EFFECT OF CONTINUOUS VASOPRESSIN INFUSION ON CIRCADIAN RHYTHMS OF FOOD AND WATER INTAKE, DIURESIS, AND ELECTROLYTE EXCRETION IN BRATTLEBORO RATS

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The suprachiasmal nuclei (SChN) are the most important component in the circadian regulatory system of mammals [9]. Neurons containing vasopressin are found in SChN of rats [16]. This neuron population is the origin of a widespread vasopressinergic innervation of the brain, which may play the role of efferent component in the regulation of circadian rhythms.

Brattleboro rats are characterized by a genetically determined vasopressin deficiency in the hypothalamo-hypophyseal system, which includes SChN [11, 15]. The possible rhythm-regulating role of the vasopressin-containing neurons of SChN and of efferent vasopressinergic pathways ought to be expressed by the absence of circadian rhythms in these animals. However, it has been shown that circadian rhythms of locomotor activity [5, 11], of food [14] and water intake [7, 12, 14], and the N-acetyltransferase level in the pineal gland [11], are preserved in Brattleboro rats despite the presence of internal desynchronization [14].

The aim of this investigation was to study circadian rhythms in Brattleboro rats during continuous vasopressin infusion, i.e., in the absence of any fluctuations of its blood level.

EXPERIMENTAL METHOD

Male Brattleboro rats weighing 305 ± 13 g were kept in individual metabolism cages [13] under constant conditions: temperature 23.5 ± 1.5°C, humidity 60 ± 10%, 12 h of daylight (8 a.m.-8 p.m.): 12 h of darkness (8 p.m.-8 a.m.), with free access to water and a standard diet. After adaptation for 14 days to the experimental conditions, the rats were anesthetized with pentobarbital (Nembutal, Abbot, 50 mg/kg, intraperitoneally) and intracardiac silicone catheters were implanted [10]. One week after the operation, the rats were given the continuous infusion of physiological saline (0.5 ml/h) for 2 days and of vasopressin solution (VP; Diapid, Sandoz, 1.0 IU daily), at the rate of 0.5 ml/h for 3 days. Food (FI) and water intake (WI), and excretion of urine (EU), sodium, and potassium were investigated during these 5 days at 4-hourly intervals. FI was determined gravimetrically and WI and EU by a volumetric method. Sodium and potassium concentrations were measured on a "Corning 902" ion-selective analyzer and "Flapho 4" flame photometer. The results were subjected to statistical analysis by the individual and group-averaged cosinor method [1] and by Student's t test.

EXPERIMENTAL RESULTS

During infusion of physiological saline the rats consumed 21.06 ± 1.15 g of food ($M \pm m$) and 183.2 ± 6.5 ml of water daily and excreted 156.1 ± 6.1 ml of urine, 2136 ± 448 μmoles of sodium, and 3216 ± 376 μmoles of potassium. These figures agree with results observed in normal intact Brattleboro rats [7, 8, 12, 15]. During the last 2 days of VP infusion (the results of the first, transitional, day were not subjected to statistical analysis) the rats consumed the same quantity of food — 20.64 ± 0.96 g, and drank much less water — 34.92 ± 4.16 ml ($p < 0.00001$). EU also was reduced — 29.10 ± 3.62 ml ($p < 0.00001$), sodium excretion was

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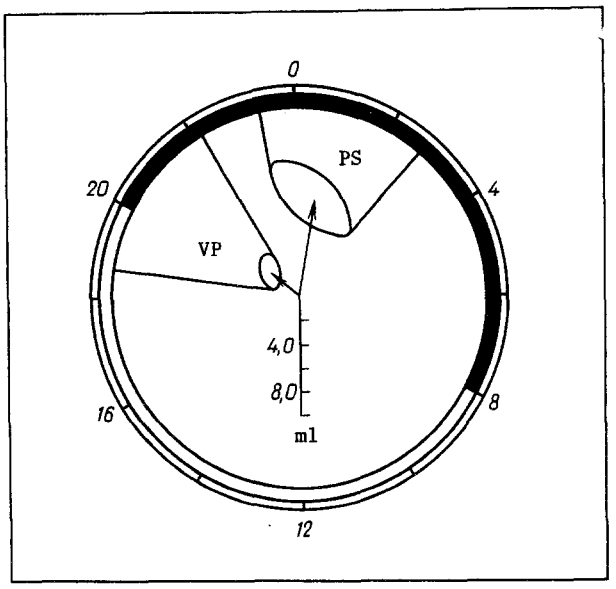

Fig. 1. Group-averaged cosinor diagram of circadian rhythms of WI in Brattleboro rats (n = 7) during infusion of physiological saline (PS) and VP.

TABLE 1

Parameters	Mesor	Amplitude	A/M, %	Acrophase	$p \leq$
Food intake, g/4 h	PS 3,51	1,44	41	—332,2°	0,001
	VP 3,44	1,36	40	—314,3°	0,0001
Urine excretion, ml/4 h	PS 26,01	6,91	27	—25,1°	0,0001
	VP 4,85*	1,08*	22	—16,0°	0,044
Sodium excretion, μmoles/4 h	PS 356	222	62	—356,0°	0,009
	VP 550	103	19	—	0,12
Potassium excretion, μmoles/4 h	PS 536	168	31	—1,2°	0,049
	VP 646	199	31	—1,6°	0,047

Legend. Group-averaged parameters of circadian rhythms of FI, EU, and electrolyte excretion in Brattleboro rats (n = 7) during infusion of physiological saline (PS) or VP. *$p < 0.05$ or below compared with infusion of PS.

increased — 3300 ± 218 μmoles ($p < 0.05$), but potassium excretion was not significantly changed at 3876 ± 339 μmoles. These results are in agreement with data in the literature on the effect of long-term vasopressin administration on these functions in Brattleboro rats [3, 8, 12].

During infusion of physiological saline all the parameters studied showed marked circadian fluctuations with the acrophase during the period of darkness, although they were somewhat reduced in amplitude, as is observed in intact rats of the same strain under normal conditions [14] (Fig. 1; Table 1). The order of the acrophases was as follows: first the acrophase of the FI rhythm, next the acrophases of rhythms of electrolyte excretion, WI, and EU. During infusion of VP the circadian rhythms of FI, EU, and potassium excretion did not exhibit any significant phase changes (Table 1), whereas a considerable phase shift (3.5 h) of the circadian rhythm of WI was observed ($p < 0.01$; Fig. 1). The grouped circadian rhythm of sodium excretion virtually disappeared due to the irregular phase shifts in different animals (according to the data of individual cosinor analysis; Table 1).

The results show that the absence of circadian fluctuations in the plasma VP level has no significant effect on the circadian rhythm of water excretion. Considering that the rhythm of EU also is maintained in the complete absence of VP [14], it can be concluded that VP does not participate in the generation of the circadian rhythm of water excretion in rats. Another possibility is that circadian fluctuations may be present in the effect of exogenous VP during the 24-h period [4], and these could give rise to circadian fluctuations in EU. This is unlikely, however, for continuous infusion even of supramaximal doses of VP has no effect on the normal circadian rhythm of VP [2].

The absence of any effect of continuous VP infusion on the total daily FI and its circadian rhythm is in complete agreement with results obtained on Wistar rats [2]. The same effect also is seen on potassium secretion, and can be explained by interdependence between rhythms of FI and potassium excretion [6].

The most important result of the investigation is the phase shift of the WI rhythm and disappearance of the group rhythm of sodium excretion because of irregular individual phase shifts. This suggests that VP participates in the mechanism of synchronization of the circadian rhythms of these parameters in rats. Desynchronization observed in the absence of endogenous VP secretion [14] confirms this hypothesis.

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