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ORIGINAL INVESTIGATION

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Abstract *Rationale:* It is widely accepted that sleep facilitates memory consolidation. Hypnotics (e.g., benzodiazepines), which reportedly increase sleep efficiency but also modify sleep architecture, could affect memory improvement that occurs during sleep. *Objectives:* The present study examined the effects of single doses of two short half-life hypnotics, zolpidem and triazolam, on sleep-induced improvement of memory. *Methods:* Twenty-two healthy volunteers participated in this randomized, double-blind, crossover study. All subjects received a single oral dose of zolpidem (10 mg), triazolam (0.25 mg) or placebo at 9 P.M. and slept for 7.5±0.2 h. The effect of sleep on memory was investigated by comparing the performance of this group of volunteers with a group of 21 subjects in wakefulness condition. Declarative memory was evaluated by using a free-recall test of ten standard word and seven nonword lists. Subjects memorized the word and nonword lists 1 h before dosing and they were asked to recall the memorized lists 10 h after dosing. Digit symbol substitution test (DSST) and forward and backward digit tests were also given 1 h before and 10 h after dosing. *Results:* Subjects who slept remembered more nonwords than those in wakefulness condition, but they did not recall significantly more standard words. Neither zolpidem nor triazolam affected the enhanced nonword recall observed after sleep. Finally, none of the hypnotics affected the improvement in the DSST performance of subjects who slept. *Conclusions:* The hypnotics tested did not interfere with the nocturnal sleep-induced improvement of memory.

Keywords Zolpidem · Triazolam · Memory consolidation · Sleep · Hypnotics

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Introduction

The idea that sleep is necessary for memory consolidation has been supported for a long time (Smith 1996). In both animals and humans, sleep deprivation after training in a new task impairs its subsequent performance (Karni et al. 1994; Smith and Rose 1997; Plihal and Born 1999; Stickgold et al. 2000a). Memory consolidation resulting from sleep has also been observed as an improvement in perceptual skill and verbal learning (Plihal et al. 1999; Gais et al. 2000; Maquet et al. 2003).

The contribution of sleep in memory consolidation was also supported by electrophysiological and functional brain activity studies. Electrophysiological recordings of rat hippocampal neurons and positron emission tomography in humans demonstrated that neuronal populations of rat hippocampus or human cortex activated by a learning experience are reactivated during post-training sleep (Wilson and McNaughton 1994; Skaggs and McNaughton 1996; Maquet et al. 2000; Lee and Wilson 2002). These reactivations would allow the strengthening of synapses and the incorporation of a new experience into long-term memory (Maquet 2001; Maquet et al. 2003).

In relation to the contribution of slow wave sleep (SWS) and rapid eye movement (REM) stages to the sleep-dependent consolidation, recent findings support the idea that both stages are required for memory processes during sleep (Giuditta et al. 1995; Stickgold et al. 2000b; Ficca et al. 2000; Ficca and Salzarulo 2004).

In view of the role of the sleep on memory consolidation, sleep disorders such as insomnia could have a detrimental

impact on cognitive functions. In fact, insomnia reportedly produced cognitive dysfunctions including memory impairments (Roth et al. 2001). On the other hand, drugs that improve sleep efficiency could be beneficial on cognitive dysfunctions observed in insomniac patients.

Benzodiazepines and nonbenzodiazepine hypnotics, zopiclone and zolpidem, are the most commonly prescribed drugs in the treatment of insomnia (Roth and Roehrs 1992). These drugs reduce sleep latency and increase total sleep time and sleep efficiency, but they alter sleep architecture (Lancel 1999). These hypnotics tend to reduce the time period spent in REM and increase the total amount of SWS, but all hypnotic drugs do not exhibit those effects (Kanno et al. 1993; Aeschbach et al. 1994; Feinberg et al. 2000; Kanno et al. 2000; Nakajima et al. 2000; Tan et al. 2003). In this regard, hypnotic agents could either improve or deteriorate the consolidation of memory that occurs during sleep. The memory consolidation improvement could be a consequence of an increase in sleep efficiency, while the negative effect could be a consequence of the reported altered sleep architecture.

Although it is well known that benzodiazepines produce anterograde amnesia (Ghoneim and Mewaldt 1990) and retrograde facilitation of memory (Ghoneim and Mewaldt 1990; Coenen and van Luijtelaar 1997), the effect of these hypnotic drugs on the memory process during sleep has not been sufficiently studied. Therefore in the present study we evaluated the effects of two short-acting hypnotic drugs —a benzodiazepine, triazolam, and a nonbenzodiazepine hypnotic, zolpidem—on memory storage during sleep in healthy volunteers. Both drugs have short half-life of approximately 2–3 h (Friedman et al. 1986; Greenblatt et al. 1998; Drover et al. 2000), but exhibit different selectivity for benzodiazepine receptors: while triazolam binds to type I and type II benzodiazepine receptors, zolpidem seems to bind with relative selectivity to type I benzodiazepine receptors (Byrnes et al. 1992; Itier et al. 1996; Sanna et al. 2002). However, the clinical consequences of the pharmacodynamic property of zolpidem have not been well established (Lobo and Greene 1997; Nowell et al. 1997).

To establish the effect of sleep on memory, we compared the declarative memory of subjects who slept with subjects who remained awake. A comparison group kept in wakefulness condition was also necessary to determine whether triazolam and zolpidem have different effects on memory storage during sleep or wakefulness. Subjects who slept received a nighttime dose of zolpidem, triazolam or placebo ("sleep condition"), while volunteers in "wakefulness condition" received a morning dose of the drugs or placebo, and remained awake during the entire day. We did not include a group of awake subjects during the night because sleep deprivation not only impairs memory consolidation but also affects other different cognitive performances that can also cause recall impairment (Harrison and Horne 1997, 1998; Drummond et al. 2000).

Declarative memory was evaluated by using a free-recall test of lists of standard words (common nouns) and nonwords. Recall of standard words has been used in the past to measure the effects of either drugs or sleep on declarative memory (Greenblatt et al. 1988; Mazzoni et al. 1999; Plihal et al. 1999; Silva et al. 2003). We included a nonword recall test to measure the subjects' memory of unamiliar materials having a minimal representation in long-term lexical knowledge (Hulme et al. 1991). Considering that these hypnotic drugs reportedly produce anterograde amnesia as a consequence of impairment in the ability to learn new information (Warot et al. 1987; Ghoneim and Mewaldt 1990; Berlin et al. 1993), subjects memorized the word and nonword lists 1 h before dosing and they were asked to remember them 10 h after dosing. Thus the effect of drugs on acquisition was excluded. We also applied the digit symbol substitution test (DSST) and the forward and backward digit tests to measure attention and short-term memory.

In summary, our aim was to demonstrate that triazolam and zolpidem could affect the memory improvement that occurs during sleep. This study may contribute to a better understanding of the mnemonic effects of hypnotic drugs during nocturnal sleep.

Materials and methods

Subjects

A total of 43 healthy young volunteers (20 men and 23 women, aged 18 to 25 years) participated in this study. The subjects were university undergraduate students; none had a history of medical disease, mental illness, drug abuse, sleep disturbance or pathological anxiety, as determined by physical examination (including measuring blood pressure and heart rate), a health questionnaire, and psychological evaluation. The Minnesota Multiphasic Personality Inventory (MMPI) adapted for the Chilean population (Risetti et al. 1989) and Rey–Osterrieth Complex Figure test (Osterrieth 1944) were also administered to exclude subjects with personality alteration and/or visuospatial memory dysfunction. All selected volunteers gave their written informed consent and were allowed to leave the trial at any time. The study was approved by the Ethics Committee of the University of Valparaíso.

None of the participants were receiving other medications, including contraceptives for women. Concurrent medication, tobacco, alcohol and caffeine containing drinks were prohibited on experimental days.

General procedures

According to a double-blind, randomized, three-way crossover design, on three different occasions each participant received a single oral dose of 10 mg zolpidem, 0.25 mg triazolam or placebo, with at least 1-week washout between treatments. The dosage forms were identically packaged in gelatin capsules and orally administered with water.

Subjects were informed that during their participation in the trial they would receive two different hypnotic drugs and a placebo. In addition to this general information, sub-

jects were blind to the type of drug administered. Subjects were told that the aim of the trial was to see how different drugs affect memory performance. Also, they were instructed to abstain from alcohol or caffeine-containing drinks, tobacco, and any other medications, 24 h before and 24 h after dosing.

One hour before dosing, subjects memorized the ten-word and seven-nonword lists. Also, we administered the digit forward and backward tests and DSST.

At 9 A.M., half of the volunteers (21) received a single dose of zolpidem, triazolam or placebo and they remained awake during the whole day ("wakefulness condition"). The other 22 volunteers received a single dose at 9 P.M. and slept for approximately 8 h ("sleep condition").

After dosing, the subjects who remained awake continued with their daily activities at the university, but they were always under supervision. These volunteers had a standard lunch in the University cafeteria. The subjects in "sleep condition" were taken to their homes by car. They were instructed to have a light dinner and then go to bed. They also were instructed to have a light breakfast for next morning.

All subjects were instructed to return to the laboratory 10 h after dosing for evaluations. Immediately upon arrival, subjects were required to answer a questionnaire. They had to answer how their sleep was, how many hours they slept and if they had complied with the instructions given.

After responding to the questionnaire, the subjects were asked to recall the words and nonwords memorized. In addition, they had to perform digit forward and backward tests and DSST again.

Tests

Digit forward and backward tests, adapted from Wechsler Adult Intelligence Scale (Wechsler 1988), essentially measure attention/concentration and short-term memory. A series of numbers were read to the subjects, who were then asked to repeat the entire series either forward or backward. The digits forward test consisted of number lists that progressively increased from three to nine digits. On the digits backward test, the numbers progressively increased from two to eight digits. The score is determined by the amount of numbers of the longest digit series remembered.

DSST adapted from Wechsler Adult Intelligence Scale (Wechsler 1988) consisted of matching symbols with numbers. The score was determined by the total number of correct responses completed in a 90-s test period.

Three versions of digit forward and backward tests and DSST were administered, one for each drug administration. However, the same version of the tests was used before and after the dosing of each drug. Subjects did not practice these tests before the trial.

The standard word recall test consisted of a list of ten standard words (two- to four-syllable common nouns from different semantic categories) that were verbally presented to the participants. The subjects were asked to repeat orally the words in any order until they were capable of memorizing the whole list. Ten hours after dosing, subjects were asked to recall as many words as possible from the list. The score was given on the number of correct words recalled.

The nonword recall test consisted of a list of 7 three-syllable nonwords without semantic meaning in English or Latin languages, taken from Condemarin and Blonquist (1970). Some examples of nonwords are ifjuti, alledo and renajto. The subjects were asked to repeat the nonwords verbally in any order until they were capable of memorizing the complete list. Ten hours after dosing, subjects were asked to recall as many nonwords as possible from the list. The score was determined by the number of correct nonwords recalled.

Three versions of word and nonword lists were used. Subjects did not practice these tests before the trial.

Statistical analysis

Statistical comparisons of the mean scores in the cognitive tests were made using linear mixed models, as described by Verbeke and Molenberghs (1997, 2000), Twisk (2003) and Dupont (2002). This statistical model is adequate for a three-way crossover design, in which each participant received triazolam, zolpidem and placebo on three different occasions (Dean and Voss 1999). The Wald test was used to check the significant dependence of the cognitive test scores on gender, wakefulness/sleep conditions, or drug treatments. The Wald test was also used to check the interaction between drug treatments and wakefulness/sleep conditions. The Bonferroni multiple comparison procedure with adjusted P values was used to check if the effects of triazolam, zolpidem or both, are different from that of the control group (placebo). The analysis was performed with the StataCorp (2003) statistical software.

Results

Twenty-one volunteers (11 women and ten men) were randomly assigned to a "wakefulness condition" and 22 volunteers were assigned to a "sleep condition" (11 women and 11 men). Both groups did not differ in age (19.5±0.38 and 19.8±0.35 years; P=0.62), education level (all them were college undergraduate students) and body mass index (22±0.6 and 21±0.5 kg/m^2; P=0.12). Volunteers in "sleep condition" slept for 7.5±0.3, 7.6±0.3 and 7.4±0.2 h after the dose of placebo, triazolam or zolpidem, respectively. Subjects in "wakefulness condition" slept for 7.3±0.3, 7.4±0.2, 7.2±0.2 h the day before the treatment with placebo, triazolam or zolpidem, respectively.

In the first evaluation, both groups had similar scores in digit forward and digit backward tests and DSST (P>0.05; Table 1). Statistical analysis showed that performance in these tests was independent of gender (P>0.05). Interestingly, linear mixed model analysis indicated that sleep improved both the DSST performance (P=0.002) and the nonword recall (P<0.0001). The performance in DSST 1 h before and 10 h after the administration of a placebo dos-

Table 1 Data show the performance on digit forward and digit backward tests and digit symbol substitution test (DSTT), in the first evaluation of subjects assigned to wakefulness or sleep condition group

	Wakefulness condition group	Sleep condition group	*P* value
Digit forward test	6.7±0.24	6.6±0.29	0.84
Digit backward test	4.9±0.25	5.4±0.25	0.26
DSST	59.1±1.9	60.8±1.4	0.44

Data are means±SE

Table 3 Recall of standard words and nonwords

	Number of words recalled	Number of nonwords recalled
Wakefulness condition		
Placebo	5.6±0.61	2.0±0.4
Sleep condition		
Placebo	6.6±0.46	3.2±0.33[a]
Triazolam	6.6±0.49	3.3±0.38
Zolpidem	6.6±0.46	3.6±0.32

Data shown are means±SE
[a]Linear mixed model analysis indicate that sleep improved the nonword recall ($P<0.0001$)

age to subjects of wakefulness and sleep condition groups is shown in Table 2. The word and nonword recall by subjects who remained awake or who slept after a placebo dosage is shown in Table 3.

Table 2 shows the performance in digit forward, digit backward tests and DSST of subjects who slept after the administration of a dose of triazolam, placebo or zolpidem in sleep condition. The tests were applied 1 h before and 10 h after dosing. Data analysis with the linear mixed model demonstrated that performances in these tests were independent of drug treatments ($P>0.05$).

Table 3 shows the recall of standard words and nonwords by subjects who slept after the administration of triazolam, placebo or zolpidem. Data analysis with the linear mixed model demonstrated that recall of both words and nonwords was not dependent on drug treatments ($P>0.05$).

In agreement with previous results of Greenblatt et al. (2000), we observed no effects of triazolam and zolpidem on the performance of digit forward and digit backward tests and DSST 10 h after dosing in subjects of wakefulness condition. Also, the drugs did not affect the recall of word and nonword lists (data not shown).

Table 2 Data (means±SE) show the performance of subjects on digit forward and digit backward tests and DSST 1 h before and 10 h after dosing

	Digit forward test	Digit backward test	DSST
Wakefulness condition			
Placebo			
Before dosing	6.8±0.28	5.3±0.30	60.3±1.9
10 h after dosing	6.4±0.40	5.4±0.43	64.3±1.9
Sleep condition			
Placebo			
Before dosing	6.8±0.25	5.5±0.22	61.4±2.2
10 h after dosing	7.1±0.32	5.4±0.28	70.1±1.9[a]
Triazolam			
Before dosing	7.0±0.25	5.3±0.22	63.8±2.0
10 h after dosing	6.9±0.28	5.6±0.33	69.3±2.2
Zolpidem			
Before dosing	6.7±0.27	5.1±0.27	61.5±1.7
10 h after dosing	6.9±0.26	5.5±0.23	70.5±2.0

[a]Linear mixed model analysis indicate that sleep improved the subjects' DSST performance ($P=0.002$)

Discussion

The main finding of this paper is that neither triazolam nor zolpidem affected the sleep-induced memory improvement of nonword recall.

It is noteworthy that the statistical analysis of our results showed that sleep improved the recall of nonwords, but it did not significantly increase the recall of standard words. Contrary to standard words, nonwords have minimal long-term lexical representations (Hulme et al. 1991, 1995; Saint-Aubin and Poirier 2000). Jenkins and Dallenbach (1924) demonstrated for the first time that sleep enhanced the recall of nonwords, suggesting that sleep plays an important role in the consolidation process of unfamiliar information. More recently, Stickgold (1998) proposed that sleep can integrate new information into associative networks. In particular, REM sleep, which is characterized by hyperassociative dreams, seems to enhance the activation of weak association (Stickgold et al. 1999). In this regard, it is tempting to speculate that weak associations of the nonwords with long-term semantic memory would be strengthened during sleep, improving the recall of nonwords in the morning. The recall of standard words, which have representations in the long-term lexical knowledge, would be less affected by sleep.

As previously mentioned, one of our hypothesis was that hypnotic agents could deteriorate the memory improvement induced by sleep as a consequence of the reported alteration of sleep architecture caused by hypnotics. To test this hypothesis, we designed a protocol that excluded the sedative and anterograde amnesia effects of these drugs: (1) subjects memorized the word and nonword lists before dosing (therefore the drugs' effect on acquisition was excluded); (2) subjects were asked to recall the memorized lists 10 h after dosing, when the plasma levels of both triazolam and zolpidem are reportedly minimum and their sedative effects are indistinguishable from those of placebo (Greenblatt et al. 2000). Thus, in accordance with the results of Greenblatt et al. (2000), our results show that 10 h after dosing the performance in the digit tests are not

significantly different from that of the placebo, by both sleep and wakefulness condition groups.

Under the experimental conditions used in this paper, we observed that the sleep-induced improvement of the nonword recall was not affected by both zolpidem and triazolam. Our results also showed that neither zolpidem nor triazolam affected the recall of standard words. Thus, these findings suggest that the effects of these hypnotic agents on sleep architecture are not sufficient to impair the sleep-induced memory improvement. In this regard, it was reported that both triazolam and zolpidem reduce delta activity and increase sigma and beta activity during non-REM sleep, but they do not significantly affect the total REM sleep time (Feinberg et al. 2000).

Data analysis with the linear mixed model showed that sleep improved the performance of DSST. Since this test assesses psychomotor performance and visual perception (Friedman et al. 1992), improvement in the DSST performance after sleep could be a consequence of the reported sleep-dependent consolidation of visuomotor skill learning (Maquet et al. 2003), which depends on both SWS and REM stages (Stickgold et al. 2000b; Mednick et al. 2003). However, it must be mentioned that DSST is a multifactorial test that also measures other cognitive abilities like attention, concentration and focus (Friedman et al. 1992).

Statistical analysis of DSST scores showed no interaction between wakefulness/sleep conditions and drug treatments, suggesting that the sleep-induced improvement of DSST performance was not affected by either zolpidem or triazolam. However, additional studies, featuring more selective paradigms, are required to determine the effect of hypnotic agents on the sleep-induced improvement of procedural memory.

We cannot discard a possible circadian influence on memory improvement for the subjects who slept. In fact, although daytime sleep can be as efficient as nocturnal sleep in improving memory (Mednick et al. 2003), some authors have proposed that the effect of sleep on memory consolidation (Nesca and Koulack 1994; Koulack 1997) and learning (Cajochen et al. 2004) may be partially due to circadian rhythms.

In summary, zolpidem and triazolam do not seem to alter the effect of nocturnal sleep on memories, since they did not affect the improvement on nonword recall and DSST performance. These findings could be of clinical relevance, considering that these drugs are administered in the treatment of insomnia. Sleep disorders such as insomnia could have a deleterious effect on memory consolidation. Therefore the use of drugs that improve sleep efficiency could prevent cognition impairments in insomniac subjects. This could be particularly advantageous for short-acting hypnotics that do not exhibit hangover effects. Nevertheless, the present results do not establish that neither triazolam nor zolpidem influence other type of memory processes during sleep. Since cognition during sleep is qualitatively distinct from that of wakefulness (Stickgold 1998), additional clinical studies are necessary to know more about other mnemonic effects of hypnotics agents during sleep.

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