Brain Research, 97 (1975) 362–366

Inferior quality of RSA during paradoxical sleep in rats with hereditary diabetes insipidus

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(Accepted June 1st, 1975)

Vasopressin and vasopressin analogues are involved in memory consolidation. Posterior lobectomized rats[15] and rats with hereditary[12] diabetes insipidus (DI) have severe disturbances in maintaining conditioned avoidance behavior. Memory impairment of hereditary DI rats can be readily shown in a one-trial learning situation[17]. Vasopressin and vasopressin analogues normalize behavioral deficits in posterior lobectomized and hereditary DI rats[15,17]. A number of behavioral and electrophysiological studies have indicated that paradoxical sleep (PS) and hippocampal theta activity, termed rhythmic slow activity (RSA), are related to memory consolidation processes. Post-trial PS deprivation interfered with response retention in mice and rats [2,4,8]. Humans deprived of PS showed inferior scores in verbal retention[1]. In addition, an increase in the amount of post-trial theta activity was reported in rats with superior retention of conditioned avoidance response[7]. This activity, which reflects an activation along midbrain limbic pathways[3,6], accompanies the initiation of movements[5,13] and dominates the hippocampus in stage of PS[11].

If the RSA during PS is a correlate of the functional state of midbrain limbic structures which is essential for consolidation processes, and if these are controlled by vasopressin or vasopressin analogues, one might expect differences in either quality and/or quantity of RSA during PS in vasopressin deprived animals. The present study reports experiments on qualitative aspects of the RSA during PS in Brattleboro strain rats with hereditary hypothalamic diabetes insipidus.

Two homozygous (HO-DI) and heterozygous (HE-DI) male rats weighing between 250 and 300 g were implanted with chronic electrodes in the dorsal hippocampus and the neck muscles to record RSA and the electromygram respectively. Two weeks after surgery, 5 habituation sessions were given to each animal in a sound attenuating experimental cage followed by 10 experimental sessions of 3 h duration per animal. During 4 of these sessions each rat received placebo only (0.5 ml of saline solution) and in the remaining sessions desglycinamide-8-arginine vasopressin (DG-AVP) was given (1 and 2 μg/100 body weight) subcutaneously. The RSA was recorded during PS. The total time of PS of the individual animals under the respective treatments was divided into 100-sec analysis epochs. The averaged power spectrum per

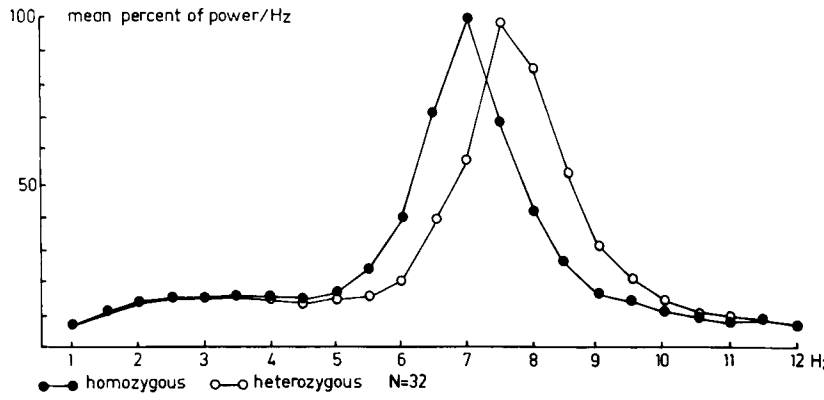

Fig. 1. Differences in hippocampal RSA between heterozygous and homozygous, hereditary diabetes insipidus rats during paradoxical sleep.

epoch was computed and stored on paper tape. In addition, subsequent parameters were computed and stored to characterize each spectrum: the 'peak frequency', and the 'mean frequency' and the 'spectrum width' at the level of half peak amplitude with corresponding frequencies. In the final analysis the mean of the averaged spectra was calculated according to animal or treatment and transformed to the percentage of power/Hz. To illustrate the global difference in spectra of RSA of HO-DI and HE-DI rats, the data in both groups were pooled and expressed as the mean percentage of power/Hz. The spectral parameters were similarly pooled with respect to treatment or animals and their means were compared using the Student's *t*-test. The localization of the recording electrodes was histologically verified at the end of the experiments.

As shown on Fig. 1 the major difference in frequency content of the RSA during PS is confined to the band of 5.5–10.0 Hz. The RSA of HO-DI animals contains lower frequencies than that of HE-DI rats. These relatively large differences can be followed in most of the spectral parameters summarized in Table I. The mean 'peak frequency' of HO-DI rats is 1 Hz and the 'mean frequency' 0.5 Hz lower than that of HE-DI animals. No significant differences exist in the 'spectrum width' parameter except that the corresponding frequencies were significantly shifted to the left on the frequency scale. This indicates that the increase in amount of lower frequencies in homozygous individuals indeed occurs at the cost of higher frequency components. The pattern of RSA of HE-DI rats strongly resembles that of Wistar rats.

The effect of a single injection of DG-AVP is illustrated in Fig. 2. In a dose-dependent manner, 1 and 2 μg of the peptide/100 g body weight enhanced the generation of RSA of higher frequencies in HO-DI animals. Table II summarizes the changes in spectral parameters in one animal obtained after treatment with 2 doses of DG-AVP. The higher dose almost normalizes the RSA except for the 'peak frequency' parameter which remained significantly below that of HE-DI rats (Table III).

These preliminary results show that there are differences in quality of the RSA during PS between HO-DI and HE-DI rats. The fact that the RSA generating substrate does not readily produce high frequency theta components might be explained

TABLE I

DIFFERENCES IN SPECTRAL PARAMETERS OF RSA BETWEEN HETEROZYGOUS AND HOMOZYGOUS DIABETES INSIPIDUS RATS DURING PARADOXICAL SLEEP

	DI-homozygous $\bar{X} \pm$ *S.D.*, $N =$ *32*	*DI-heterozygous* $\bar{X} \pm$ *S.D.*, $N =$ *30*	*P level*
Mean frequency in Hz	7.6 ± 0.1	8.1 ± 0.04	$P < 0.001$
Peak frequency in Hz	6.8 ± 0.5	7.8 ± 0.4	$P < 0.001$
Spectrum width at ½ peak amplitude	0.7 ± 0.2	0.9 ± 0.3	n.s.
Frequencies at ½ peak amplitude	$6.4 \pm 0.4 - 7.1 \pm 0.5$	$7.0 \pm 0.3 - 7.9 \pm 0.4$	$P < 0.001$

either by a disturbed Na^+ and K^+ balance or by assuming a more specific role of vasopressin in membrane processes and transmission. The hypokalemia and hypernatremia which have been found in HO-DI rats[9,10], however, are not responsible for the abnormal electrophysiological activity. Treatment with DG-AVP, an analogue of vasopressin which does not ameliorate the symptoms of the diabetes insipidus[16], almost completely normalized RSA. Core temperature is also known to influence the frequency content of RSA in rats[14]. According to our observation HO-DI rats do not exhibit hypothermia. So far only quantitative differences in the amount of RSA or

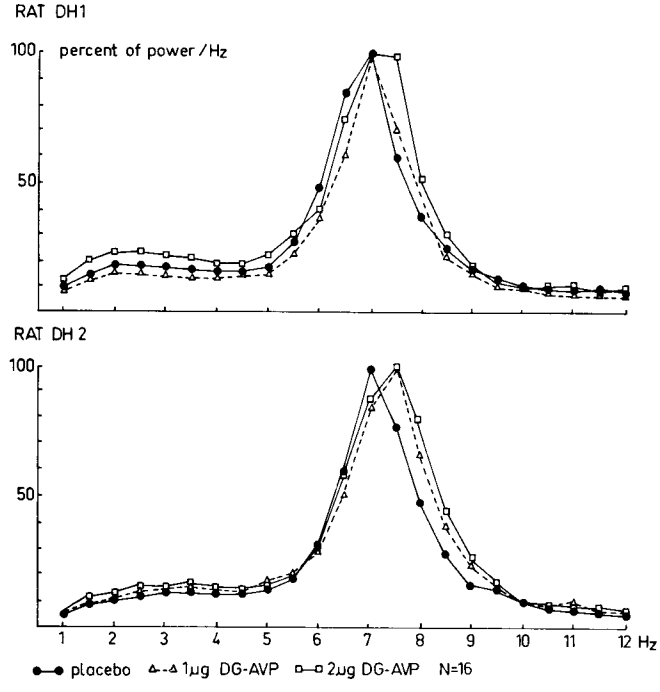

Fig. 2. Effect of DG-AVP treatment on hippocampal RSA of homozygous diabetes insipidus rats during paradoxical sleep.

TABLE II

EFFECT OF DG-AVP TREATMENT ON SPECTRAL PARAMETERS OF RSA DURING PARADOXICAL SLEEP IN HOMOZYGOUS DIABETES INSIPIDUS RATS

	Placebo	*DG-AVP 1 μg/100 g*	*DG-AVP 2 μg/100 g*
Mean frequency in Hz	7.7 ± 0.08	7.9 ± 0.1§	7.9 ± 0.1§
Peak frequency in Hz	7.0 ± 0.4	7.4 ± 0.4**	7.5 ± 0.2***
Spectrum width at ½ peak amplitude	0.6 ± 0.3	0.8 ± 0.5	0.7 ± 0.4
Frequencies at ½ peak amplitude	6.6 ± 0.3 – 7.2 ± 0.4	6.8 ± 0.4* – 7.6 ± 0.4*	7.1 ± 0.3*** – 7.8 ± 0.2***

§ $P < 0.1 > 0.05$.
* $P < 0.05$.
** $P < 0.02$.
*** $P < 0.01$.

TABLE III

COMPARISON OF SPECTRAL PARAMETERS OF RSA DURING PARADOXICAL SLEEP IN THE HETEROZYGOUS AND HOMOZYGOUS DIABETES INSIPIDUS RATS, TREATED WITH DG-AVP

	Heterozygous	*Homozygous (2) + DG-AVP 2 μg/100 g*	*P level*
Mean frequency in Hz	8.1 ± 0.04	7.9 ± 0.1	n.s.
Peak frequency in Hz	7.8 ± 0.4	7.5 ± 0.2	$P < 0.05$
Spectrum width at ½ peak amplitude	0.7 ± 0.5	0.8 ± 0.3	n.s.
Frequencies at ½ peak amplitude	7.1 ± 0.4–7.8 ± 0.2	7.0 ± 0.4–7.8 ± 0.3	n.s.

PS have been demonstrated to interfere with consolidation processes[1,2,4,7,8]. The quantitative aspect of the RSA was not specifically investigated in the present study. It may well be that both quality and quantity are equally important in consolidation processes. Experiments are in progress to elucidate this problem. However, the inferior quality of RSA during PS in the absence of vasopressin and the beneficial effect of vasopressin treatment support the hypothesis derived from previous studies that vasopressin plays an important role in the consolidation of learned responses.

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