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Effect of chronic treatment with milnacipran on sleep architecture in rats compared with paroxetine and imipramine

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Abstract

A number of studies in humans and various other species have shown that chronic treatment with antidepressants, such as tricyclics or selective serotonin reuptake inhibitors (SSRIs), induces a decrease or suppression of rapid eye movement (REM) sleep. The effect of a new selective serotonin and noradrenaline reuptake inhibiting (SNRI) antidepressant, milnacipran, on REM sleep has been investigated and compared with that of the SSRI, paroxetine, and the tricyclic, imipramine. Rats injected with vehicle or milnacipran twice a day showed, over 24 h, a similar amount of REM sleep, number and duration of REM sleep episodes to control rats. In contrast, rats treated acutely with imipramine or paroxetine showed a statistically significant decrease in the total quantity of REM sleep. The number of REM sleep episodes was decreased while their duration was increased. A more detailed analysis showed further that the quantity of REM sleep was decreased for the first 4 h following the 9 a.m. injection but not the 7 p.m. injection for milnacipran, during the first 6 h for paroxetine and for the entire light–dark period for imipramine. For all drugs, the quantities of slow-wave sleep and waking over 24 h were not significantly different from control conditions and no rebound of REM sleep occurred during the day following withdrawal. Power spectrum analysis revealed no global changes in the different electroencephalogram (EEG) waves (delta, theta, gamma) between the control condition and the different treatments during waking, slow-wave sleep or REM sleep. Taken together our results indicate that the SNRI, milnacipran, at therapeutic doses, induces only minor disturbances of REM sleep compared with a SSRI and tricyclic antidepressant used. Possible mechanisms responsible for the difference of action on REM sleep of milnacipran are discussed.

Keywords: Wakefulness; Slow-wave sleep; REM sleep; Milnacipran; Paroxetine; Imipramine; Rats; Chronic treatments; Frontal and occipital cortices

1. Introduction

A large body of work suggests a strong relationship between the psychopathology of depression and the regulation of sleep. Indeed, in depressed patients the first phase of rapid eye movement (REM) sleep following sleep onset is delayed (increased latency of REM sleep) (Kupfer, 1976; Gillin et al., 1979; Vogel et al., 1980). Depressed patients also display an increased frequency of rapid eye movements during REM sleep (Vogel et al., 1980, 1990) and low amounts of Stage 3 and 4 of slow-wave sleep (Gillin et al., 1979). Further, selective REM sleep or total sleep deprivation has strong antidepressant effects (Vogel et al., 1980; Wu and Bunney, 1990). In addition, most antidepressant drugs induce sleep modifications in animals (Hilakivi et al., 1987) and humans (Nicholson and Pascoe, 1986). In depressed patients or healthy volunteers, treatment with tricyclic antidepressants (TCA), such as imipramine (Jobert et al., 1999; Sonntag et al., 1996; Yamadera et al., 1998), or selective serotonin reuptake inhibitors (SSRIs), such as paroxetine (Schlosser et al., 1998), fluoxetine (Trivedi et al., 1999) or zimelidine (Nicholson and Pascoe, 1986) induces a loss or a strong decrease in the amount of REM sleep. Treatment with selective noradrenaline reuptake inhibitors such as Org 4428 (van Bemmel et al., 1999) also induces a strong decrease in the quantity of REM sleep. A major decrease in the amount of REM sleep was also seen under chronic treatment with these drugs and a rebound was observed after withdrawal from fluoxetine (Trivedi et al., 1999) and paroxetine (Staner et al., 1995). In rats and cats, acute and chronic treatments with TCA, such as imipramine (Hill et al., 1980), amitryptiline (Obal et al., 1985) or SSRIs, such as zimelidine (Sommerfelt, 1990), alaproclate (Sommerfelt and Ursin, 1991), citalopram (Neckelmann et al.,

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1996), cericlamine (Maudhuit et al., 1994), indalpine (Kafi de Saint Hilaire et al., 1984), fluoxetine (Pastel and Fernstrom, 1987) or paroxetine (Kleinlogel and Burki, 1987) induced a sustained decrease in REM sleep during the whole treatment period. In addition, a rebound of REM sleep was observed on the first day following indalpine, zimelidine and cericlamine withdrawal (Kafi de Saint Hilaire et al., 1984; Sommerfelt, 1990; Maudhuit et al., 1994). Both in humans and animals, the effect on slow-wave sleep and waking was not consistent, some authors reporting an increase and others a decrease in slow-wave sleep.

Recently, a new class of antidepressants that block the serotonin and the noradrenaline reuptake (SNRI) without side effects have been introduced (see the review of Feeney and Nutt, 1999). Venlafaxine, which inhibits uptake of 5-HT, noradrenaline and dopamine (in decreasing order of potency), has been shown to decrease REM sleep in rats (Salin-Pascual and Moro-Lopez, 1997). In normal volunteers this compound reduced REM sleep time after the first dose and, by the fourth night, REM sleep was completely suppressed (Salin-Pascual et al., 1997). Venlafaxine induced an increase in the onset latency of REM sleep and a decrease in total REM sleep duration in patients with major depression (Luthringer et al., 1996). A newer substance, milnacipran, which blocks the two reuptake systems equally (Moret et al., 1985) and has recently been introduced in France, Japan and elsewhere as an antidepressant (Puech et al., 1997), is also a representative of this type of compound. In addition, milnacipran is characterized by an absence of affinity for the receptors, such as histamine H_1 and muscarinic receptors, and α_1-adrenoceptors, responsible for the adverse effects of TCAs (Moret et al., 1985). The aim of the experiments reported here was therefore to study in rats the effect on sleep of acute and chronic treatment of milnacipran in comparison with that of the SSRI, paroxetine, and the TCA, imipramine. Clinically milnacipran is used at 100 mg/day, paroxetine at 20–40 mg/day and imipramine at 120–150 mg/day. The doses used in this study (30, 10 and 20 mg/kg per day, respectively) were chosen to represent the same ratio between the compounds. In fact, it was not possible to give the full dose of imipramine (40–50 mg/kg per day) for reasons of toxicity.

2. General method

2.1. Animals

Male OFA rats weighing 300–340 g were implanted under pentobarbital (60 mg/kg ip) with electrodes for polygraphic sleep monitoring. Three stainless steel screws were placed on the surface of the dura mater at the level of the frontal and occipital cortices (electroencephalographic [EEG] electrodes). Three stainless wires were inserted into the neck muscles (electromyographic [EMG] electrodes). The electrodes were secured to the skull using dental acrylic cement and were soldered to a connector, also cemented to the skull. After completion of the surgery, the scalp was sutured and the animals were allowed 9 days for recovery and habituation to the experimental conditions. Rats were housed individually in a Plexiglas jar placed in a soundproof recording box and maintained under standard laboratory conditions: 12–12 h light–dark cycle with light on at 5 a.m., 22–24 °C ambient temperature, food pellets (Extra Labo, Lyon, France) and water ad libitum. All animals were housed and handled according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1985).

2.2. Recordings

The animals were connected to a rotating recording cable, allowing free movements in the jar. Control recordings were performed during 24 h. On the next 2 days, the animals were injected twice daily at 9 a.m. and 7 p.m. with the vehicle and recorded. They were then recorded on Days 1, 2 and 21 during treatment with vehicle, milnacipran, paroxetine or imipramine. They were finally recorded on Day 22, the withdrawal day.

The states of vigilance were scored visually from polygraphic recordings stored with "Spike 2" software (CED, Cambridge, UK). Every 10-s period was classified as wakefulness, slow-wave sleep or paradoxical sleep, according to the usual criteria (Gonzalez et al., 1996). The hypnograms were drawn directly in the Spike 2 file using a custom script. The values were then exported to Microsoft Excel to calculate the amounts of each vigilance state. Statistical significance of the effects of treatments was assessed by analysis of variance (ANOVA) and post hoc Fisher test ($P < .05$ as a level of significance).

2.3. Pharmacological treatments

Milnacipran, (Pierre Fabre Médicament, Castres, France), paroxetine (synthetised by Pierre Fabre Médicament), and imipramine (Sigma, St. Louis, MO) were dissolved in dimethyl sulfoxide then diluted in NaCl 0.9%. Injection of 1 ml/kg of the vehicle was performed intraperitoneally (ip) at 9 a.m. and 7 p.m. during 2 baseline days. Then, milnacipran (15 mg/kg, $n = 6$), paroxetine (5 mg/kg, $n = 5$), imipramine (10 mg/kg, $n = 4$) or vehicle ($n = 6$) were injected at 9 a.m. and 7 p.m. for 21 days. On the withdrawal day, no injection was given.

3. Results

3.1. Symptomatology and weight

Following acute and chronic treatment with milnacipran, the animals presented no abnormal behaviour as compared with vehicle. In contrast, animals treated with paroxetine or

Table 1
Weight of the animals on the day of implantation and the first and last days (21) of treatment

Day	Weight (g)			
	Control ($n=6$)	Milnacipran ($n=6$)	Paroxetine ($n=5$)	Imipramine ($n=4$)
Implantation	315.5 ± 8.8	314.5 ± 8.7	317.5 ± 9.8	324.0 ± 8.5
1	346.5 ± 7.6 *	332.5 ± 12.8	342.0 ± 10.3	345.0 ± 6.2
21	407.5 ± 5.4* * *	365.5 ± 13.3 * *	360.5 ± 20.3	354.5 ± 10.8

Values represent means ± S.E.M.

* $P<.05$ when compared with the weight at the time of the implantation.

** $P<.01$ when compared with the weight at the time of the implantation.

*** $P<.001$ when compared with the weight at the time of the implantation.

imipramine were hyporeactive and unresponsive after 2 days of treatment and remained so for the entire treatment. Rats injected with vehicle significantly gained weight during the treatment. Rats treated with milnacipran also gained weight but to a lesser extent. In contrast, rats treated with paroxetine or imipramine failed to gain weight during the 21-day treatment (Table 1).

3.2. REM sleep

3.2.1. Amount of REM sleep

Under control conditions, the rats had 121.9 ± 20.5 min (mean ± S.E.M.) of REM sleep per 24 h, 78.0 ± 2.1 min during the light period and 30.3 ± 1.1 min during the dark period. Acute or chronic injections of the vehicle or milnacipran did not induce a significant change in the amount of REM sleep per 24 h (Fig. 1). In contrast, acute treatment with paroxetine and imipramine induced, respectively, significant decreases of 29–34% ($P<.01$) and 61–70% ($P<.001$) in the amount of REM sleep per 24 h compared with vehicle injections (Fig. 1). On Day 21 of treatment, only imipramine continued to produce a significant (62%) decrease in the amount of REM sleep. Paroxetine treatment tended to produce a reduction in REM sleep but this was not significant. On Day 22, after drug discontinuation, the

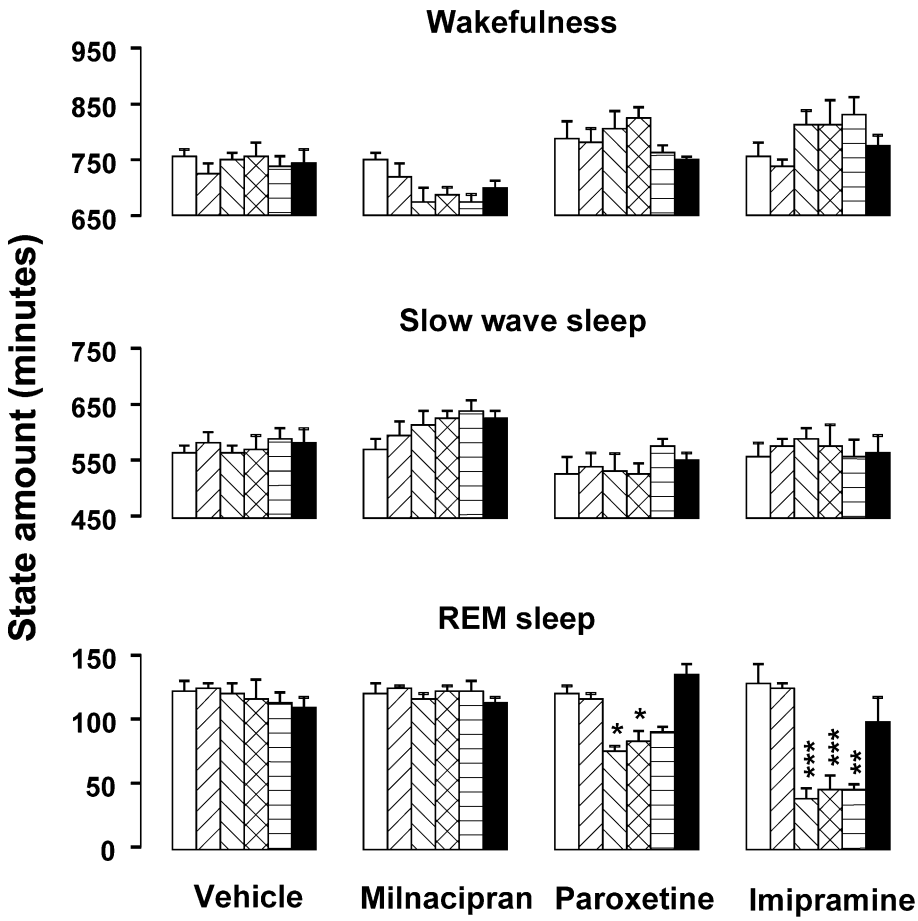

Fig. 1. Amount of wakefulness, slow-wave sleep and REM sleep per 24 h in animals treated ip with vehicle, milnacipran (15 mg/kg), paroxetine (5 mg/kg) or imipramine (10 mg/kg) twice a day (9 a.m. and 7 p.m.) acutely (Day 1), subacutely (Day 2), chronically (Day 21) and during withdrawal (Day 22). The comparisons were made with the vehicle injections. Data (means ± S.E.M.) are expressed in minutes. * $P<.05$, * * $P<.01$, * * * $P<.001$ when compared with vehicle. Open bars: control. Hatched bars (bottom left to top right): vehicle. Hatched bars (top left to bottom right): Day 1 (acute). Cross-hatched bars: Day 2. Horizontal hatched bars: Day 21 (chronic). Filled bars: Day 22 (withdrawal).

amount of REM sleep for all rats was not statistically different from that of the control days with vehicle injections or without injections (Fig. 1).

Injections at the beginning of the dark cycle (7 p.m.) of milnacipran or paroxetine but not imipramine were not followed by a significant change in the amount of REM sleep (data not shown). In contrast, all drug injections at the beginning of the light cycle (9 am) induced a decrease in the amount of REM sleep compared with vehicle with a duration depending on the drug injected (Fig. 2). Vehicle injection at 9 a.m. induced, on the first day only, a significant reduction in the amount of the REM sleep during the first 2 h compared with noninjected rats (data not shown). Injections of milnacipran, paroxetine and imipramine resulted in a significant decrease in the amount of REM sleep during acute and chronic treatment (40–50%, 65–85%, 75–95%, respectively) during the first 4 h period following the 9 a.m. injection (Fig. 2). In the case of paroxetine, the decrease in REM sleep continued for the first 6 h following the 9 a.m. injection while in the case of imipramine the decrease lasted for the entire light–dark period. Only in the case of milnacipran was the deficit in REM sleep compensated for by a nonsignificant increase in the amount of REM sleep during the period from 4 to 6 h after the 9 a.m. injection.

3.2.2. Number and duration of REM sleep episodes

Acute or chronic injections of vehicle or milnacipran caused no significant change in the number or duration of the REM sleep episodes (Table 2). Acute and chronic treatment with paroxetine or imipramine were followed by a strong decrease in the number of REM sleep episodes per 24 h compared with vehicle injections (Table 2). In addition, acute treatment with paroxetine and chronic treatment with paroxetine or imipramine induced a significant increase in the duration of the REM sleep episodes compared with vehicle injections (Table 2). During the withdrawal day, the number and the duration of the REM sleep episodes returned to a normal value in the case of paroxetine whereas, in the case of imipramine-treated rats, the recovery in the number of episodes and the duration of REM phases was only partial (Table 2).

Following the 9 a.m. and 7 p.m. acute or chronic injections of vehicle or milnacipran, the latency of the first

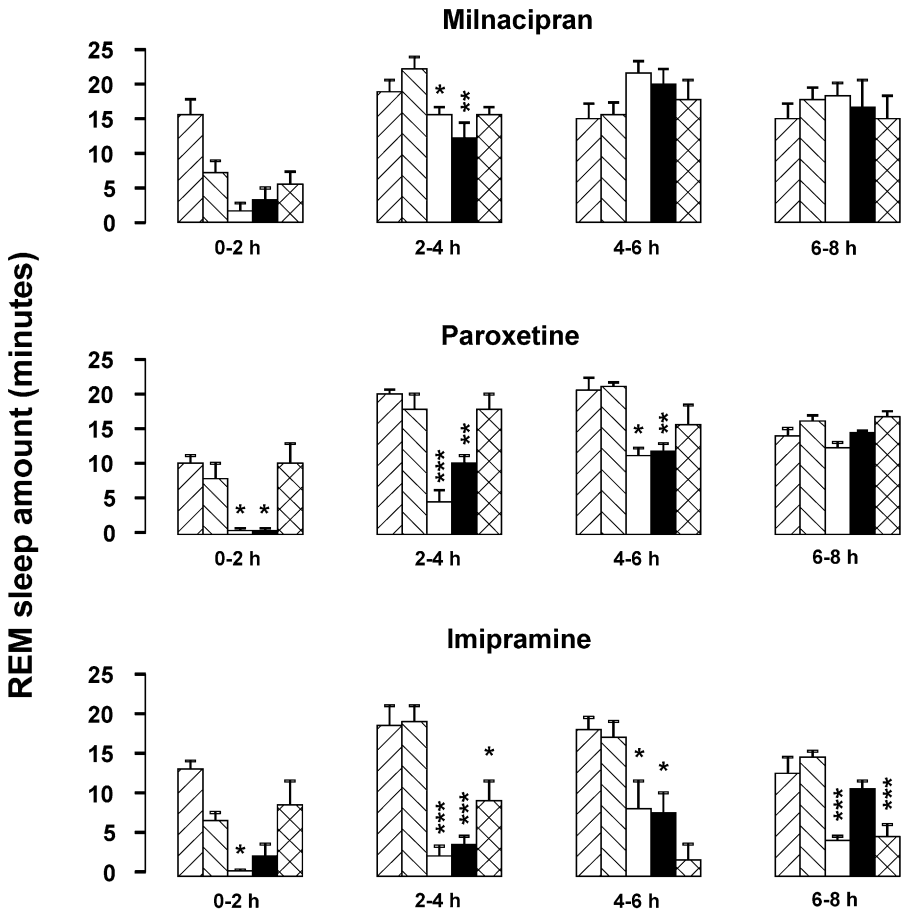

Fig. 2. Amount of REM sleep per 2-h periods following the 9 a.m. ip injection of vehicle, milnacipran (15 mg/kg, $n=6$), paroxetine (5 mg/kg, $n=5$) or imipramine (10 mg/kg, $n=4$) acutely (Day 1), chronically (Day 21) or during withdrawal (Day 22). The comparisons were made with the vehicle injections. Data (means ± S.E.M.) are expressed in minutes. $*P<.05$, $**P<.01$, $***P<.001$ when compared with vehicle. Hatched bars (bottom left to top right): control. Hatched bars (top left to bottom right): vehicle. Open bars: Day 1 (acute). Filled bars: Day 21 (chronic). Cross-hatched bars: Day 22 (withdrawal).

Table 2
Characteristics of REM sleep episodes (number, duration and latency following the injections) induced by the different treatments

Treatment	REM sleep			
	Number per 24 h	Mean duration (min)	Mean latency 9 a.m. (min)	Mean latency 7 p.m. (min)
Vehicle (n = 6)				
Vehicle	90.2 ± 5.7	1.4 ± 0.1	66.2 ± 11.4	70.9 ± 11.7
1	88.7 ± 6.3	1.4 ± 0.0	61.6 ± 6.1	92.7 ± 26.9
21	84.7 ± 6.7	1.4 ± 0.1	39.0 ± 11.1	130.4 ± 10.9
22	84.7 ± 9.5	1.3 ± 0.1	38.3 ± 7.9	116.1 ± 24.9
Milnacipran (n = 6)				
Vehicle	97.0 ± 4.7	1.3 ± 0.1	73.5 ± 12.4	77.2 ± 8.0
1	91.0 ± 5.9	1.3 ± 0.0	109.2 ± 12.5	158.2 ± 14.0
21	99.5 ± 2.8	1.2 ± 0.1	83.3 ± 24.4	137.5 ± 29.5
22	99.7 ± 10.6	1.2 ± 0.1	52.1 ± 20.4	121.3 ± 31.8
Paroxetine (n = 5)				
Vehicle	85.6 ± 7.6	1.4 ± 0.1	66.7 ± 19.1	136.6 ± 26.7
1	39.0 ± 4.6 **	2.0 ± 0.2 **	130.8 ± 33.0	305.3 ± 48.4 *
21	46.4 ± 3.5 **	2.0 ± 0.2 **	123.0 ± 16.4	209.6 ± 32.2
22	91.8 ± 5.7	1.5 ± 0.0	62.6 ± 16.8	106.7 ± 61.8
Imipramine (n = 4)				
Vehicle	97.8 ± 18.3	1.5 ± 0.2	66.1 ± 10.4	65.0 ± 8.1
1	24.8 ± 5.3***	1.6 ± 0.2	148.2 ± 50.2 *	315.0 ± 131.0 **
21	25.5 ± 5.9***	2.1 ± 0.2 **	159.0 ± 69.0 *	186.3 ± 62.8
22	49.5 ± 11.1 **	2.0 ± 0.1 **	102.6 ± 56.3	122.5 ± 73.8

Values represent means ± S.E.M.
* $P < .05$ when compared with vehicle injections.
** $P < .01$ when compared with vehicle injections.
*** $P < .001$ when compared with vehicle injections.

REM sleep period was not significantly modified (Table 2). In contrast, following imipramine, the latency of REM sleep was increased and became highly variable following 9 a.m. and 7 p.m. injections in acute and chronic conditions compared with vehicle injections. For paroxetine, the latency of REM sleep tended to be longer in acute and chronic conditions for injections at 9 a.m. and 7 p.m., but was significant only on the second day of injection (178.1 ± 36.3 min for the 9 a.m. injection and 455.3 ± 186.1 min for the 7 p.m. injection) compared with vehicle (66.7 ± 19.1 min). As with imipramine, the latency of REM sleep was more variable under paroxetine than under control conditions.

3.3. Slow-wave sleep and waking

No changes in the amount of wakefulness and slow-wave sleep per 24 h were observed in rats treated with milnacipran, paroxetine or imipramine compared with vehicle-treated animals. A more detailed analysis, 2 h per 2 h revealed no significant macroscopic change in the quantities of waking and slow-wave sleep.

3.3.1. Power spectrum analysis

Following acute treatment with milnacipran, paroxetine or imipramine, there was no significant effect on the mean EEG power spectrum analyzed between 11 a.m. and 1 p.m. during waking, slow-wave sleep REM sleep phases.

Following chronic treatment (Day 21) with vehicle, milnacipran, paroxetine or imipramine, the mean power density during all the vigilance states was reduced across all the frequency bands compared with the control vehicle injections done at the beginning of the experiments. No other changes were noted during waking, slow-wave sleep and paradoxical sleep for the different bands of the EEG power spectrum.

4. Discussion

In this study the three antidepressants investigated had different effects on REM sleep. Milnacipran decreased the amount of REM sleep only during the first 4 h following the 9 a.m. injections with a recovery during the subsequent 4-h period. There was thus no modification in the total amount of REM sleep per 24 h. Paroxetine strongly diminished REM sleep during the first 6 h only following the morning injection with a partial recovery under chronic condition. Finally, imipramine induced a drastic decrease in the quantity of REM sleep and the number of REM sleep episodes during the entire light–dark period under acute and chronic conditions.

In agreement with the present results, a decrease in the amount of REM sleep has been found in rats treated with the same doses of paroxetine (Kleinlogel and Burki, 1987) or imipramine (Khazan and Brown, 1970; Hill et al., 1980) as used here. In addition, we found that paroxetine and imipramine treatments induced an increase of the duration of the REM sleep episodes. To our knowledge, this effect has not been reported before.

A decrease in the amount of REM sleep and an increase in the latency of REM sleep have been observed in patients or healthy volunteers treated with paroxetine (Roschke et al., 1997; Sharpley et al., 1996; Schlosser et al., 1998; Staner et al., 1995) or imipramine (Sonntag et al., 1996; Jobert et al., 1999; Yamadera et al., 1998). The effect of withdrawal has been studied only in one study with paroxetine (Staner et al., 1995). These authors found that the withdrawal values were not different from the baseline values for any of the variables tested except the latency of REM sleep that was still significantly decreased after withdrawal.

In the present study, paroxetine induced only a slight nonsignificant increase of the total amount of waking per 24 h. Treatment with paroxetine in rats has also been reported to increase waking and decrease slow-wave sleep (Kleinlogel and Burki, 1987). Subchronic treatment with paroxetine in healthy male volunteers or in patients induced no change in the total sleep time, sleep onset latency and spectral power values (Schlosser et al., 1998; Roschke et al., 1997) or decrease in sleep time (Sharpley et al., 1996). In agreement with our results, imipramine treatment in patients

induced no effect on the slow-wave sleep (Sonntag et al., 1996). In contrast, imipramine treatment in healthy subjects has been reported to increase Stage 1 or 2 sleep (Yamadera et al., 1998).

In contrast to paroxetine and imipramine, acute and chronic administration of milnacipran, at therapeutically equiactive doses, did not induce any major changes in the amount of REM sleep. The absence of effect of milnacipran on REM sleep at the dose investigated (15 mg/kg ip) can be contrasted with the clear effects of milnacipran in a similar dose range in two behavioral models of depression in the rat, learned helplessness (Lacroix et al., 1995) and olfactory bulbectomy (Redmond et al., 1999), whereas unpublished pharmacokinetic data (Autorisation de Mise sur le Marché MR134er, Part III, 1996) suggest good bioavailability with a half-life of approximately 2 h in the same species. Milnacipran, in the same dose range, increases extracellular levels of noradrenaline and serotonin (Moret and Briley, 1997). Furthermore, it blocks the serotonin and noradrenaline reuptake systems equally while having no direct effect on receptors (Moret et al., 1985). The absence of a strong disruption of REM sleep might therefore be due to the fact that milnacipran does not disturb the balance of serotonergic and noradrenergic activity in contrast to the SSRIs or selective noradrenaline reuptake inhibitors. Indeed, as with the SSRIs, treatment with a selective noradrenaline reuptake inhibitor in healthy volunteers has been reported to produce a strong decrease in the amount of REM sleep (Nicholson and Pascoe, 1986; van Bemmel et al., 1999). Treatment with TCAs that, like milnacipran, block the serotonin and noradrenaline reuptake systems, also induces a strong decrease in the amount of REM sleep. However, TCAs have an antimuscarinic effect that might be implicated in the modification of REM sleep. Indeed, it is well accepted that established activation of cholinergic neurons results in the appearance of REM sleep and its maintenance (Jouvet, 1972; Sakai, 1988). The administration of physostigmine, a cholinesterase inhibitor, together with imipramine, blocks the effect of imipramine on the latency of REM sleep (Hill et al., 1980). In contrast to milnacipran, which does not modify the total amount of REM sleep, venlafaxine has been shown to produce several sleep disturbances in rats (Salin-Pascual and Moro-Lopez, 1997), in normal volunteers (Salin-Pascual et al., 1997) and in patients suffering from depression (Luthringer et al., 1996), therefore showing a sleep profile comparable with that of most classical antidepressants. A possible difference between the effects of milnacipran and venlafaxine may reside in the fact that venlafaxine exerts more marked effects on serotonin reuptake (Briley and Moret, 1997; Melichar et al., 2001; Millan et al., 2001a,b) whereas milnacipran shows an equipotent inhibitory action on 5-HT and noradrenaline reuptake (Moret et al., 1985).

In conclusion, in contrast to paroxetine and imipramine, acute or chronic administration of the SNRI milnacipran induces little or no effect on the overall architecture of sleep. The lack of anticholinergic activity and a balanced activity on serotonergic and noradrenergic neurotransmission are plausible hypotheses for this lack of sleep disturbance.

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References

Briley M, Moret C. Antidepressant properties of specific serotonin–noradrenaline reuptake inhibitors. In: Skolnick P, editor. Antidepressants: new pharmacological strategies. Totowa (NJ): Humana Press, 1997. pp. 35–52.

Feeney A, Nutt DJ. The neuropharmacology of serotonin and noradrenaline in depression. Int J Psychiatry Clin Pract 1999;3:S3–8.

Gillin JC, Duncan W, Pettigrew KD, Frankel BL, Snyder F. Successful separation of depressed, normal, and insomniac subjects by EEG sleep data. Arch Gen Psychiatry 1979;36:85–90.

Gonzalez MM, Valatx JL, Debilly G. Role of the locus coeruleus in the sleep rebound following two different sleep deprivation methods in the rat. Brain Res 1996;740:215–26.

Hilakivi I, Kovala T, Leppavuori A, Shvaloff A. Effects of serotonin and noradrenaline uptake blockers on wakefulness and sleep in cats. Pharmacol Toxicol 1987;60:161–6.

Hill SY, Reyes RB, Kupfer DJ. Imipramine and REM sleep: cholinergic mediation in animals. Psychopharmacology 1980;69:5–9.

Jobert M, Jahnig P, Schulz H. Effect of two antidepressant drugs on REM sleep and EMG activity during sleep. Neuropsychobiology 1999;39:101–9.

Jouvet M. The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep–waking cycle. Ergeb Physiol Biol Chem Exp Pharmakol 1972;64:166–307.

Kafi de Saint Hilaire S, Merica H, Gaillard JM. The effects of indalpine—a selective inhibitor of 5-HT uptake—on rat paradoxical sleep. Eur J Pharmacol 1984;98:413–8.

Khazan N, Brown P. Differential effects of three tricyclic antidepressants on sleep and REM sleep in the rat. Life Sci 1970;1:279–84.

Kleinlogel H, Burki HR. Effects of the selective 5-hydroxytryptamine uptake inhibitors paroxetine and zimeldine on EEG sleep and waking stages in the rat. Neuropsychobiology 1987;17:206–12.

Kupfer DJ. REM latency: a psychobiologic marker for primary depressive disease. Biol Psychiatry 1976;11:159–74.

Lacroix P, Rocher N, Gandon JM, Panconi E. Antidepressant effects of milnacipran in the learned helplessness test in rats. Eur Psychopharmacology 1995;5(Suppl 3):2–8.

Luthringer R, Toussaint M, Schaltenbrand N, Bailey P, Danjou PH, Hackett D, Guichoux JY, Macher JP. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression. Pyschopharmacol Bull 1996;32:637–46.

Maudhuit C, Jolas T, Lainey E, Hamon M, Adrien J. Effects of acute and chronic treatment with amoxapine and cericlamine on the sleep–wakefulness cycle in the rat. Neuropharmacology 1994;33:1017–25.

Melichar JK, Haida A, Rhodes C, Reynolds AH, Nutt DJ, Malizia AL. Venlafaxine occupation at the noradrenaline reuptake site: in-vivo determination in healthy volunteers. J Psychopharmacol 2001;15:9–12.

Millan MJ, Gobert A, Lejeune F, Newman-Tancredi A, Rivet JM, Auclair A, Peglion JL. S33005, a novel ligand at both serotonin and norepinephrine transporters: I. Receptor binding, electrophysiological, and neurochemical profile in comparison with venlafaxine, reboxetine,

citalopram, and clomipramine. J Pharmacol Exp Ther 2001a;298: 565–80.

Millan MJ, Dekeyne A, Papp M, La Rochelle CD, MacSweeny C, Peglion JL, Brocco M. S33005, a novel ligand at both serotonin and norepinephrine transporters: II. Behavioral profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine. J Pharmacol Exp Ther 2001b;298:581–91.

Moret C, Briley M. Effects of milnacipran and pindolol on extracellular noradrenalin and serotonin levels in guinea pig hypothalamus. J Neurochem 1997;69:815–22.

Moret C, Charveron M, Finberg JP, Couzinier JP, Briley M. Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug. Neuropharmacology 1985;24: 1211–9.

Neckelmann D, Bjorvatn B, Bjorkum AA, Ursin R. Citalopram: differential sleep/wake and EEG power spectrum effects after single dose and chronic administration. Behav Brain Res 1996;79:183–92.

Nicholson AN, Pascoe PA. 5-Hydroxytryptamine and noradrenaline uptake inhibition: studies on sleep in man. Neuropharmacology 1986;25: 1079–83.

Obal F, Benedek G, Lelkes Z, Obal F. Effects of acute and chronic treatment with amitryptyline on the sleep–wake activity of rats. Neuropharmacology 1985;24:223–9.

Pastel RH, Fernstrom JD. Short-term effects of fluoxetine and trifluoromethylphenylpiperazine on electroencephalographic sleep in the rat. Brain Res 1987;436:92–102.

Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: an overview of its antidepressant activity and clinical tolerability. Int Clin Psychopharmacol 1997;12:99–108.

Redmond AM, Kelly JP, Leonard BE. The determination of the optimal dose of milnacipran in the olfactory bulbectomised rat model of depression. Pharmacol Biochem Behav 1999;62:619–23.

Roschke J, Kogel P, Schlosser R, Wagner P, Mann K, Rossbach W, Benkert O. Analysis of sleep EEG microstructure in subchronic paroxetine treatment of healthy subjects. Psychopharmacology 1997;132:44–9.

Sakai K. Executive mechanisms of paradoxical sleep. Arch Ital Biol 1988; 126:239–57.

Salin-Pascual RJ, Moro-Lopez ML. Effects of venlafaxine in the sleep architecture of rats. Psychopharmacology 1997;129:295–6.

Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry 1997;58:348–50.

Schlosser R, Roschke J, Rossbach W, Benkert O. Conventional and spectral power analysis of all-night sleep EEG after subchronic treatment with paroxetine in healthy male volunteers. Eur Neuropsychopharmacol 1998;8:273–8.

Sharpley AL, Williamson DJ, Attenburrow ME, Pearson G, Sargent P, Cowen PJ. The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. Psychopharmacology 1996;126:50–4.

Sommerfelt L. Chronic zimeldine administration to cats: sustained increase of serotonergic effect as measured with sleep parameters. Pharmacol Toxicol 1990;66:128–32.

Sommerfelt L, Ursin R. Behavioral, sleep–waking and EEG power spectral effects following the two specific 5-HT uptake inhibitors zimeldine and alaproclate in cats. Brain Behav Res 1991;45:105–15.

Sonntag A, Rothe B, Guldner J, Yassouridis A, Holsboer F, Steiger A. Trimipramine and imipramine exert different effects on the sleep EEG and on nocturnal hormone secretion during treatment of major depression. Depression 1996;4:1–13.

Staner L, Kerkhofs M, Detroux D, Leyman S, Linkowski P, Mendlewicz J. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. Sleep 1995;18:470–7.

Trivedi MH, Rush AJ, Armitage R, Gullion CM, Grannemann BD, Orsulak PJ, Roffwarg HP. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 1999;20: 447–59.

van Bemmel AL, Vermeeren MT, Ruigt G, Sennef C. The acute effects of the noradrenaline reuptake inhibitor Org 4428 on EEG sleep in healthy volunteers. Neuropsychobiology 1999;40:107–14.

Vogel GW, Vogel F, McAbee RS, Thurmond AJ. Improvement of depression by REM sleep deprivation. New findings and a theory. Arch Gen Psychiatry 1980;37:247–53.

Vogel GW, Buffenstein A, Minter K, Hennessey A. Drug effects on REM sleep and on endogenous depression. Neurosci Biobehav Rev 1990;14: 49–63.

Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry 1990;147:14–21.

Yamadera H, Nakamura S, Suzuki H, Endo S. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci 1998;52:439–43.