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Effect of Vinpocetine on the Sleep-Wake Cycle of Rats

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ABSTRACT

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Vinpocetine given orally for five consecutive days in weekly, ascending doses produced changes in the sleep-wake cycle of the rat, as measured by the electrocorticogram. The effect of vinpocetine on the sleep-wake cycle was interpreted as an increase in alertness, and was most prevalent at the highest dose of 30 mg/kg/day p.o. This effect lasted for two weeks following the discontinuation of the treatment. Hypoxia-induced sleep disturbances were not improved by daily administration of vinpocetine in rats. These data support three conclusions: 1) vinpocetine may evoke functional and/or metabolic processes in the brain that are related enhanced alertness; 2) within the dose range examined vinpocetine had no "antihypoxic" activity during moderate hypoxic episodes; and 3) the effect of vinpocetine appears to be extended beyond the treatment period.

Key words: sleep-wake pattern, hypoxia, vinpocetine

INTRODUCTION

Recent investigations revealed that oral administration of vinpocetine improve performance in scopolamine-induced and hypoxia-induced learning and memory impairments in rats [Groo et al., 1987, 1988]. These data raise two questions: 1) whether prolonged oral administration of vinpocetine influences the normal sleep-wake pattern, since many compounds having specific action on the central nervous system tend to alter the sleep pattern, and, 2) whether daily oral administration of vinpocetine reverses the sleep-wake pattern disturbance evoked by moderate degree of hypoxia in rats.

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MATERIALS AND METHODS

Surgery

Outbred male RG-Wistar rats of the Hannover strain (63 ± 2 days of age) were prepared for chronic electrophysiological investigations. Under pentobarbitone (60 mg/kg i.p.) anesthesia, electrodes were placed on the visual cortex (stereotaxic coordinates according to atlas of Pellegrino et al. [1979] were A:0.0; L:3.0-3.5). The uninsulated spiral disk cortical electrodes of 1.5-mm diameter were made of 0.25-mm-diameter insulated nichrome wire; interelectrode distance for the bipolar leads was 1.5 mm. The outer end of the electrodes were crimped into the pins of a subminiature connector, and the connector was fixed to the skull with an acrylate cement. Impedance measurements were used to confirm proper electrode function four weeks after recovery from surgery.

Recording Procedure

Recordings were made in the laboratory under conditions of diffuse low-intensity artificial light and masking noise. Electrocorticograms of the animals were recorded simultaneously for 120 min. Scoring of the sleep stages was performed visually according to the following criteria: 1) awake (AW)—irregular cortical activity of 4 to 8 cps when the animal is orienting, moving or lying quietly with open eyes; 2) arousal reaction (AR)—a short awake-like electrographic pattern, lasting for a few seconds, accompanied by minimal or no movements inserted into sleep stages or between two sleep stages; 3) light sleep (SWS1)—alternation of awake-like background activity with the appearance of cortical sleep spindles mixed with waves of slower theta range when the animal is lying quietly with dropping or closed eyes; 4) deep sleep (SWS2)—high-amplitude irregular cortical activity of 2–6 cps when the animal is in the characteristic sleep posture; 5) paradoxical sleep (PS)—regular cortical rhythm of 5–7 cps when the animal is lying relaxed with slack head and limbs, occasionally some ear-jerks occur.

Analysis of time-stage data was performed by a computer; it printed out total sleep time (TST), the proportion of each sleep stage from TST, the occurrence of each stage, and the time-stage diagram (sleep-print) of a measured recording period (RP). An unpaired t-test was used for statistical analysis.

Experimental Procedure

The experimental schedule (Table 1) was performed on two groups of animals simultaneously: animals in the first ("normoxic") group ($n = 6$) slept in their own standard cages, while animals of the second ("hypoxic") group ($n = 4$) were placed in artificially ventilated $25 \times 25 \times 25$-cm plastic chambers. The oxygen content of the chambers was lowered to 10.5% until the beginning of the recording session made on the second to seventh weeks of the experimental schedule.

Vinpocetine was dissolved in 1% (w/v) carboxy-methylcellulose, and ascending doses of 1, 3, 10, and 30 mg/kg were administered orally at a maximum volume of 0.4 ml/100 g/animal. Each dose was given daily at 6:30 A.M., 3.5 hr prior to the beginning of an EEG recording, for five consecutive days. There was no treatment on weekend days.

RESULTS

Behavior

Some animals slept more lightly after three weeks of vinpocetine treatment. All of the animals appeared more alert and sometimes restless during sleep during the sixth week. No changes were observed in the behavior of the animals during handling.

TABLE 1. The Experimental Schedule

Weeks	Event		Recording
−1	Habituation of animals to the recording situation: the stabilization of sleep pattern characterizing each animal		None
0			Daily
1	Habituation of animals to the recording situation from 9:30 to 12:00 A.M. (control)		
2	Daily treatment with	Vehicle (vehicle)	Tuesday (2nd drug day)
3		1 mg/kg	
4		3 mg/kg	Friday (5th drug day)
5		10 mg/kg	(On the other days sleep situation only)
6		30 mg/kg	
7		Vehicle (Pt-vehicle)	
8	Post-treatment control (Pt-control)		

VINPOCETINE

Normal Sleep-Wake Pattern

The proportions of AW, expressed in percentage of recording periods (RP%), decreased in the third week (i.e., 1 mg/kg/day vinpocetine) and increased to values greater than initial control levels during subsequent weeks (Fig. 1, upper diagram). The time spent awake during the 30-mg/kg/day vinpocetine treatment schedule was two times greater than that observed in pretreatment recordings and remained unchanged following the discontinuation of treatment.

There were no changes in the proportions of SWS1, SWS2, and PS, expressed as percentage of total sleep time (TST%), until the fifth week (upper diagrams of Figs. 2–4). During the fifth week (i.e., the 10 mg/kg/day vinpocetine dose) SWS1 tended to increase and SWS2 and PS tended to decrease. During the last three weeks (30 mg/kg/day vinpocetine and post-treatment recordings) the proportions of SWS1 were two times greater than pretreatment recordings. The proportion of SWS2 was approximately 40% less and PS was 60% less in the last three weeks of recordings compared to pretreatment values.

None of the sleep-wake stages recorded during the fifth drug day (Friday) showed statistically significant difference in comparison to recordings made on Tuesday (second drug day) of the same week.

The occurrence of each sleep stage changed in parallell to total-time proportions, with the exception of the number of AWs. The number of arousal reactions (AR) within TST decreased in parallel to increased total-time spent awake while the proportions of summed AR-times expressed in TST% remained unchanged in the recordings of the last four weeks. That is, the animal remained awake for longer time period when aroused during the recordings of the second half of the experiment.

Hypoxic Sleep-Wake Pattern

The disturbance of sleep-wake pattern induced by 10% oxygen content of inspired air was characterized by at least two times greater AW/RP and SWS1/TST ratios, a slight decrease

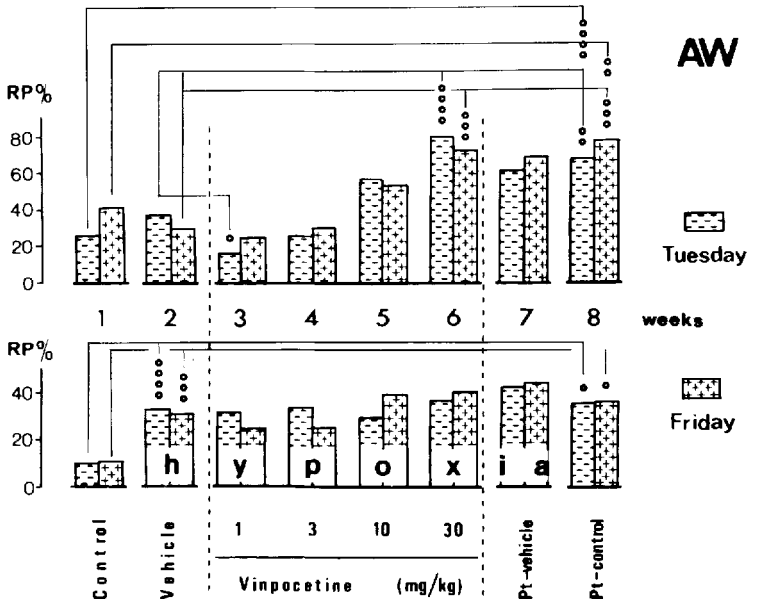

Fig. 1. Changes of mean total time spent awake (AW) expressed in percentage of each recording period (RP%) during the experimental procedure in normal (upper diagram) and hypoxic (lower diagram) circumstances. Each bar is based on data of 5 to 6 rats in the case of "normoxic" group and on data of 4 rats in the case of "hypoxic" group. Unpaired t-tests: $^{o}P < 0.05$; $^{oo}P < 0.01$; $^{ooo}P < 0.005$; $^{oooo}P < 0.001$.

in SWS2/TST ratios and a 80% decrease in PS/TST ratios in comparison to normal values of deep sleeping animals (control vs. vehicle [first week vs. second week] in lower diagrams of figures).

These hypoxia-induced changes were not influenced by subchronically administered doses of 1 and 3 mg/kg/day vinpocetine. Higher doses of subchronically administered vinpocetine tended to increase the hypoxia-enhanced proportions of AW and decrease the hypoxia-lowered proportions of PS. Post-treatment control values (eighth week) remained almost at the same level as during hypoxia in the case of the proportion of AW and SWS1. The proportion of PS was also 30% less on the eighth week than that of the first week in normoxic animals.

DISCUSSION

Vinpocetine administered subchronically in 10- and 30-mg/kg/day doses caused a shift of normal sleep-wake pattern towards waking. This effect may be attributed to the activation of catecholaminergic mechanisms. According to Jouvet [1972] the ascending noradrenergic axons in the dorsal bundle or the catecholamine-containing group of the mesencephalic tegmentum might be equally responsible for controlling the level of tonic behavioural and EEG arousal. Vinpocetine has been shown to accelerate selectively turnover of cerebral noradrenaline (NA) within the same dose range used in our investigations [Kiss et al., 1982]. Further studies showed that increased NA turnover or NA utilization elicited by vinpocetine was more apparent in lower midbrain, pons, medulla, and cerebellum [Kiss and Szporny, 1988].

The alertness-increasing effect of vinpocetine appeared within the same dose range which produced enhanced retrieval of passive avoidance responses in rats [Groo et al., 1987,

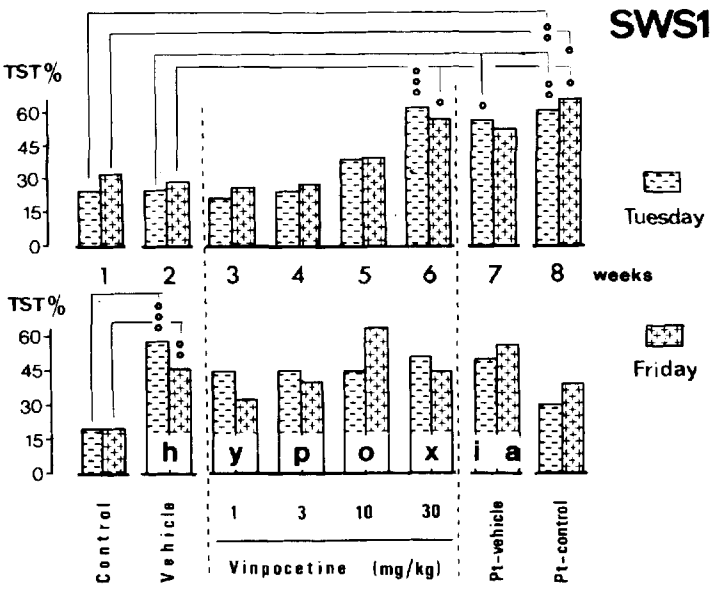

Fig. 2. Changes of mean total time spent in light sleep (SWS1) expressed in percentage of total time spent in sleep (TST%) during the experimental procedure in normal (upper diagram) and hypoxic (lower diagram) circumstances. Conventions for the presentations of data are the same as in Figure 1.

1988]. We have to add, however, that the vinpocetine-elicited alertness is far less than that of evoked by a new vigilance enhancer, a TRH analogue [Sarkadi et al., 1988].

In these contexts our results suggest that higher doses of vinpocetine may evoke such functional processes in the rat's brain which are connected to enhanced alertness.

Vinpocetine did not reverse the changes of sleep-wake pattern evoked by 10.5% oxygen content of inspired air. In fact, the effect of vinpocetine was qualitatively similar to that observed in the sleep-wake pattern of normoxic circumstances. This finding is in aggreement with the above-discussed role of NA in the vinpocetine effect. Davis and Carlsson [1973] showed that the rate of catecholamine synthesis was reduced up to 50% while no changes in monoamine levels were measured in brainstem, striatum, and whole brain of rats exposed to 5.6% oxygen environment for up to 2 hr. In contrast, vinpocetine prevented the reduction of NA levels of above-mentioned brain regions of rats exposed to an hypoxic environment of 8% oxygen as well [Kiss and Szporny, 1988].

In hypoxemia produced by 7% oxygen in the inspired air in spontaneously breathing conscious rats, a complete redistribution of the local rates of glucose utilization while overall average cerebral glucose utilization remained unchanged [Sokoloff, 1982]. Kety and Schmidt [1948—cited in Sokoloff, 1982] found in man that the breathing of 10% oxygen produced a wide variety of mental symptoms without altering the average oxygen consumption of the brain as a whole. Reversal of hypoxia-induced sleep disturbance by a drug might point either to an effect increasing the tolerance of brain tissue against hypoxia ("antihypoxic" effect) or to hypnotic effect. Hypnotic effect of vinpocetine was not expected in our experiments. According to our results, however, vinpocetine showed no direct "antihypoxic" effect, although it might have been expected.

The sleep-wake pattern signs of increased alertness evoked by subchronically administered 30 mg/kg/day dose of vinpocetine persisted for two weeks following the cessation of the treatment in the recordings of both "normoxic" and "hypoxic" group of animals. We do not

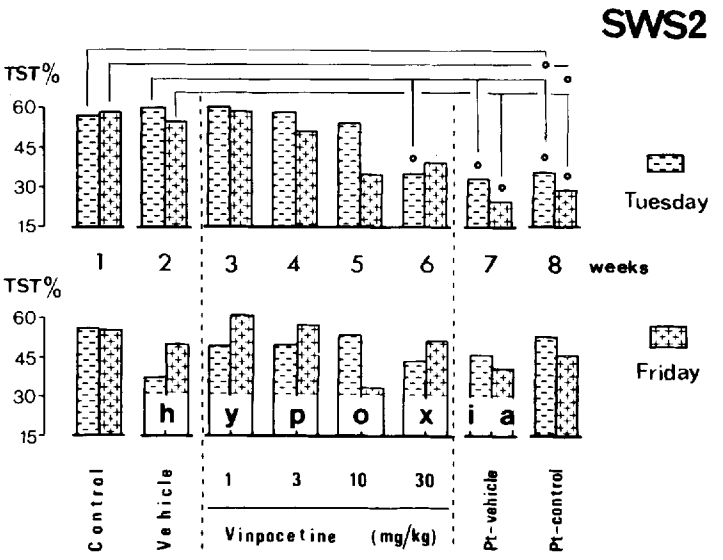

Fig. 3. Changes of mean total time spent in deep sleep (SWS2) expressed in percentage of total time spent in sleep (TST%) during the experimental procedure in normal (upper diagram) and hypoxic (lower diagram) circumstances. Conventions for the presentations of data are the same as in Figure 1.

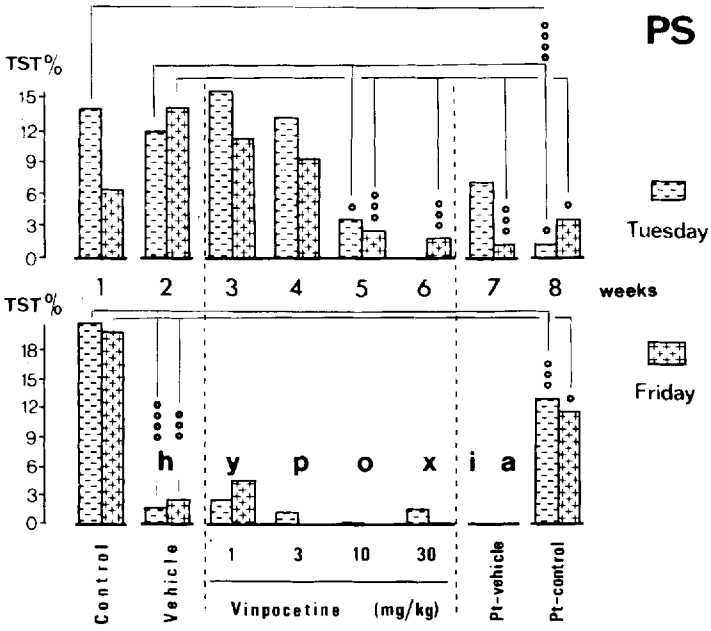

Fig. 4. Changes of mean total time spent in paradoxical sleep (PS) expressed in percentage of total time spent in sleep (TST%) during the experimental procedure in normal (upper diagram) and hypoxic (lower diagram) circumstances. Conventions for the presentations of data are the same as in Figure 1.

know when this post-treatment effect would have begun to decline, since the evaluation of collected data was performed some weeks after the experimental schedule had been finished. The observed fact suggests, however, that vinpocetine given in high doses for a long time may have the capability of prolonging binding to or accumulation in the brain tissue.

In conclusion, our results support the view that vinpocetine may produce an increased alertness, in which the probability of profound memory decay may decrease, and the recall of memory content may improve.

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