EFFECTS OF ANTIDEPRESSANTS ON SLEEP IN RATS

Ph.D. Thesis

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I. F. Obál Jr., G. Benedek, Z. Lelkes, F. Obál: Effects of acute and chronic treatment with amitriptyline on the sleep-wake activity of rats. Neuropharmacol. 24: 223-229, 1985.

II. Z. Lelkes, F. Obál jr., G. Benedek, G. Rubicsek, P. Alföldi, F. Obál: Effects of acute and chronic treatment with an atypical antidepressant drug, nomifensine, on the sleep-wake activity in rats. Naunyn-Schmiedeberg's Arch. Pharmacol. 335: 149-153, 1987.

III. Z. Lelkes, F. Obál jr., P. Alföldi, A. Erdős, G. Rubicsek, G. Benedek: Effects of acute and chronic treatment with trazodone, an antidepressant, on the sleep-wake activity in rats. Pharmacol. Res. Vol. 30(2): 105-115, 1994.

IV. Z. Lelkes, P. Alföldi, A. Erdős, G. Benedek: Rolipram, an andidepressant which increases the availability of cAMP, transiently enhances wakefulness in rats. Pharmacol. Biochem. Behav. 60(4): 835-839, 1998.

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CONTENTS

INTRODUCTION

Many functions of organisms display circadian variations. Diurnal fluctuations in sleep-wake activity are among the best-known circadian rhythms. Two states of sleep are differentiated: rapid eye movement sleep (REMS) and non-REM sleep (NREMS). NREMS is characterized by slow waves and sleep spindles in the EEG. The EEG is desynchronized and muscle tone is lost in REMS. The depth of NREMS can be characterized by the amount of slow waves in the EEG. NREMS can be divided into several stages (Kelly 1985).

Although a much information has accumulated on sleep, its exact function is still not known. The mechanisms of sleep regulation are not clear either. Two main factors are obviously of importance in sleep regulation: the need for sleep ("sleep pressure") and the circadian changes (Borbély 1982). On the basis of these two factors, Borbély created a model of sleep regulation comprising two processes: Process S, a sleep-dependent process, and Process C, a sleep-independent circadian process. The level of Process S, which is reflected by the slow-wave activity during NREMS, undergoes an increase during wakefulness (W) and a decline during sleep. In the model, sleep propensity and the duration of sleep are determined by the combined action of the two processes. Several brain regions are implicated in sleep regulation, including the thalamus, the basal forebrain and the brainstem (Kelly 1985). Various hormones and neurotransmitters contribute to or modulate sleep regulation. The exact roles of neurotransmitters, e.g. monoamines, are not fully understood, but several effects of these substances on sleep are already known. Noradrenalin (NA) transmission promotes the maintenance of W, at least in part, in consequence of the stimulation of α_1 receptors (for a review, see Gaillard 1985; Stenberg and Hilakivi 1985). Serotonin (5-HT) may be involved in the induction of NREMS, since 5-HT suppression by the administration of p-chlorophenylalanine almost totally abolishes sleep (for reviews, see Koella 1985 and Wauquier and Dugovic 1990). Suppression of sleep by 5-HT agonists (for a review, see Dugovic and Adrien 1991), however, indicates that 5-HT mediated processes may also be involved in increases in W. A large dose of dopamine (DA), which acts mainly on postsynaptic receptors, enhances W (for a review, see Wauquier et al. 1985).

The delicate balance between sleep and W can easily be disturbed. Sleep is often changed in psychiatric illnesses, e.g. in schizophrenia or in depression (Benson et al. 1993). Not only are the alterations in sleep characteristic findings in some of these diseases, but the

underlying mechanisms of changes in sleep and the mechanisms of these illnesses may somehow be related to each other. Study of these changes in sleep may therefore promote a better understanding of the etiology of these diseases.

Several lines of evidence (e.g. sleep disturbances in depression, the effects of sleep deprivation on mood, and the roles of monoamines in both sleep regulation and the pathomechanism of depression) indicate links between sleep disturbances and the pathomechanism of depression, and study of the effects of antidepressants on sleep is therefore of interest.

REVIEW OF THE LITERATURE

It has long been known that patients suffering from major depression often complain sleep disturbances. Polysomnographic studies have revealed changes in both REMS and NREMS. Sleep continuity is also impaired. Sleep latency is prolonged, and sleep is fragmented. There are many nocturnal awakenings and sleep terminates early in the morning. The most consistently reported finding is a shortened first NREMS period, leading to an advanced occurrence of REMS. Cholinergic agonists, such as arecoline, induce REMS. Following the administration of arecoline, depressed patients enter REMS more rapidly than do normal controls, indicating an increased sensitivity (Gillin et al. 1991). Decreases in delta sleep and in the delta activity of the EEG during NREMS have also been reported (for a review, see Reynolds and Kupfer 1987). The sleep architecture is changed. The slow-wave activity is shifted from the first to the second NREMS period. The intranocturnal temporal REMS distribution is also altered: REMS increases in the first half of the night (for a review, see Reynolds and Kupfer 1987). Sleep measures are not merely the indicators of the disease, but are also of prognostic value in the treatment (Svendsen and Christensen 1981). Sleep can additionally influence mood. Manipulations of sleep-W activity (total or partial sleep deprivation, selective REMS deprivation and phase advancement of the sleep-W cycle) are effective in relieving depression (for a review, see Reynolds and Kupfer 1987; Schilingen and Tölle 1980; Van den Hoofdacker and Elsenga 1981; Vogel et al. 1975; Wher and Wirz-Justice 1979).

Several theories have been proposed to explain the interactions between abnormalities in sleep, mood disturbance and the pathogenesis of depression. The cholinergic/aminergic theory suggests that affective disorders are caused by alterations in cholinergic/aminergic balance (Janowsky et al. 1972). Depression is characterized by a decreased monoaminergic activity. The concentrations of metabolites of NA and 5-HT are decreased in some depressed patients. Suppression of the NA level is an animal model of depression; drugs that deplete NA induce or worsen depression, while drugs that enhance NA and 5-HT have an antidepressant effect. Although several lines of evidence (recovery from depression requires the administration of antidepressants for several weeks, the levels of monoamines are not always decreased in depression, etc.) indicate that the relation between deficiency in monoamines and depression is not so clear-cut as previously thought, monoamines are still believed to be implicated in the pathogenesis of depression (for reviews, see Asnis and Praag 1989 and Klaus et al. 1989). The Hobson-McCarley (McCarley 1982; McCarley and

Hobson 1975) model of sleep regulation postulates noradrenergic and serotonergic "REM-off" cells and cholinergic "REM-on" cells. Thus, the short REMS latency and the altered cholinergic REMS induction responsiveness in depression may reflect an imbalance between cholinergic and monoaminergic activity, which is implicated in the pathomechanism of depression (for a review, see Buysse and Kupfer 1990). Borbély and Wirz-Justice (1982) put forward a hypothesis in which the deficiency of NREMS rather than the disturbance of REMS is the causal link between sleep and depression. According to this hypothesis, Process S (the sleep-dependent process of sleep regulation) is deficient in depression; thus, the impairment in sleep onset and sleep maintenance and the diminution of slow-wave sleep in depression can be attributed to the low level of Process S. Since the cyclic alterations in NREMS and REMS are assumed to result from a reciprocal interaction between these two sleep states, the abnormalities of REMS in depression (earlier appearance of REMS) may be attributed to the failure of NREMS to inhibit REMS. This model can explain the beneficial effect of sleep deprivation on the mood of depressed patients, for sleep deprivation increases the level of Process S. Sleep abnormalities in depression may also be linked to disturbances of biological rhythms. It has been suggested that the onset of REMS, the distribution of REMS density, the body temperature rhythm, and the cortisol levels may be phase advanced in depression (for a review, see Reynolds and Kupfer 1987; Wher et al 1979).

All these lines of evidence support the opinion that the mechanisms underlying depression are related to those of sleep disturbances. Study of the effects of antidepressants may promote our understanding of the relationship between sleep and depression. Previously, only the REMS-suppressive effect of antidepressants was emphasized (Scherschlicht et al. 1982; Vogel 1975; Vogel et al. 1975). Later, several papers indicated the importance of the promotion of NREMS (Borbély and Wirz-Justice 1982; for a review, see Reynolds and Kupfer 1987). Although at least one of these two characteristic sleep effects can often be observed after the administration of antidepressants, the sleep responses vary, e.g. REMS can be suppressed (for a review, see Reynolds and Kupfer 1987) or enhanced (Sharpley et al. 1992), while W may be increased (Nicholson and Pascoe 1988) or decreased (Monti 1989).

In our present studies we have tested the effects on sleep of the chronic administration of 4 structurally different antidepressants with various mechanisms of action, influencing various monoamines and, since disturbances in second messenger signaling are also implicated in the pathogenesis of depression (Wachtel 1990; Warsh and Li 1996), the cAMP system.

All the drugs studied, amitriptyline, nomifensine, trazodone and rolipram, are clinically effective antidepressants (Blacker et al. 1988; Horowski and Sastre-Y-Hernandez 1985; Overall 1984). Amitriptyline, a classical tricyclic antidepressant, inhibits the reuptake of NA and 5-HT (Baldessarini 1985) and also has anticholinergic and antihistaminergic effects (Richelson 1979; Snyder and Yamamura 1977). Nomifensine, a tetrahydroisoquinoline derivative, is a NA and DA reuptake inhibitor (Hanks 1977; Hunt et al. 1974; Schacht et al. 1982). Trazodone, an atypical antidepressant, a phenylpiperazine derivative of triazolopyridine, inhibits the reuptake of 5-HT (Stefanini et al. 1976). Rolipram, 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-pyrrolidone, increases the availability of cAMP by selectively inhibiting a PDE IV isoenzyme (Nemoz et al. 1985; Schneider 1984; Thompson 1991).

THE AIMS OF THE STUDY

Several lines of evidence indicate that the mechanisms underlying depression are related to those of sleep disturbances. Our investigation were designed to compare the effects of antidepressants with various pharmacological characters, amitriptyline, nomifensine, trazodone and rolipram, on the sleep-W activity of rats. Clinical recovery from depression requires the administration of antidepressants for a long period of time. Accordingly, in our experiments drugs were administered chronically. Our aim was to study:

1. acute effects on the sleep-W activity and on the power density spectra of the EEG;

2. chronic effects on the sleep-W activity;

3. circadian variations in the effects on the sleep-W activity.

METHODS

Animals, surgery. Male CFY rats were used; the animals weighed 300-350 g at the time of the sleep experiments. Under pentobarbital anaesthesia (50 mg/kg), gold-plated screws were implanted over the frontal and parietal cortices and over the cerebellum for EEG recordings.

Experimental conditions, treatments. The rats were raised in a light:dark cycle of 12 h each (lights on from 8:30 to 20:30) and at an ambient temperature of 21 ^{o}C. The same conditions were maintained in the sound-attenuated experimental chambers. Loudspeakers provided low-level continuous noise.

After the implantation operation, the rats lived in individual Plexiglas cages in the experimental chamber. They were allowed 6 to 10 days to recover. Then, in order to habituate them to the experimental procedure, the rats were connected to light flexible recording cables, and received intraperitoneal (ip.) injections of physiological saline twice a day for 6 days. The injections were timed to 15 to 20 min before light onset and dark onset. After the period of physiological saline injections, an antidepressant was administered twice a day for 5 (amitriptyline) or 11 (nomifensine, trazodone or rolipram) days. After the period of antidepressant injections, on the final day of the experiments (day 6 or 12, withdrawal day), the antidepressant was withdrawn and physiological saline was injected again.

The rats were divided into groups and treated as follows. Three doses of amitriptyline were given: 1 mg/kg (n=8), 5 mg/kg (n=8) or 15 mg/kg (n=8). Two groups of rats received 0.1 (n=15) or 1 (n=11) mg/kg doses of nomifensine. Two groups of rats were treated with 2.5 (n=10) or 10 (n=6) mg/kg trazodone. Two groups of rats received 0.1 (n=9) or 1 (n=9) mg/kg rolipram. One group of rats (n=9) was injected with saline throughout the experiment in order to study whether any spontaneous changes in sleep-W activity occur during the long period of the experiment. The drugs were dissolved in physiological saline, and injected ip. in a volume of 0.3-0.4 ml.

Recording, data analysis: The sleep-W activity was recorded for either 24 h (both light and dark periods starting with light onset; rats treated with nomifensine, trazodone or 1 mg/kg amitriptyline) or for 12 h (light period only; rolipram, 5 and 15 mg/kg amitriptyline) on day 6 of physiological saline administration (baseline day), on days 1, 5 and 11 of antidepressant treatment and on the day following the last antidepressant day (day 6 or 12, withdrawal day). The EEG and motor activity (the latter assessed via an electromagnetic transducer activated by cable movements) were recorded on a paper chart (7.5 mm/s). The vigilance states were scored in 40-s intervals, W, NREMS and REMS were distinguished. The percentages of the vigilance states were calculated for consecutive 1-h and 3-h recording periods.

The EEG effects of 0.1 mg/kg nomifensine and 2.5 and 10 mg/kg trazodone were also studied (each dose in 8 rats) by means of spectral analysis. A 3-h period was evaluated following light onset on the baseline day and on trazodone day 1. (It was not possible to separate samples taken from W and NREMS.) The EEG signals were subjected to analog-to-digital conversion, and fed into a computer for fast Fourier analysis. Power density values ($\mu V^2/0.5$ Hz) were computed for consecutive 2.5-s periods. Values were integrated in 2-Hz frequency ranges between 0.5 and 12 Hz, and in 4-Hz frequency ranges between 12.5 and 20 Hz, and the mean power density values were calculated for consecutive 1-h periods. The differences between the power density values on the antidepressant day and the baseline day were expressed as percentages of the baseline power density values.

Treatment day data were compared with the baseline data. The effects of antidepressant treatment were assessed by means of the paired t-test (two-sided), ANOVA and the Dunnett test. P values < 0.05 were regarded as statistically significant.

RESULTS AND DISCUSSION

The sleep-W activity of the animals displayed the usual diurnal rhythmicity characteristic of rats, with high percentages of sleep and W in the light and dark periods, respectively. The chronic administration of saline failed to alter the sleep-W activity (II). The effects of antidepressants are described and discussed below.

Effects of amitriptyline

Amitriptyline affected both NREMS and REMS. In the light period (after the morning injection), when the sleep-W activity was recorded after all the three doses (1, 5 and 15 mg/kg), NREMS was increased in the first 3-h period, while both REMS and W were decreased; the effects depended on the dose applied. The changes in NREMS and W were followed by compensatory reactions (i.e. changes in the opposite directions) 6-12 h after the injections. The effects of chronic injections of amitriptyline on NREMS revealed a definite attenuation only in the case of the 15 mg/kg dose. A REMS rebound appeared after withdrawal of the 5 and 15 mg/kg doses. In the case of the 1 mg/kg dose, the sleep-W activity was recorded both in the light and in the dark period. The effects of 1 mg/kg amitriptyline revealed circadian variations. The sleep-W activity was not changed in the dark period (after the evening injection) (I, V).

The results show that the increase in NREMS is as characteristic of the effects of amitriptyline as is the reduction of REMS, and that these effects are resistant to chronic treatment when the dose is not high. The enhancement in NREMS may be due, in part, to an enhancement in 5-HT transmission by inhibition of the uptake process (Baldessarini 1985), since serotonergic mechanisms may be involved in the induction of NREMS (for reviews, see Koella 1985 and Wauquier and Dugovic 1990). A role of 5-HT in sleep and of enhanced 5-HT transmission in the increase of NREMS by amitrityline, however, is not completely clear, since several specific 5-HT agonists that act on particular 5-HT receptor subtypes suppress NREMS (for a review, see Dugovic and Adrien 1991). The antihistaminic effect of amitriptyline on H_1 receptors (Richelson 1979) may also contribute to the enhancement in NREMS. Acetylcholine is involved in the induction of REMS (for a

review, see Gillin et al. 1985). The suppression of REMS may be attributed, at least in part, to the anticholinergic effect of amitriptyline (Snyder et al. 1977). Since many selective 5-HT uptake blockers suppress REMS (Sommerfelt and Ursin 1991; for a review, see Wauquier and Dugovic 1990), the role of the 5-HT reuptake inhibition by amitriptyline in the suppression of REMS can not be excluded.

Effects of nomifensine

The response to the lower (0.1 mg/kg) dose of nomifensine depended on the timing of the injection. In the light period, NREMS was increased at the expense of W. The effects persisted throughout the chronic treatment. Nomifensine failed to affect the sleep-W activity in the dark period. As evaluated through spectral analysis of the EEG, the increase in NREMS was accompanied by an increase in slow-wave activity. The higher (1 mg/kg) dose of nomifensine elicited increases in W and a reduction in both sleep states, followed by changes in W and NREMS in the opposite directions. These changes in sleep were observed in both the light and the dark periods of the day. Nomifensine (1 mg/kg) altered sleep throughout the chronic treatment, but some changes in the effects were noted. The arousal response to nomifensine increased in the light period and decreased in the dark period during the chronic treatment (II, V).

The sleep effects of nomifensine depended on the dose. The lower dose of the drug promoted sleep, whereas the higher dose enhanced W. The behavioural effects of nomifensine depend on the dose in a similar manner. A low dose of nomifensine reduces locomotor activity, whereas high doses increase motility (for a review, see Hoffmann 1977). Nomifensine inhibits the reuptake of NA and DA (Hunt et. al. 1974; Schacht et al. 1982). The dose-dependent effects of nomifensine, an indirect DA agonist, are similar to those of apomorphine, a direct DA agonist. A low dose of apomorhine has been reported to reduce locomotor activity (Di Chiara et al. 1976; Strömbom 1976) and to increase sleep in rats (Lelkes 1990; Mereu et al. 1979), while a high dose induces hyperactivity with a reduction of sleep (Kafi and Gaillard 1976). DA may also elicit opposite effects, depending on the dose: a low dose of DA injected into the caudate nucleus enhanced the EEG spindle activity elicited by caudate stimulation, whereas higher doses suppress spindles (Okuyama et al. 1985). The behavioural depression and sleep in response to a low dose of DA agonist has been attributed to DA autoreceptors mediating an inhibition of dopaminergic

transmission (Gessa et al. 1985). In contrast, the behavioural activation induced by high doses is due to the activation of postsynaptic DA receptors (Carlsson 1975). An inhibition of DA reuptake by nomifensine may explain the indirect DA agonist activity of the drug, through which it can mimic the effects of a high dose of apomorphine. A blockade of NA reuptake may contribute to the effect, since NA mechanisms are also known to produce arousal due to stimulation of α_1-adrenoceptors (for a review, see Koella 1985). The mechanism of the promotion of sleep by the low dose of nomifensine is not clear. It might be speculated that a slight increase in DA in the synaptic cleft in response to the lower dose of nomifensine preferentially stimulates autoreceptors. These receptors, in fact, have been suggested to be more sensitive to DA than the postsynaptic ones (for a review, see Roth 1979). Similarly, the possibility can not be excluded that an inhibition of NA reuptake may cause an autoreceptor-mediated feedback inhibition of NA transmission. Such a mechanism has been implicated in the acute sedative action of some tricyclic antidepressants (Svenson 1984). The effects of nomifensine revealed circadian variations. Diurnal variations in the drug effects might be related to a diurnal rhythm of NA (Kafka et al. 1981) and DA (Bruinik et al. 1983; Watanabe and Seeman 1984) receptors and transmitter metabolisms (Lemmer and Berger 1978; Perlow et al. 1977). The numbers of several receptors, e.g. adrenoceptors, have been found to change during chronic antidepressant treatment, and these changes are different in the light and dark periods (Maj et al. 1985). This observation might contribute to an explanation of the changes in the effects of the high dose of nomifensine during the chronic administration.

Effects of trazodone

Trazodone administration enhanced NREMS at the expense of W. The increase in NREMS was dose-related and more pronounced during the dark cycle. After administration of the lower (2.5 mg/kg) dose of the drug, only a tendency to an increase in NREMS was noted during the light cycle and during the dark cycle on day 1 of trazodone treatment, and significant changes in W and NREMS were found only during the chronic treatment in the dark phase. The higher (10 mg/kg) dose of the drug elicited larger increases in NREMS than did the lower one. After administration of 10 mg/kg trazodone, significant increases in NREMS at the expense of W were noted during both the light and dark cycles. The promotion of NREMS was enhanced during the chronic treatment. There were no consistent

changes in REMS. Spectral analysis of the EEG revealed increases in slow-wave activity after administration of the high dose (10 mg/kg) of the drug (III).

Trazodone, a 5-HT reuptake blocker, dose-dependently enhanced NREMS. Since trazodone acts predominantly on the serotonergic system, it is likely that the serotonergic mechanisms mediate the effects of trazodone on sleep. Serotonergic mechanisms may be involved in the induction of NREMS. However, the role of 5-HT in sleep regulation is not entirely clear. Suppression of 5-HT or administration of 5-HT antagonists can suppress sleep, while increases in 5-HT activity promote sleep, particularly NREMS, and administration of tryptophan or a 5-HT agonist, quipasine, induces EEG synchronization (for a reviews, see Koella 1985 and Wauquier and Dugovic 1990). However, sleep is suppressed by several 5-HT agonists that act on particular 5-HT subtypes, while ritanserin, a predominantly 5-HT_2 antagonist, enhances NREMS (for reviews, see Dugovic and Adrien 1991 and Wauquier and Dugovic 1990). Trazodone, however, also has direct 5-HT antagonistic properties (Baran et al. 1979). The 5-HT antagonist and 5-HT mimetic actions of trazodone appear biphasically, depending on the dose. In rats, a low dose (1 mg/kg) of trazodone displays 5-HT antagonist activity, whereas higher doses (6-8 mg/kg) act as a 5-HT agonist (Maj et al. 1979). In doses enhancing NREMS, and especially in the high dose used in our experiments, therefore, trazodone is considered to be an indirect 5-HT agonist. Trazodone has a metabolite, mCPP, which is a mixed 5-HT_{2C}/5-HT_{1B} agonist (Caccia et al. 1981), but promotion of NREMS by trazodone can not be attributed to mCPP, because this metabolite suppresses sleep. (for a review, see Dugovic and Adrien 1991). In conclusion, promotion of NREMS by trazodone may be attributed to an enhanced 5-HT transmission resulting from an inhibition of 5-HT reuptake.

Effects of rolipram

The lower (0.1 mg/kg) dose of rolipram had no marked effect on sleep. Only tendencies to an enhancement of W and to a suppression of NREMS were observed after the injections. On day 5 of rolipram treatment, a tendency to a decrease in REMS was noted in postinjection h 1. The high (1 mg/kg) dose of rolipram enhanced W and suppressed NREMS significantly in postinjection h 1 on day 1 of the treatment. These changes in W and NREMS diminished during the chronic treatment and did not reach the level of

statistical significance on days 5 and 11. On day 1 of rolipram treatment, a tendency to a decrease in REMS was observed in postinjection h 2 (IV).

Rolipram, a PDE inhibitor, which increases the availability of cAMP (Nemoz et al. 1985; Schneider 1984; Thompson 1991), enhanced W in our experiments. In the preoptic region, an area implicated in sleep regulation, cAMP concentrations exhibit spontaneous oscillations across the sleep-W cycle, with maximum levels occurring in W (Perez et al. 1991; Perez et al. 1995). These findings support the idea that cAMP-mediated processes may be involved in sleep-W regulation. Rolipram increases the synthesis and release of NA (partially by cAMP-induced changes in tyrosine hydroxylase activity) (Kehr et al. 1985; Wachtel 1983). NA enhances W, at least in part in consequence of the stimulation of α_1-receptors (for a review, see Gaillard 1985; Stenberg and Hilakivi 1985). The effects of rolipram on sleep may be at least partially mediated by the increased release of NA. An enhancement of the cAMP system by rolipram can also influence the postsynaptic mechanism of neurotransmission (Wachtel and Schneider 1986), but it is not clear what the effect of these postsynaptic changes on sleep is. Increases brought about in cAMP by receptor agonists (acting on receptors positively coupled to adenylate cyclase, e.g. β-adrenergic receptors or dopamine D_1 receptors) or antagonists (acting on receptors negatively coupled to adenylate cyclase, e.g. D_2 receptors) can be accompanied by both enhancements and suppressions of sleep (Adrien et al. 1985; Hilakivi 1983; Ongini and Trampus 1992; Ongini et al. 1993) A tolerance developed against the awakening effect of the high (1 mg/kg) dose of rolipram during the chronic treatment. This dose, however is, much higher than those used in clinical practice. For the lower (0.1 mg/kg) dose, only a tendency to an increase in W was noted, but this tendency seemed to persist throughout the chronic treatment.

GENERAL DISCUSSION

Antidepressants alter both REMS and NREMS. The most characteristic changes in sleep in response to antidepressants include a suppression of REMS, a prolongation of REMS latency and an enhancement of NREMS (for a review, see Reynolds and Kupfer 1987; Scherschlich et al. 1982; Vogel 1975; Vogel et al. 1975). REMS suppression, accompanied by a prolongation of REMS latency, is the most frequently reported effect of antidepressants on sleep. A correlation between the extent of REMS suppression and the clinical response to antidepressant therapy has also been reported (for a review, see Reynolds and Kupfer 1987). The importance of REMS suppression in the action of antidepressants is also demonstrated by the observation that selective REMS deprivation is as effective in relieving depression as imipramine treatment (Vogel et al. 1975). Drugs producing an arousal-type REMS deprivation (a large reduction in REMS, a persistent effect during the chronic treatment, followed by a REMS rebound) improve endogenous depression, but REMS deprivation does not seem to be absolutely necessary for an antidepressant effect. In a review by Vogel et al. (1990), all drugs producing arousal-type REMS deprivation displayed antidepressant activity, and only 4 drugs were reported to improve endogenous depression without producing arousal-type REMS deprivation. Besides the suppression of REMS, changes in NREMS are also important. Several antidepressants enhance NREMS. The enhancement of NREMS by antidepressants is in accordance with the hypothesis of Borbély and Wirz-Justice (1982), which postulates that the generation of NREMS is impaired (Process S is deficient) in depression, and the enhancement of NREMS-promoting processes may be beneficial.

In our experiments, both suppression of REMS and enhancement of NREMS were observed in response to antidepressants. REMS was suppressed by 5 and 15 mg/kg amitriptyline and 1 mg/kg nomifensine, whereas the administration of rolipram caused only a tendency to a suppression of REMS. NREMS was enhanced by all doses (1, 5 and 15 mg/kg) of amitriptyline, 0.1 mg/kg nomifensine and both doses (2.5 and 10 mg/kg) of trazodone. Our findings are in accordance with the opinion that, though the suppression of REMS is a very frequently reported effect of antidepressants, increases in NREMS in response to antidepressants are also of importance.

There were likewise differences between the sleep effects of the various drugs. Various effects of antidepressants on sleep have been reported from both animal and human studies,

e.g. REMS can be suppressed (for a review, see Reynolds and Kupfer 1987) or enhanced (Sharpley et al. 1992), and W may be increased (Nicholson and Pascoe 1988) or decreased (Monti 1989). These findings do not support the existence of a direct, uniform relationship between the antidepressive and sleep-modifying effects.

Sleep deprivation is effective in relieving depression (for a review, see Reynolds and Kupfer 1987). Sleep deprivation results in increases in NA activity (Müller 1993) and 5-HT function (Salomon 1994). These transmitters are also enhanced by those antidepressants which inhibit the uptake of monoamines or the MAO enzyme. In addition to improving mood, sleep deprivation results in rebound sleep. NA release may contribute to the rebound sleep following sleep deprivation (Gonzales et al. 1994; Lelkes et al. 1994; Lelkes unpublished data) and, since 5-HT is implicated in the rebound sleep following stress (Cespuglio et al. 1995), a similar role of 5-HT can not be ruled out. The suppression of REMS by antidepressants is again followed by a compensatory increases (Vogel et al. 1990). There are similarities in the effects of sleep deprivation and the effects of those antidepressants which inhibit the uptake of monoamines. 5-HT may be involved in both the enhancement of NREMS by some antidepressants (amitriptyline and trazodone in the present study) and the compensatory increase in NREMS following sleep deprivation. NA may be involved in the suppression of REMS and the following rebound induced by both certain antidepressants (amitriptyline and nomifensine in the present study) and sleep deprivation. However, the effects of sleep deprivation and those of antidepressants additionally reveal differences. Antidepressants can induce an immediate increase in NREMS without any previous suppression. The antidepressant activity of sleep deprivation vanishes following rebound sleep (for a review, see Buysse and Kupfer 1990), whereas antidepressants result in both an improvement in mood and increases in NREMS, i.e. the improvement in mood following sleep deprivation is accompanied by suppression of sleep, whereas that induced by antidepressants is accompanied by increases in NREMS.

In our studies, the effects of antidepressants on sleep revealed a circadian variation. Such a circadian variation can result from changes in the concentrations of neurotransmitters, in the number and sensitivity of receptors, etc. Changes in the sensitivity to neurotransmitters influenced by antidepressants could also contribute to the circadian variations in the effects. In fact, the effects of several agonists that act on various NA, 5-HT and DA receptors display circadian variations (Dugovic et al. 1989; Lelkes 1996; Lelkes et al. 1990), but these diurnal variations are not parallel to those induced by antidepressants acting on the corresponding transmitters. This means that changes in the

sensitivity to neurotransmitters probably have no essential role in the circadian variations in the effects of antidepressants on sleep.

The effects of antidepressants on sleep persisted throughout the chronic treatment. Tolerance developed only against the 15 mg/kg dose of amitriptyline and the 1 mg/kg dose of rolipram. These doses, however, were very high as compared to the therapeutic doses. Clinical recovery from depression requires the administration of antidepressants for a long period of time. During this time, a tolerance may develop to various acute biochemical and behavioural effects of the drugs, but the action needed to relieve the symptoms is not expected to fade away (Barbaccia et al. 1983; Cuomo et al. 1983; Hano et al. 1981; Racagni et al. 1983). The observation that the effects of antidepressants on sleep persisted throughout the chronic treatment supports the view, that the therapeutic effects of antidepressants are related to those on sleep.

Finally, it must be emphasized that in the present study the effects of antidepressants were studied in healthy rats and not in depressed patients, and the results must therefore be interpreted with caution. Nevertheless, in the majority of cases, similar effects of antidepressants on sleep are reported in rats and depressed patients in the literature [e.g. our findings in rats are similar to those reported in humans in response to amitriptyline, trazodone and a high dose of nomifensine (Nicholson et al. 1986; for a review, see Reynolds and Kupfer 1987; Scharf and Sachais 1990)].

SUMMARY

Patients suffering from major depression often complain of sleep disturbances. Several lines of evidence indicate that the mechanisms underlying depression are related to those of sleep disturbances. Studies of the effects of antidepressants may therefore promote our understanding of the relationship between sleep and depression. In our experiments, changes in the sleep of rats were studied in response to the chronic administration of antidepressants with various mechanisms of action. The antidepressants included the noradrenalin and serotonin uptake inhibitor amitriptyline, the noradrenalin and dopamine uptake inhibitor nomifensine, the serotonin uptake inhibitor trazodone and the phosphodiesterase inhibitor rolipram.

Amitriptyline (1, 5 or 15 mg/kg) enhanced non-REM sleep (NREMS). The 5 and 15 mg/kg doses also suppressed REM sleep (REMS). The effects were dose-dependent. A low (0.1 mg/kg) dose of nomifensine enhanced NREMS. A high (1 mg/kg) dose increased wakefulness (W) at the expense of both sleep states. Trazodone (2.5 or 10 mg/kg) dose-dependently enhanced NREMS. A high (1 mg/kg) dose of rolipram enhanced W on day 1 of the treatment. In response to a low (0.1 mg/kg) dose of rolipram, only a tendency to an increase in W was noted. The effects of antidepressants on sleep persisted throughout the chronic treatment. Tolerance developed only to the sleep effects of 15 mg/kg amitriptyline and 1 mg/kg rolipram. These doses, however, were high as compared to the doses used in therapy.

In our studies, the most characteristic effects of these antidepressants on sleep included suppressions of REMS and enhancements of NREMS. These findings corroborate previous observations. Nevertheless, there are obvious differences in the sleep effects of antidepressants, which does not support the existence of a direct, uniform relationship between their antidepressive and sleep-modifying effects.

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