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BRIEF COMMUNICATION

Effect of a New Cognitive Drug-Enhancer S-12024-2 on EEG Sleep Recordings in Rats

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DE SAINT HILAIRE, Z., J.-M. GAILLARD, S. DETOLLE-SARBACH AND D. GUEZ. *Effect of a new cognitive drug-enhancer S-12024-2 on EEG sleep recordings in rats.* PHARMACOL BIOCHEM BEHAV **52**(4) 819–823, 1995.—A newly synthesized agent S-12024-2 was shown to improve some aspects of cognitive processes such as memory consolidation. The relationships between sleep and memory lead us to investigate the effects of the intraperitoneal administration of three different doses (1, 3, and 10 mg/kg) of S-12024-2 on sleep variables in the rat. The results showed that S-12024-2 (10 mg/kg) increased slow wave sleep (SWS) and decreased wakefulness during the light period of the first 24 h of sleep recording. During day 1 of sleep recording, S-12024-2 tended to increase paradoxical sleep (PS) with a maximal effect observed with 3 mg/kg. Four days after administration of S-12024-2 (3 mg/kg), PS remained significantly high. These data suggest an active role for S-12024-2 on SWS and PS, compatible with its favourable effects on memory.

Cognition Memory Vasopressin Paradoxical sleep Rat

SLEEP STAGES, in particular slow wave sleep (SWS) and paradoxical sleep (PS), have been shown to play a key role in the process of learning and memory consolidation (2,13, 21,24). PS deprivation impairs memory fixation (19). Thus, SWS plays a role in rats in "place" memory consolidation (13) and the learning process is facilitated by the occurrence of PS (14) and PS may be involved in memory reorganization (9). Recent results also indicate that a process of consolidation of human perceptual learning is strongly dependent on PS (13).

Numerous previous studies suggest a cholinergic role in the induction and realization of PS and in some aspects of wakefulness (5,12). Such evidence for the involvement of cholinergic mechanisms with PS comes from both human and animal studies; PS is increased and its latency is decreased by administration of cholinomimetic agents such as arecholine and physostygmine (5,18). Conversely, PS is reduced and its onset is delayed by administration of anticholinergic agents such as scopolamine and atropine (9,19,20). The involvement of cholinergic systems and cholinergic neurons in learning and memory processes has been suggested for many years (4,7,16). A deficit in cholinergic neurotransmission has also been reported in cognitive deficits in elderly subjects (16,17).

A new pharmacological agent, S-12024-2, the methane sulphonate salt of R, S methyl-1(morpholinyl-2 methoxy)-8 tetrahydro-1,2,3,4 quinoline (Fig. 1), has been shown to improve some aspects of cognitive processes such as attention, curiosity, motivation, acquisition and recall of memory (3,15). These results as well as results from two other tests of memory (i.e., social interaction, passive avoidance) revealed the ability of S-12024-2 to enhance the processes of both declarative memory and perceptual learning (3,15).

S-12024-2 has also been shown to reduce the effect of an anticholinergic drug such as scopolamine that induces memory deficits such as the avoidance of performance tasks in the rat (15). But it cannot be assumed that this compound acts only via the cholinergic system because scopolamine's amnestic effect after peripheral administration is blocked without specificity. Thus, this classical pharmacological model cannot be used to evaluate a drug's mechanism of action (8).

Other pharmacological investigations have shown no effect

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on noradrenergic and cholinergic receptor binding sites. S-12024-2 did not affect the release of noradrenaline, and the direct interaction of this compound with noradrenergic neurons appears to be limited (3).

Consistent with the absence of effects in studies of central neurotransmitters (release, turnover, reuptake, receptor binding), the distribution of [^{3}H]-S-12024-2 is extremely localized. The most interesting feature of this distribution is the binding to those parts of the brain associated with neuroendocrine function and containing a high concentration of vasopressin: the paraventricular nucleus and the supraoptic nucleus (15). Considering that vasopressin is probably involved in memory and cognition (10), it is possible that an interaction of S-12024-2 with vasopressin could in part explain the memory facilitating effects of this drug. However, the exact mechanism of action of this molecule remains uncertain.

The facilitatory effect of S-12024-2 on scopolamine-induced amnesia and its binding sites to those of vasopressin would suggest that S-12024-2 may also have some effect on PS. Also, it is likely that S-12024-2 enhances learning and memory by affecting both SWS and PS.

Because of the apparent role of SWS and PS in the processes of learning and memory (13,14,24), we attempted to test the effects of S-12024-2, a new cognitive enhancer, on different sleep variables and particularly on SWS and PS by means of electroencephalogram (EEG) sleep recordings in rats.

METHOD

Male adult Wistar rats (n = 18) weighing 250 g at the beginning of the experiment were operated on under pentobarbital (55 mg/kg) anaesthesia. In the neck muscles, each rat had four electrodes for recording EEG, and two electrodes for electromyograms (EMG) implanted.

One week postoperatively, the rats were acclimatized to the experimental recording cages fitted with flexible EEG recording cables. Standard laboratory food and water were available throughout the habituation period and all experimental sessions. A 12L : 12D cycle was maintained and ambient temperature was kept at 25°C.

Injections were made intraperitoneally (IP) at 0800 h. To prevent interference between different doses of the treatment, either saline or S-12024-2 dissolved in 0.9% NaCl was given to three different groups of six rats:

- Group 1, NaCl or 1 mg/kg of S-12024,
- Group 2, NaCl or 3 mg/kg of S-12024,
- Group 3, NaCl or 10 mg/kg of S-12024.

Rats received one single injection, either NaCl or S-12024, on day 1 of the study. The animals were registered continuously (24 h/day) on days 1 and 4 after drug administration. The vigilance states were visually scored, blind to the experimental condition, according to conventional criteria for waking (W), SWS, and PS by 20-s epochs throughout the experiments. Sixteen different sleep variables in minutes were studied (see Tables 1 and 2) and for all sleep variables statistical estimation was made by using an analysis of variance (ANOVA) followed by posthoc Student's t-test.

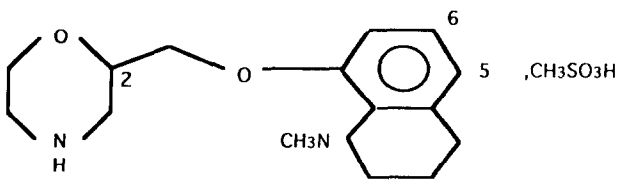

FIG. 1. Chemical structure of S-12024-2, the methane sulphonate salt of R,S-methyl-1(morpholinyl-2 methoxy)-8 tetrahydro-1,2,3,4 quinoline. Molecular wt. 358.46.

RESULTS

The following results were obtained under the three different dosage schedules.

Day 1

S-12024-2 (1 mg/kg): Light period. Tables 1 and 2 show the different sleep variables following IP administration of S-12024-2, throughout the 12 h of EEG sleep recordings during the light part of the light/dark cycle. A slight increase in total sleep time and SWS was observed. The discrete increase in SWS led to a significant lengthening of the sleep cycle ($p < 0.05$). PS remained unchanged.

S-12024-2 (1 mg/kg): Dark period. There was no difference between controls and S-12024-2 treated rats during 12 h of EEG recording; however, during this period there was a tendency, albeit insignificant, towards an increase in PS episodes.

S-12024-2 (3 mg/kg): Light period. As shown in Table 1, the decrease of sleep latency observed following administration of S-12024-2 (3 mg/kg) was unexpected. PS was significantly enhanced ($p < 0.05$).

S-12024-2 (3 mg/kg): Dark period. No difference between controls and drug-treated rats was observed (Table 1).

S-12024-2 (10 mg/kg): Light period. Table 1 shows that S-12024-2 at high doses significantly increased total sleep time, SWS, and the mean duration of the sleep cycle. PS was also increased but did not reach statistical significance (Table 2). Waking time and its percent significantly decreased.

S-12024-2 (10 mg/kg): Dark period. No changes were observed during this period.

Day 4

S-12024-2 (1 mg/kg): Light period. Table 3 shows the results of EEG sleep recording 4 days after acute administration of S-12024-2 (1 mg/kg) in rats. Although there was no change in PS during the light period of day 1, PS duration as well as the number of episodes were found to be higher during the light period of day 4 (Table 4). When expressed in percent, SWS and PS were significantly higher than in controls. The number of stage shifts as well as the number of awakenings were significantly increased. The mean duration of sleep cycles was reduced.

S-12024-2 (1 mg/kg): Dark period. Total sleep time and SWS were significantly increased, and sleep latency was shorter than in the control group. Waking time and its percent were significantly decreased (Table 3).

S-12024-2 (3 mg/kg): Light period. Four days after acute administration of S-12024-2, PS still remained significantly higher than in the control rats (Table 4). This increase was due only to an increase in the number of PS episodes. On the other hand, SWS decreased significantly, expressed in percentage. The mean duration of sleep cycles was shortened although not significantly. On the contrary, an increase was seen in the number of stage shifts as well as in the number of awakenings (Table 3).

S-12024-2 (3 mg/kg): Dark period. There was no modification in the dark period.

TABLE 1

MODIFICATIONS IN SLEEP VARIABLES AFTER IP INJECTION OF NaCl OR S-12024-2 DURING THE LIGHT AND DARK PERIODS OF DAY 1

	S-12024-2 (n = 18)					
Sleep Variables (min)	0	1 mg/kg	0	3 mg/kg	0	10 mg/kg
Light period						
Total sleep	487.5 ± 68	506 ± 22.5	477 ± 58	515 ± 54	491 ± 67	539 ± 50*
Total waking time	232.5 ± 68	214 ± 22.5	243 ± 58	205 ± 54	229 ± 67	181 ± 50*
Slow-wave sleep	403.7 ± 62	420.5 ± 24	401 ± 59	432.5 ± 50	413 ± 62	452 ± 39*
% Waking	32.3 ± 9	29.7 ± 3	34 ± 8	28.6 ± 7	31.8 ± 9	25 ± 7*
% SWS	83 ± 2	83 ± 1.6	84 ± 3	84 ± 2.5	84 ± 2.5	84 ± 2.5
Sleep latency	31.7 ± 19	30 ± 13.5	34 ± 15	2 ± 1.6*	26 ± 18	14.5 ± 10
No. cycles	41.7 ± 5	41.1 ± 2.5	37.7 ± 5	40.3 ± 3.4	41 ± 7	42 ± 7
Mean duration of cycles	10.2 ± 2.5	10.7 ± 1*	10.6 ± 2.2	11 ± 1.3	10 ± 1.7	11.4 ± 2*
No. stage shifts	365 ± 90	362.5 ± 55	354.5 ± 102	309.2 ± 103	329.5 ± 105	300 ± 84
No. awakenings	152 ± 50	152 ± 27	153 ± 49	124.5 ± 56	137 ± 54	120 ± 40
Dark period						
Total sleep	222.3 ± 3.7	277 ± 88	213.3 ± 43	233 ± 34.4	216 ± 27	233 ± 42
Total waking time	498 ± 37	443 ± 88	506.7 ± 43	487 ± 34.4	504 ± 27	487 ± 42
Slow-wave sleep	198 ± 35	246.5 ± 78	190 ± 40	215 ± 29	193 ± 24	212 ± 39
% Waking	69 ± 5	61.6 ± 12	70.4 ± 6	68 ± 5	70 ± 4	68 ± 6
% SWS	89 ± 2	89 ± 2	90 ± 2.1	90.5 ± 1.4	89 ± 2	90±
Sleep latency	9 ± 9	10 ± 8	10.5 ± 12.5	21 ± 10	13.6 ± 12.3	22 ± 11
No. cycles	16.5 ± 3.6	19.7 ± 7.5	15.8 ± 4.3	15 ± 4.5	16 ± 4	19.7 ± 7.5
Mean duration of cycles	7.8 ± 1.3	8.2 ± 1.5	8.6 ± 2	8.8 ± 1.8	7.8 ± 2	7.5 ± 0.8
No. stage shifts	264 ± 61	264 ± 82	250 ± 57	252.2 ± 56	275 ± 31	271 ± 50
No. awakenings	122 ± 67	119.6 ± 38	116 ± 27	117 ± 26	128 ± 14	128 ± 24

Doses of S-12024-2 are in mg/kg. Data are means ± SD, expressed throughout the first 12 h (0800–2000 h) and the second 12 h (2000–0800 h) of EEG sleep recordings. Statistically significant differences from controls by ANOVA and posthoc test: *$p < 0.05$.

S-12024-2 (10 mg/kg): Light period. The decrease in latency of PS was the only significant modification observed 4 days after administration of S-12024-2 (Table 4).

S-12024-2 (10 mg/kg): Dark period. Although there was no significant modification of PS on day 1 after S-12024-2 (10 mg/kg), 4 days after its administration, PS was significantly increased in comparison with controls (Table 4).

DISCUSSION

On day 1, S-12024-2 at the doses studied was found to have a dose-dependent hypnogenic effect during the light period. Some hypnogenic effect was apparent, but insignificant, during the dark period. The hypnogenic action of S-12024-2 with the doses of 1 mg/kg and 10 mg/kg was probably reflected

TABLE 2

MODIFICATIONS IN PARADOXICAL SLEEP VARIABLES AFTER IP INJECTION OF NaCl OR S-12024-2 DURING THE LIGHT AND DARK PERIODS OF DAY 1

	S-12024-2 (n = 18)					
Sleep Variables (min)	0	1 mg/kg	0	3 mg/kg	0	10 mg/kg
Light period						
Paradoxical sleep	84 ± 11.8	85 ± 7	76 ± 13	82 ± 15*	78 ± 14	87 ± 19
% PS	17 ± 2	17 ± 1.6	16.2 ± 3	16 ± 2.5	16 ± 2.5	16 ± 2.5
PS latency	14.4 ± 8	18.3 ± 9.5	13 ± 6	15.5 ± 9.4	13.4 ± 8	23 ± 11
No. cycles	41.7 ± 5	41.1 ± 2.5	37.7 ± 5	40.3 ± 3.4	41 ± 7	42 ± 7
Mean duration of PS episodes	2.1 ± 0.4	2.2 ± 0.3	2.1 ± 0.5	2.1 ± 0.4	2 ± 0.3	2.2 ± 0.4
Dark period						
Paradoxical sleep	24 ± 4	30.3 ± 10.5	23.4 ± 5.2	22.3 ± 6	22 ± 5.4	21 ± 8
% PS	11 ± 2.2	11 ± 2	11.1 ± 2.1	9.5 ± 1.4	10 ± 2	9 ± 3
PS latency	8 ± 6	9.7 ± 4	10 ± 7	16.4 ± 14	10 ± 6.7	9.7 ± 4
No. PS	16.5 ± 3.6	19.7 ± 7.5	15.8 ± 4.3	15 ± 4.5	16 ± 4	19.7 ± 7.5
Mean duration of PS episodes	1.5 ± 0.3	1.6 ± 0.2	1.6 ± 0.4	1.6 ± 0.3	1.5 ± 0.4	1.5 ± 0.3

Doses of S-12024-2 are in mg/kg. Data are means ± SD, expressed throughout the first 12 h (0800–2000 h) and the second 12 h (2000–0800 h) of EEG sleep recordings. Statistically significant differences from controls by ANOVA and posthoc test: *$p < 0.05$.

TABLE 3

MODIFICATIONS IN SLEEP VARIABLES AFTER IP INJECTION OF NaCl OR S-12024-2 DURING THE LIGHT AND DARK PERIODS OF DAY 4

	S-12024-2 (n = 18)					
Sleep Variables (min)	0	1 mg/kg	0	3 mg/kg	0	10 mg/kg
Light period						
Total sleep	534 ± 28	521.5 ± 24	532 ± 30	513 ± 48	528 ± 28	523 ± 34
Total waking time	186 ± 28	198.5 ± 24	187 ± 30	206 ± 48	192 ± 28	197 ± 34
Slow-wave sleep	485 ± 32	438 ± 32	465 ± 29	426 ± 42	459 ± 32	451 ± 19
% Waking	26 ± 4	27.5 ± 3	26 ± 4	29 ± 7	27 ± 4	27 ± 5
% SWS	86 ± 3	84 ± 3*	88 ± 4	83 ± 2*	87 ± 4	86 ± 3
Sleep latency	16.5 ± 13	13.2 ± 6	6.3 ± 8	17 ± 14	12 ± 14	17 ± 14
No. cycles	37 ± 4	46 ± 6*	34 ± 7	40 ± 3*	35 ± 7	40 ± 3
Mean duration of cycles	12 ± 1.6	10 ± 1*	13 ± 1.5	11 ± 1	12 ± 1.5	11 ± 1
No. stage shifts	270 ± 37	385 ± 60*	248 ± 50	13 ± 80*	255 ± 50	306 ± 58
No. awakenings	152 ± 50	159 ± 32*	101 ± 21	178 ± 42*	104 ± 21	127 ± 29
Dark period						
Total sleep	192 ± 41	245.6 ± 47*	200 ± 38	215 ± 35	195 ± 43	225 ± 26
Total waking time	528 ± 17	474.4 ± 47*	520 ± 37	506 ± 35	524 ± 43	494 ± 26
Slow-wave sleep	172 ± 16	221 ± 43*	179 ± 37	190 ± 28	176 ± 40	202 ± 26
% Waking	73 ± 2.3	66 ± 7*	72 ± 5	70 ± 5	73 ± 6	69 ± 4
% SWS	89 ± 1	89 ± 1	89 ± 2	88 ± 3	90 ± 1	89 ± 2
Sleep latency	22 ± 2	13.3 ± 4*	22 ± 6	15 ± 10	23 ± 8	28 ± 30
No. cycles	14 ± 1.5	20 ± 9	14 ± 3	17 ± 9	13 ± 4	17 ± 2
Mean duration of cycles	7.8 ± 1.3	7.5 ± 1.5	8.5 ± 2	8 ± 2	7 ± 1	7 ± 2
No. stage shifts	251 ± 26	271 ± 14	234 ± 48	245 ± 36	256 ± 58	259 ± 32
No. awakenings	118 ± 12	123 ± 20	109 ± 21	112 ± 21	121 ± 27	119 ± 23

Doses of S-12024-2 are in mg/kg. Data are means ± SD, expressed throughout the first 12 h (0800–2000 h) and the second 12 h (2000–0800 h) of EEG sleep recordings. Statistically significant differences from controls by ANOVA and posthoc test: *$p < 0.05$.

in changes of sleep cycle duration. Because S-12024 has a facilitatory effect on memory, our results are compatible with recent studies showing that SWS plays a role in memory consolidation (13)

On day 4, the recordings showed no effect on total sleep time. The number of sleep cycles was greater but their mean duration was shorter than in controls.

During these recordings, the compound tended to increase PS and the number of its episodes with a maximal increase at the dose of 3 mg/kg. However, in this case PS was increased

TABLE 4

MODIFICATIONS IN PARADOXICAL SLEEP VARIABLES AFTER IP INJECTION OF NaCl OR S-12024-2 DURING THE LIGHT AND DARK PERIODS OF DAY 4

	S-12024-2 (n = 18)					
Sleep Variables (min)	0	1 mg/kg	0	3 mg/kg	0	10 mg/kg
Light period						
Paradoxical sleep	76 ± 18	83 ± 10	67 ± 24	87 ± 12*	69 ± 18	73 ± 20
% PS	14 ± 3	16 ± 3*	12 ± 4	17 ± 2*	13 ± 4	14 ± 3
PS latency	18 ± 7	16.1 ± 4.2	21 ± 10	10 ± 4	19 ± 7	10 ± 4*
No. PS	37 ± 4	46 ± 6*	34 ± 7	40 ± 3*	35 ± 7	40 ± 3
Mean duration of PS episodes	2.1 ± 0.4	1.9 ± 0.3	2 ± 0.4	2.2 ± 0.2	2 ± 0.4	1.9 ± 0.2
Dark period						
Paradoxical sleep	21 ± 1	25 ± 6	21 ± 3	25 ± 9	20 ± 3	23 ± 3*
% PS	11 ± 1	10 ± 1	11 ± 2	11 ± 3	10 ± 1	10 ± 2
PS latency	12 ± 4	13.5 ± 23	8 ± 5	20 ± 20	13 ± 10	17 ± 10
No. PS	14 ± 1.5	20 ± 9	14 ± 3	17 ± 9	13 ± 4	17 ± 2
Mean duration of PS episodes	1.5 ± 0.2	1.3 ± 0.1	1.6 ± 0.2	1.6 ± 0.3	1.5 ± 0.2	1.5 ± 0.1

Doses of S-12024-2 are in mg/kg. Data are means ± SD, expressed throughout the first 12 h (0800–2000 h) and the second 12 h (2000–0800 h) of EEG sleep recordings. Statistically significant differences from controls by ANOVA and posthoc test: *$p < 0.05$.

by a dose that did not affect SWS but slightly increased the number of awakenings on day 4. This seems to suggest some pharmacological interaction between central cholinergic pathways and vasopressin neurons (21).

The sleep-inducing properties of the compound may be related to interaction with vasopressin binding sites. W is slightly increased and PS is decreased in vasopressin-deficient rats, e.g., Brattleboro rats (6). However, the time of being awake is increased by chronic infusions of vasopressin and W duration is decreased by vasopressin antibodies in normal rats (1). This effect (increased wakefulness) is mimicked by an agonist of vasopressin in the rat (1).

A further implication would be that PS enhancing properties may be related to both the cholinergic and vasopressin systems, as both these systems are involved in PS, learning, and memory (4,7,10,11).

The finding of an increase in PS, as well as in the number of stage shifts that reflect sleep fragmentation, is compatible with some facilitatory effect of both cholinergic (9,15) and vasopressin transmissions. It is generally admitted that the stimulation of the cholinergic system facilitates the initiation of PS (number of PS episodes) and determines some aspects of wakefulness (18,19). It is likely that cholinergic pathways to the paraventricular nucleus and supraoptic nucleus modulate vasopressin release: the cholinergic stimulation of vasopressin release is due to activation of muscarinic receptors in these two areas (22).

Depending on the area studied, a significant decrease of approximately 30% in the number of immunocytochemically stained vasopressin neurons in the suprachiasmatic nucleus, locus coeruleus, and medial amygdala of the senile rat (23) and the binding of S12024-2 in the paraventricular nucleus and the supraoptic nucleus, may constitute an anatomical substrate for sleep and memory disturbances during the aging process.

If this is so, then S-12024-2, by increasing both SWS and PS, and, by improving cognitive processes, could be a useful drug in the treatment of memory disturbances in elderly patients.

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