INTERACTION BETWEEN OXYTOCIN AND ANTIDIURETIC HORMONE AND ITS EFFECT ON THE MILK SECRETION BY ALVEOLI OF THE MAMMARY GLAND OF LACTATING RATS

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UDC 612.664-06:612.434.018

Interaction between exogenous and endogenous oxytocin and vasopressin was found to affect the mechanism of milk ejection by the alveoli of the mammary gland in lactating rats. Inhibition and stimulation of the effect of oxytocin on milk ejection by vasopressin was demonstrated. On the basis of the principles observed the concentrations of these hormones were investigated in the plasma of dogs deprived of water for 3 days and then allowed to drink.

KEY WORDS: oxytocin; vasopressin; hormone interaction; milk secretion.

The combined action of oxytocin and antidiuretic hormone (ADH) in their lactogenic effect has not yet been adequately studied. Evidence for their interaction exists. For instance, the suckling of young animals is accompanied by antidiuresis [9]. The increase in the reabsorption of water in the kidneys under the influence of ADH creates favorable conditions for the elimination of water by another channel – with the milk [6, 8, 9]. It might even be admitted that ADH itself, secreted during the period of lactation, induces both antidiuresis and the secretion of milk, more especially because during this period a response is observed chiefly in the cells of the supraoptic and not the paraventricular nucleus [1]. However, physiological doses of ADH without oxytocin are themselves hardly sufficient to induce milk ejection [6]. Interaction must evidently take place between these hormones both at the level of the mechanisms of their liberation and at the level of the target organ.

The object of this investigation was to study interaction between oxytocin and ADH at the level of the alveoli of the mammary gland.

EXPERIMENTAL METHOD

Part of the mammary gland of a lactating rat, removed under pentobarbital anesthesia, was cut into pieces measuring about 1 mm^3 in Tyrode solution. A series of standard solutions of oxytocin (Gedeon Richter, Hungary) and of 8-lysine-vasopressin (Sandoz, Switzerland), corresponding to 49 combinations of their different concentrations in the range from 0 to 10^{-2} i.u./ml, was made up. The time between placing the piece of tissue in the test medium and the ejection of milk (observed under the microscope) was measured with a stopwatch. Statistical analysis of the results was carried out by the two-factor dispersion method [4, 5], enabling not only the significance of the effect of each separate factor but also their interaction to be estimated.

EXPERIMENTAL RESULTS AND DISCUSSION

The mean logarithms of the reaction time of the pieces of mammary gland of the lactating rats to different combinations of hormones are given in Table 1. With each combination the mean was determined

Department of Normal Physiology and Course in Biophysics, Daghestan Medical Institute, Makhachkala. (Presented by Academician of the Academy of Medical Sciences of the USSR N. K. Bogolepov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 78, No. 7, pp. 12-14, July, 1974. Original article submitted April 18, 1973.

TABLE 1. Combined Effect of Oxytocin and Vasopressin on Reaction of Pieces of Mammary Gland of Lactating Rats

Vasopressin (in i.u./ml)	Oxytocin (in i.u./ml)						
	10^{-2}	10^{-4}	10^{-6}	10^{-8}	10^{-10}	10^{-12}	0
10^{-2}	0,84	0,98	1,10	1,11	1,09	0,89	0,92
10^{-4}	1,05	1,15	1,16	1,26	1,29	1,10	1,15
10^{-6}	1,05	1,19	1,24	1,37	1,40	1,19	1,19
10^{-8}	1,00	1,16	1,31	1,46	1,41	1,25	1,22
10^{-10}	0,97	1,08	1,32	1,30	1,28	1,17	1,26
10^{-12}	0,87	1,00	1,09	1,17	1,24	1,20	1,30
0	0,65	0,95	1,15	1,36	1,45	1,52	—

TABLE 2. Effect of Factors of Time and Dilution of Plasma (taken after drinking at the end of 3 days' deprivation of water) from Dogs on Reaction of Pieces of Rat Mammary Gland

Time (in min)	Undiluted plasma	Diluted plasma	
		$1:10^2$	$1:10^4$
25	0,91 (0,98) (10^{-4}, 10^{-2})	1,16 (1,16) (10^{-6}, 10^{-4})	1,34 (1,37) (10^{-8}, 10^{-6})
60	1,19 (1,19) (10^{-4}, 10^{-6})	1,28 (1,31) (10^{-6}, 10^{-8})	1,32 (1,30) (10^{-8}, 10^{-10})
100	1,04 (1,08) (10^{-4}, 10^{-10}	1,02 (1,09) (10^{-6}, 10^{-12})	1,12 (1,17) (10^{-8}, 10^{-12})

Note. Explanation of table in text.

for a sample consisting of 16 pieces taken from five rats. The mean weighted dispersion of the random factor was assessed as 0.0489, with 785 degrees of freedom. The two-factor dispersion analysis of these data gave the following results. Both hormones had a significant ($P < 0.01$) effect on the milk output. The dependence of the reaction time on the dose of the hormones was less marked for vasopressin than for oxytocin. Meanwhile interaction took place ($P < 0.05$) between the hormones; i.e., extremal sensitivity of the pieces was observed only with definite combinations of concentrations of oxytocin and vasopressin.

On the basis of these results three regions of interaction between the hormones can be distinguished: 1) a region of high oxytocin concentrations (10^{-2}, 10^{-4} i.u./ml). All doses of vasopressin had an inhibitory action against oxytocin; 2) a region of low oxytocin concentrations (10^{-10}, 10^{-12} i.u./ml). All doses of vasopressin had an accelerating action; 3) a region of mean oxytocin concentrations (10^{-2}, 10^{-8} i.u./ml). Large ($10^{-2}-10^{-4}$ i.u./ml) and small 10^{-10}, 10^{-12} i.u./ml) doses of vasopressin (except the combination of 10^{-6} i.u./ml oxytocin and 10^{-10} i.u./ml vasopressin) had a stimulant action, but average doses (10^{-6}, 10^{-8} i.u./ml) an inhibitory action against the effect of oxytocin.

The interaction thus revealed between oxytocin and vasopressin applied strictly speaking to exogenous hormones, and there is no guarantee that it also occurred between endogenous hormones. To analyze the effects of interaction of endogenous oxytocin and ADH the plasma of four dogs taken after drinking at the end of 3 days deprivation of water was investigated. In this case the plasma has both oxytocin and antidiuretic activity [2, 3]. With the course of time inactivation of the hormones takes place in the plasma and, according to some workers [7, 10], ADH in this case is destroyed more rapidly than oxytocin. With this in mind samples of plasma and two dilutions of it ($1:10^2$ and $1:10^4$) were tested at different times after taking. By carrying out the experiment in this way unknown levels of endogenous oxytocin and ADH could be combined.

The mean values of the logarithm of the action time, determined for a sample of 12 pieces, are given in Table 2. The mean weighted dispersion of the random factor was estimated as 0.0427 with 89 degrees of freedom. It is interesting to note that in this case only the interaction between the time and dilution factors, i.e., the effect of interaction between the endogenous hormones, was significant ($P < 0.05$).

Comparison of the data in Tables 2 and 1 shows that those in Table 2 correspond to the mean values of the logarithm of the reaction time obtained on incubating pieces of the gland with fixed levels of exogenous oxytocin of 10^{-4}, 10^{-6}, and 10^{-8} i.u./ml, if a combination of 10^{-4} i.u./ml oxytocin and 10^{-2} i.u./ml vasopressin was taken as the starting point (for the subsequent dilutions these values must be reduced by 10^2 and 10^4 times, respectively).

If the hypothesis of the more rapid destruction of ADH than of oxytocin in the plasma is correct, with the course of time the reaction velocities ought to pass through values found in the same columns of Table 1 below the accepted initial values. The mean values of the logarithm of the reaction time taken from Table 1 and corresponding to the hypothetical combinations of oxytocin and ADH levels and these combinations themselves are given in Table 2 in parentheses. The figures on the left in the lower parentheses give the oxytocin concentration, those on the right the ADH concentration in i.u./ml. Comparison of the mean logarithms of the reaction time corresponding to endogenous and exogenous hormones, with Student's criterion, showed no significant ($P > 0.2$) differences between them, so that the oxytocin activity of the plasma of this group of dogs could be estimated as 10^{-4} i.u./ml and its antidiuretic activity as 10^{-2} i.u./ml.

The effect of interaction between exogenous oxytocin and vasopressin revealed by these experiments is thus valid also for physiological doses of endogenous hormones.

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