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Inactivation of Antidiuretic Hormone by Blood Serum of the Pregnant Woman.* (20490)

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It is assumed that the secretion of minimum amounts of antidiuretic hormone (vasopressin) by the hypophysis is sufficient to insure a normal reabsorption of water by the kidney. This amount corresponds to 1 to 5 mU per hour in the dog(1-3) and a similar amount in man(4,5). Furthermore, blood plasma and tissues contain enzymes that inactivate vasopressin and oxytocin(6-10). The oxytocin-inactivating ability increases considerably in the blood serum during pregnancy (11). An increase of 1000 times was observed by Page(12) from the time of conception to the ninth month of pregnancy. Similar observations were recorded by Croxatto(13) for the pressor effects of vasopressin.

No systematic study of the inactivation of the antidiuretic properties of vasopressin in pregnancy has been undertaken. Aside from the physiological importance of such study, it is of interest because of the difference in stability of the antidiuretic and pressor effects of vasopressin *in vitro*. The antidiuretic activity appears to be more resistant to changes in pH (Heller(14)). Ralli(15) using sodium thioglycollate, and Almeyda(16) and Croxatto(17) with thiosorbitol have shown that the pressor activity disappears completely or almost completely, whereas the antidiuretic activity is not affected. The present communication deals with the determination of the ability of blood serum from non-pregnant, pregnant and postpartum women to inactivate the antidiuretic effects of vasopressin.

Methods. Recently obtained blood serum, kept at a temperature of −5° was used throughout. A vasopressin preparation† containing 10 U per ml was added to the serum and the conveniently diluted mixture adjusted to pH 7.3 and incubated at 37°. The time of incubation varied from 30 to 300 minutes for the serum of pregnant women and from 1 to 24 hours for the non-pregnant. At the end of incubation, 1 ml of the solution per 100 g of body weight was injected intraperitoneally into 4 hyperhydrated rats following the technique of Burn(18). The inactivation of the antidiuretic hormone by the serum was measured by the effect on diuresis of the incubated material. Controls were run on the hormonal preparation and the sera *per se*. With injections of 0.1 to 0.2 ml of serum per 100 g body weight of the rat, the effect on diuresis was negligible and could be disregarded. A higher dose of serum produced antidiuretic effects (Croxatto and coworkers) (19,20). The same solutions assayed in rats were tested on the blood pressure of anesthetized cats, by injection into the femoral vein in small doses and at relatively long intervals, to determine whether or not the loss of pressor activity of the substrate paralleled the loss of antidiuretic activity.

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The "antidiuretasic activity" of the sera of pregnant women at half and full term was determined by measuring the time required for the destruction of 50% of the antidiuretic potency of the added hormone. The "antidiuretasic units" were calculated applying the same formula $\left(\frac{0.693}{t} \times 100 \times \text{dilution of the serum}\right)$ proposed by Page(21) for the calculation of the "oxytocinasic units". The time (t) is that required for the destruction of 50% of the substrate and was determined by injecting, after different intervals of incubation, a mixture of serum and vasopressin into properly prepared rats.

The results obtained with blood sera of 50 pregnant women indicate that in the course of pregnancy there is a progressive increase in the enzymatic activity responsible for the destruction of the antidiuretic properties of vasopressin (Fig. 1). In the last week of pregnancy 0.1 ml of blood serum destroys 300

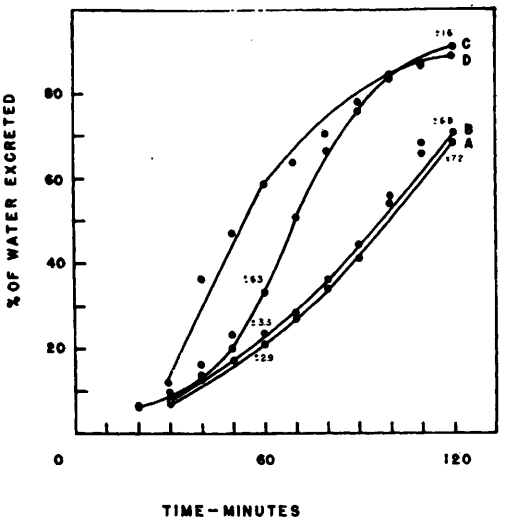

FIG. 1. Average percentages of urine volume excreted by 4 groups of 36 rats each, as related to amount of water administered by stomach tube (5% of body wt, Burn test) (18). Injected (intrap. per 100 g body wt) at: A. 1 ml of vasopressin solution containing 62.5 mU. B. 1 ml of vasopressin solution (62.5 mU) after 240 min. incubation with 0.01 ml of blood serum of non-pregnant woman. C. 1 ml of vasopressin solution (62.5 mU) after 240 min. incubation with 0.01 ml of blood serum from 9th month of pregnancy. D. 1 ml of 0.9% NaCl. Figures on the curves indicate stand. dev. of the averages (D.S.) at 60 and 120 min.

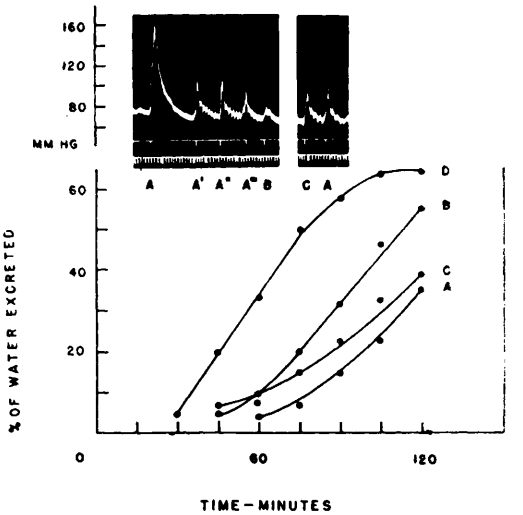

FIG. 2. Percentage of urine volume excreted by 4 groups, each of 4 rats, as related to amount of water administered by stomach tube (Burn test) (18). Intraperitoneal injection per 100 g of body wt at: A. 1 ml of vasopressin solution containing 62.5 mU. B. 1 ml of vasopressin solution (62.5 mU) after 60 min. incubation with 0.01 ml of blood serum (9th month of pregnancy). C. 1 ml same as B, incubated with 0.1 ml of blood serum of non-pregnant woman. D. 1 ml 0.9% NaCl. Upper part of the figure represents the variations of arterial pressure registered at the carotid of a cat under "Dial" anesthesia. Injected in the femoral vein with: A. 1 ml of vasopressin solution containing 125 mU. A.' 1 ml of vasopressin solution containing 90 mU; A." 1 ml of vasopressin solution containing 60 mU; A."' 1 ml of vasopressin solution containing 30 mU. B. 125 mU of vasopressin after 60 min. incubation with 0.02 ml of blood serum (9th month of pregnancy). C. 125 mU of vasopressin after 60 min. incubation with 0.02 ml of blood serum of non-pregnant woman.

to 350 mU of vasopressin in the course of 40 to 50 minutes, whereas the same amount of blood serum of a nonpregnant woman inactivates only 30 to 35 mU in 960 minutes.

The blood serum of women at half term showed from 16 to 20 U and that of women at term (9th month) 150 to 170 U of "antidiuretasic activity", calculated with the formula of Page. These values are similar to the ones obtained by Page, 15 U and 100 U respectively, for the "oxytocinasic activity".

The "antidiuretasic activity" rapidly decreases in the post-partum period and reaches the values preceding pregnancy 5 or 6 days after delivery.

The pressor activity, as determined by measuring arterial pressure in cats, (Fig. 2)

is destroyed by blood sera at the same rate as the antidiuretic activity.

These observations lead to the assumption that the same enzyme is involved in the inactivation of both hormones, oxytocin and vasopressin. The large and progressive increase in the capacity to inactivate the antidiuretic property of the hormone during pregnancy, poses the question of why, as pregnancy progresses, there is no development of diabetes insipidus. This could be due to a large increase in the production of hormone by the hypophysis, thus compensating for the greater inactivating capacity of the blood serum or to the gradual development of another compensatory mechanism, as yet unknown, that would make unnecessary the action of the hormone. It is also possible that the fetus or the placenta produce large amounts of antidiuretic substances. The increase in "antidiuretasic activity" would be a regulatory mechanism to eliminate the excessive antidiuretic activity.

A more active autolysis of plasma proteins during pregnancy, would explain the larger liberation of antidiuretic substances similar to the hormone. It is known that hydrolysis of hypertensinogen and other proteins of plasma with pepsin produces considerable amounts of antidiuretic and oxytocic substances (Croxatto and coworkers(22)).

Summary. The "antidiuretasic activity" (activity responsible for the destruction of the antidiuretic properties of vasopressin) of the blood sera increases progressively in the course of pregnancy. In the last week of pregnancy 0.1 ml of blood serum destroys 300 to 350 mU of vasopressin in 40 to 50 minutes, whereas in the nonpregnant woman it inactivates only 30 to 35 mU in 960 minutes. The "antidiuretasic activity" rapidly decreases in the post-partum period and reaches the values preceding pregnancy after 5 or 6 days of delivery.

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