† in normal saline. The amount of Pitressin infused ranged from 6.8 to 30.0 units. Blood samples were drawn at 60-minute intervals for 5 consecutive periods; then 2 samples were drawn at 120-minute intervals. Breakfast was served following the 2-hour infusion period. Free plasma and total urinary 17-hydroxycorticosteroid concentrations were determined by the method of Silber and Porter(6), as modified by Peterson, *et al.*(7). Blood for eosinophil counts was obtained at the beginning of infusion (8 A. M.) and 4 hours later (12 M.). Duplicate eosinophil counts were made in a Speirs-Levy eosinophil counting slide with Randolph's solution as diluting fluid. Control data were obtained with a 2-hour infusion of a similar volume of saline.

Results. Fig. 1 shows the mean changes in plasma 17-hydroxycorticosteroid concentration over the 8-hour period in which they were determined. The plasma 17-hydroxycorticosteroid levels associated with the infusion of Pitressin are significantly‡ higher than the saline control values during the first 4 hours of the test.

The possibility that ACTH contamination of the Pitressin preparation was responsible for the rise in the plasma 17-hydroxycorticosteroids was considered and two procedures were employed to ascertain whether this was the case. The first procedure consisted of inactivating the Pitressin by the method of Smith, *et al.*(8), and administering it to 2 subjects to determine whether a rise in plasma 17-hydroxycorticosteroids resulted. The second procedure consisted of calculating the amount of ACTH administered to these subjects using the figure of 0.1 milliunit of ACTH per unit of Pitressin(9). Neither of these procedures caused a significant rise in the plasma levels of 17-hydroxycorticosteroids.

The 4-hour eosinophil counts were significantly lower when Pitressin was administered than when saline alone was infused. The 12-hour urinary excretion of 17-hydroxycorticosteroids on the Pitressin test day averaged 34% higher than on the saline test day. This difference, however, is not significant ($P < 0.1$).

Blood pressure and pulse data are shown graphically in Fig. 2. No significant changes in blood pressure were associated with administration of Pitressin. Pulse rate was de-

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† Parke, Davis & Co., lot nos. R66F and L909E.

‡ The term "significant" is used to indicate statistical significance at 1% level of confidence as determined by the t-test of Fisher.

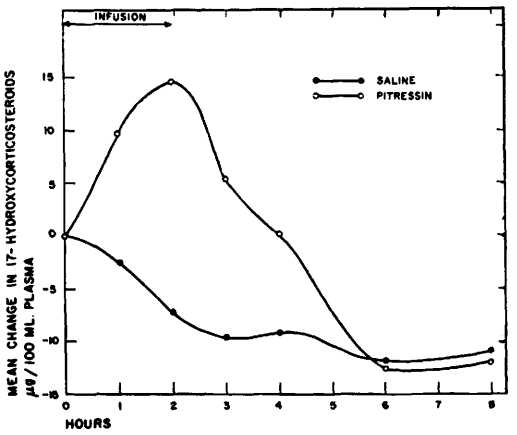

FIG. 1. Effect of Pitressin on plasma 17-hydroxycorticosteroid concentration. Individual points represent mean values for group of 7 young, normal subjects receiving between 6.8 and 30 units of Pitressin in a 2-hr intravenous infusion.

creased significantly during the second hour of Pitressin infusion.

Discomfort in the form of anorexia, moderate nausea, abdominal cramping sensations, and defecatory urges were noted frequently. Three of the 4 female subjects noted uterine cramping. Vomiting did not occur in any patient. No attempt was made to quantify the discomfort. Marked facial pallor, coldness of the hands, and diminution of the radial artery pulsations, frequently to the point of imperceptibility, were noted. In spite of this remarkable diminution in peripheral pulsation, no significant changes in the auscultatory blood pressures were noted.

Comments. The fact that intravenous administration of Pitressin is associated with a marked rise in plasma 17-hydroxycorticosteroid concentration is consistent with the suggestion that vasopressin is the neurohormone involved in ACTH stimulation in acute stress situations. However, the mechanism by which this stimulation is effected is not apparent. As was noted, administration of Pitressin caused the subjects considerable discomfort which could result in a release of ACTH. In this regard, it is of interest to note that addition of Pitressin to the nutrient fluid of rat anterior pituitary glands maintained in organ culture caused a release of ACTH, indicating that such a release is possible by direct action of Pitressin on the anterior pituitary gland(5).

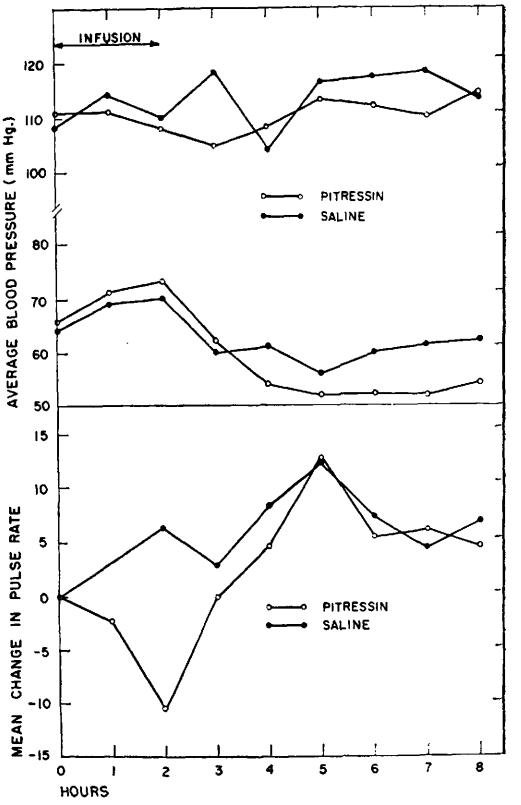

FIG. 2. Effect of Pitressin on pulse rate and blood pressure. Individual points represent mean values for group of 7 young, normal subjects receiving between 6.8 and 30 units of Pitressin in a 2-hr intravenous infusion.

Summary. Intravenous administration of Pitressin causes a significant increase in plasma 17-hydroxycorticosteroid concentration in human subjects.

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Effect of Oxytocin on Adrenocortical Activity in Man. (22400)

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In evaluation of the effect of hypothalamic neurohormones on ACTH release in man, it has been shown that intravenous administration of commercial vasopressin (Pitressin) causes a significant rise in plasma 17-hydroxycorticosteroid concentration(1). In view of the fact that both oxytocin and vasopressin are present in the hypothalamus as well as in the posterior pituitary gland(2-5), we have extended our initial observation to evaluate the effect of the intravenous administration of oxytocin on the plasma 17-hydroxycorticosteroid concentrations. In the present study, both commercial oxytocin (Pitocin)† and a highly purified preparation of oxytocin‡ have been employed.

Methods. Four male and 4 female, normal subjects, ranging from 18 to 21 years of age, were studied. The general procedure and laboratory analyses have been previously described(1). Saline was the control infusion for the Pitocin study and saline plus oxytocin diluent was the control infusion for the oxytocin study. All infusions were given from 8 A. M. to 10 A. M.

Results. Effect of Pitocin. Fig. 1 shows the mean change in the plasma 17-hydroxycorticosteroid concentration associated with the infusions of Pitocin and the control solution. There is no significant difference between the 2 curves. Pitocin was without effect on the 12-hour urinary excretion of 17-hydroxycorticosteroids and on the number of circulating eosinophils. Pulse and blood pressure recorded hourly for the 8-hour period showed no difference between the days of Pitocin and saline infusions.

Effect of Highly Purified Oxytocin. Since Pitocin has only 50-70% of the purity of du Vigneaud's highly purified oxytocin(6), it was deemed necessary to test the latter preparation. Four individuals were infused with 9 units of highly purified oxytocin in saline on one day and with a comparable volume of the control solution on another day. No significant difference between plasma 17-hydroxycorticosteroid levels during the 2 tests was noted (Fig. 2).

In another series of observations, 6 subjects were infused with an increased amount

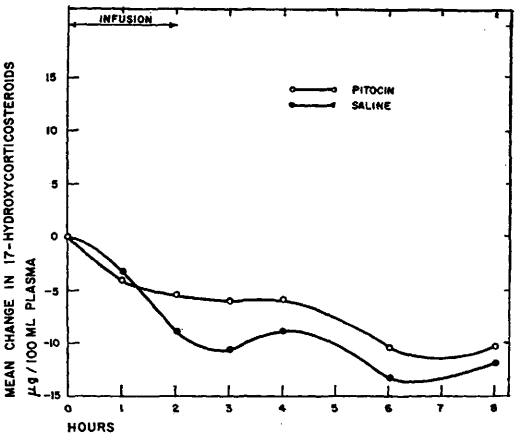

FIG. 1. Effect of Pitocin on plasma 17-hydroxycorticosteroid concentration. Individual points represent mean values for group of 7 young, normal subjects receiving between 22.6 and 34.6 units of Pitocin in a 2-hr intravenous infusion.

* NIH, Public Health Service, U. S. Dept. of Health, Education, and Welfare.

† Parke, Davis & Co., lot nos. S-1970 and M-307M.

‡ Dr. Vincent du Vigneaud, Cornell University Medical College, kindly supplied us with this preparation of oxytocin.