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EFFECTS OF SEVERAL CENTRALLY ACTIVE DRUGS ON THE SLEEP–WAKEFULNESS CYCLE OF CATS

P. POLC, J. SCHNEEBERGER and W. HAEFELY
Pharma Research Department, Building 69/70, F. Hoffmann–La Roche & Co. Ltd, Grenzacherstrasse 124, CH 4002 Basle, Switzerland

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Summary—Eighteen drugs were injected intraperitoneally at different doses in cats and their effects on the sleep–wakefulness cycle studied in 6-hr sessions of telemetric EEG and EMG recording.

At the lowest doses that affected the sleep–wakefulness cycle, clinically used and potential antidepressants (imipramine, clomipramine, desipramine, amitriptyline, nortriptyline, maprotiline, Ro 03-5939, mianserin, iprindole, viloxazine, pargyline, Ro 11-1163) as well as 5-hydroxy-L-tryptophan selectively depressed rapid eye movement (REM) sleep.

Other psychotropic drugs also reduced REM sleep but, in contrast to the above antidepressants, simultaneously affected non-rapid eye movement (NREM) sleep at minimum effective doses: LSD, methylphenidate and, to a lesser degree, haloperidol, depressed, whereas cyproheptadine augmented NREM sleep. Chlorpromazine non-significantly reduced REM sleep at a dose that induced ataxia.

The results reveal a selective suppressant effect of antidepressant drugs on REM sleep in cats which seems to reflect an increased activation of 5-hydroxytryptamine and/or noradrenaline receptors in the brain as the consequence of either inhibition of monoamine uptake or monoamine oxidase, increased release of monoamines or some yet unknown mechanisms.

Several tricyclic antidepressant drugs and monoamine oxidase (MAO) inhibitors were found to markedly reduce REM sleep in animals and man (for references see Hartmann, 1968; King, 1971; Jouvet, 1972; Passouant, Cadilhac and Ribstein, 1972; Vogel, 1975). This effect is not surprising if it is considered that most antidepressants in use affect the dynamics of brain monoamines (Biel and Bopp, 1974) and that monoamines have been implicated in the regulation of the sleep–wakefulness cycle (SWC) and, particularly, of REM sleep (King, 1971; Jouvet, 1972; Morgane and Stern, 1974). The alteration of REM sleep by antidepressants might be a relevant or irrelevant side effect which results from a similar modification of those monoamine systems that are presumed to act in the control of sleep and of affective states; if this were the case, alterations of sleep that occur with antidepressants could serve as an indicator of the direction and the intensity of changes induced by these drugs in those monoamine systems that are supposed to determine the affective balance. Alternatively, changes in sleep behaviour might be causally related to the effect of antidepressants on mood and drive. In favour of this view Vogel, Thurmond, Gibbons, Sloan, Boyd and Walker (1975) obtained relief of endogenous depression in patients with repeated REM sleep deprivation, which they found to be equal to the therapeutic effect occurring with imipramine. They proposed that the reduction in REM sleep resulting in an increase of "REM pressure" might underlie the therapeutic action of antidepressants in endogenous depression. Compatible with this view is the finding that electroconvulsive shock, an alternative therapy for depressive states, has been shown to depress REM sleep and to affect brain monoamine turnover in cats (Kaelbling, Koski and Hartwig, 1968).

Whatever the connection between the REM sleep suppressant action and the antidepressant effect, contingent or causal, a more detailed knowledge of the effects of antidepressants on SWC is likely to provide useful information on their mechanism of action. In most sleep studies in animals reported so far, psychotropic drugs were administered in somewhat high doses, and are likely to have exerted nonspecific effects on SWC and thus precluded possible selective effects of drugs on particular aspects of sleep (King, 1971). Therefore, the particular aim of the present study was to investigate the dose-related effects of some antidepressant compounds, including those with an atypical pharmacological profile, and of several other psychotropic agents, on SWC with the particular emphasis given to the lowest doses that modified the cycle. Some of the results have been reported in a preliminary form (Polc, Haefely and Schneeberger, 1977).

METHODS

Preparation of the animals

One hundred and eight adult male cats weighing 2.2–2.8 kg were used. Under pentobarbitone anaesthesia, concentric bipolar stainless-steel electrodes

Key words: sleep–wakefulness cycle, REM sleep, tricyclic antidepressants, MAO inhibitors, 5-hydroxytryptamine, noradrenaline.

(0.6 mm diameter), isolated except at the tip, were implanted stereotactically in the dorsal hippocampus and the lateral geniculate body, and two stainless-steel screws placed on the epidural surface of the right parietal cortex. A stainless-steel flexible wire electrode was implanted in the neck muscles. A two-pin connector was secured to the calvarium and fixed with dental cement. Immediately after surgery a dummy device of the same weight and dimensions as the telemetry unit to be used later for recording was mounted on the connector and the cats were placed into large observation chambers. Antibiotics were given prophylactically on the day of operation. Except for the early morning hours, cats did not leave the chambers until they died spontaneously or were sacrificed for histological verification of the electrode location.

The observation chambers were continuously illuminated, maintained at a constant temperature (20°C) and ventilated. They were sound-attenuated and music in the chambers served to keep a constant level of noise. In order to correlate electroencephalogram (EEG) with behaviour, the cats were observed with telemonitors. A radar system recorded the movements of the animal. Food and water were presented at 8 a.m. Two weeks were allowed for recovery from the surgery and for adaptation to the observation chambers.

Recording

The EEG (parietal cortex, hippocampus, lateral geniculate body) and EMG (neck muscle) were recorded on a Grass polygraph, which received brain and muscle signals from a 4-channel telemetry unit described elsewhere (Polc and Wolfang, 1974) by means of a conventional antenna and a FM receiver. This technique permits complete freedom of motion of the animal and minimizes the mechano-electrical artifacts.

The following testing procedure was used in all experiments, which included recording sessions on 3 consecutive pre-drug days, on the day of drug administration and on the post-drug day. Intraperitoneal (i.p.) injections were made at 9 a.m. and immediately afterwards EEG and EMG were recorded continuously for 6 hr on five consecutive days. On the first 3 days 0.1 ml kg^{-1} of physiological saline was injected in order to obtain control hypnograms. On the 4th day one of the psychotropic agents, dissolved in the same volume of saline, was administered. On the 5th day possible delayed effects of the drug given on the 4th day were checked for. At least two weeks elapsed between subsequent drug administrations in the same cat.

Evaluation of drug effects

The effects of compounds and saline on SWC were evaluated by dividing the EEG and EMG records into 1-min segments and assigning the predominant electrographic activity of each epoch to one of the three basic vigilance states, discriminated by the following criteria:

(a) *Wakefulness* (W). Rapid waves of small amplitude in the electrocorticogram (ECoG) and high amplitude EMG activity, cats either moving, sitting or lying down with open eyes;

(b) *NREM sleep*. ECoG with spindles and/or slow waves of high amplitude, accompanied by a decrease of the EMG activity in cats lying down with closed eyes;

(c) *REM sleep*. High frequency low amplitude ECoG, theta rhythm in the hippocampus, ponto-geniculo-occipital waves (PGO) waves in the lateral geniculate body, and a silent EMG in cats lying down and showing occasional muscle twitches.

The amounts of these three states (no attempt was made to distinguish betweeen "spindle" and "slow wave" NREM sleep) were calculated in minutes as well as in % of the recording and/or total sleep time. Hypnograms were thus constructed for each experimental 6-hr session. Since all cats served as their own controls, control values were taken as 100%, and the amounts of the three states after a drug injection expressed as percentage of this value in a particular cat. Additional parameters studied included the total sleep and waking time, number and duration of REM and NREM sleep episodes, latency between the time of injection and the first appearance of a REM and/or NREM sleep period and qualitative changes of the EEG and behaviour, as compared to controls. At least 4 cats were used for each dose and drug. Means with their standard errors were calculated for each drug group. Wilcoxon-test and Student's two-tailed *t*-test were used for comparison between the control and respective drug group.

Drugs used

Amitriptyline, chlorpromazine, clomipramine, cyproheptadine, desipramine, haloperidol, 5-hydroxy-L-tryptophan (5-HTP), imipramine, iprindole, LSD, maprotiline, methylphenidate, mianserin, nortriptyline, pargyline, Ro 03-5939 (1,2,6,7-tetrahydro-2-methyl-1-[2-(methylamino)ethyl]-indolo [1,7-ab] [1]benzazepine HCl), Ro 11-1163 (*p*-chloro-*N*-(2-morpholinoethyl) benzamide), viloxazine were dissolved in saline and injected intraperitoneally. The total amount of solution injected was always 0.1 ml kg^{-1}.

RESULTS

Antidepressants of the imipramine type

Tricyclic and tetracyclic compounds with imipramine-like pharmacological profile selectively depressed REM sleep in cats at doses that did not significantly affect other parameters of SWC. Representative hypnograms are shown for clomipramine in Figure 1 and a graphical presentation of the results with imipramine-like drugs is given in Figure 2.

The depression occurring with minimum effective doses was mainly due to a decreased average duration

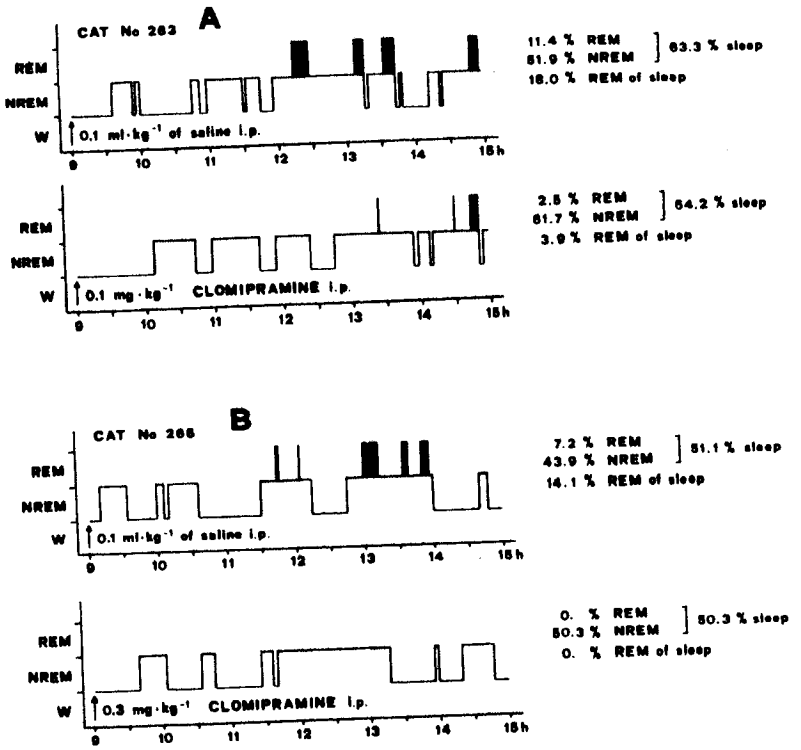

Fig. 1. Effects of clomipramine, 0.1 mg kg^{-1} (A) and 0.3 mg kg^{-1} (B), on the sleep–wakefulness cycle of two cats. Upper hypnograms in A and B are constructed from the values calculated for rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep and wakefulness (W), obtained in the third of three consecutive control sessions following the injection of 0.1 ml kg^{-1} of physiological saline at arrow. Lower hypnograms represent sessions recorded on the 4th day, immediately following the administration of a low (A) and a higher (B) dose of clomipramine dissolved in the same amount of saline (0.1 ml kg^{-1}), respectively. On the right are given amounts of REM and NREM sleep, calculated in % of the recording time, and of REM sleep, expressed as percentage of the total sleep time.

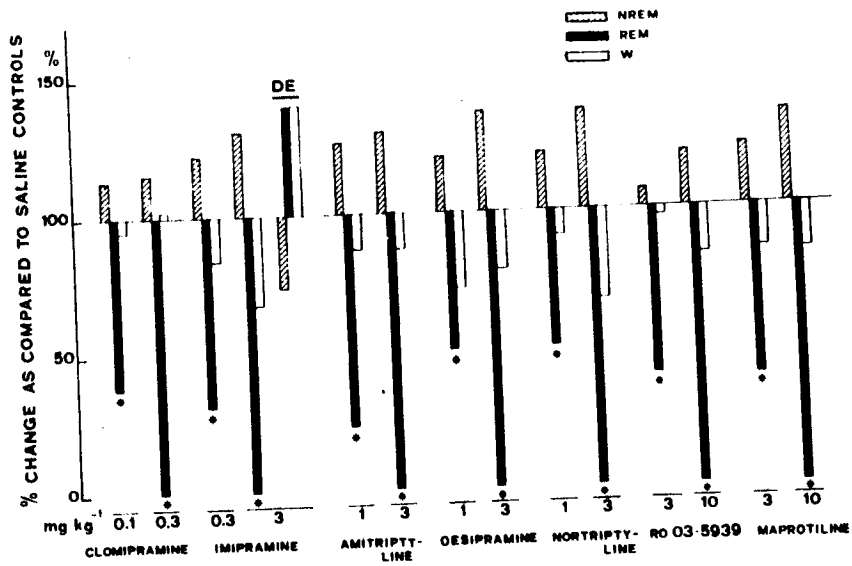

Fig. 2. Effects of imipramine-like antidepressants on the amount of NREM sleep, REM sleep and wakefulness, obtained on the day of administration in 6 hr sessions and expressed in % of controls (100%). DE: Effects recorded 24 hr after the injection. Columns are the means of 4 cats. Values significantly different from controls (Wilcoxon test) are indicated by asterisks.

of individual REM sleep episodes, whereas their number remained essentially unaltered. At doses approximately 3 times higher than the lowest doses that affected SWC, most compounds abolished REM sleep and non-significantly increased the amount of NREM sleep. In addition, at this higher dose level the amplitude of cortical and hippocampal EEG waves increased somewhat in all three states, their frequency remaining virtually unaltered. On the day following application all parameters reached control values, except for a moderate, non-significant rebound increase of REM sleep found after the higher dose (3 mg kg^{-1}) of imipramine (Fig. 2).

The compounds containing a secondary and a tertiary amine in the side chain differed clearly in their potencies as depressants of REM sleep. Tertiary amines, such as clomipramine (minimum effective dose 0.1 mg kg^{-1}) and imipramine (0.3 mg kg^{-1}), were more potent than the secondary amines, desipramine (1 mg kg^{-1}), nortriptyline (1 mg kg^{-1}), Ro 03-5939 (3 mg kg^{-1}) and maprotiline (3 mg kg^{-1}) (Fig. 2).

Antidepressants with an atypical pharmacological profile

An effect on SWC essentially similar to that observed after imipramine-like drugs was obtained with mianserin, viloxazine and iprindole (Fig. 3A).

The tetracyclic compound, mianserin, significantly depressed REM sleep already at 0.3 mg kg^{-1}, without affecting other parameters of SWC. On the day following injection of the next higher dose (1 mg kg^{-1}), a pronounced rebound increase of REM sleep appeared (Fig. 3A).

Viloxazine, which differs markedly from imipramine-like antidepressants in its chemical structure, significantly reduced REM sleep at 10 mg kg^{-1} (Fig. 3A). After 30 mg kg^{-1}, which suppressed REM sleep, epileptoid crises occurred in 2 out of 4 cats lasting up to 1 week after intraperitoneal application, suggesting a small non-toxic range for this compound in cats, as opposed to most other antidepressants.

Iprindole, a tricyclic indole derivative, had no effect at 10 mg kg^{-1}, but significantly depressed REM sleep at 30 mg kg^{-1} without inducing changes of other components of SWC.

MAO inhibitors and 5-HTP

Pargyline and a new short-acting MAO inhibitor, Ro 11-1163 (*p*-chloro-*N*-(2-morpholinoethyl)benzamide), had no effect on SWC at 10 mg kg^{-1}, but abolished REM sleep at 30 mg kg^{-1}. Interestingly, after this higher dose of pargyline, a pronounced REM sleep rebound appeared on the day following administration (Fig. 3B).

5-Hydroxytryptophan, given 15 min after the peripheral decarboxylase inhibitor, benserazide (50 mg kg^{-1}) had no effect at 5 mg kg^{-1}. A high dose of 5-HTP (50 mg kg^{-1}), injected shortly after the same dose of benserazide, suppressed REM sleep and had no significant effect upon NREM sleep. A clear rebound increase of REM sleep was noticed on the day following the injection of this high dose (Fig. 3B).

Miscellaneous compounds

Cyproheptadine, like mianserin a peripheral 5-HT antagonist, significantly augmented NREM sleep and reduced REM sleep at the lowest dose that affected SWC (1 mg kg^{-1}). The next higher dose (3 mg kg^{-1}) of this drug almost abolished REM sleep (Fig. 4).

Low doses of methylphenidate (0.3 mg kg^{-1}), an amphetamine-like drug, and of the psychotomimetic

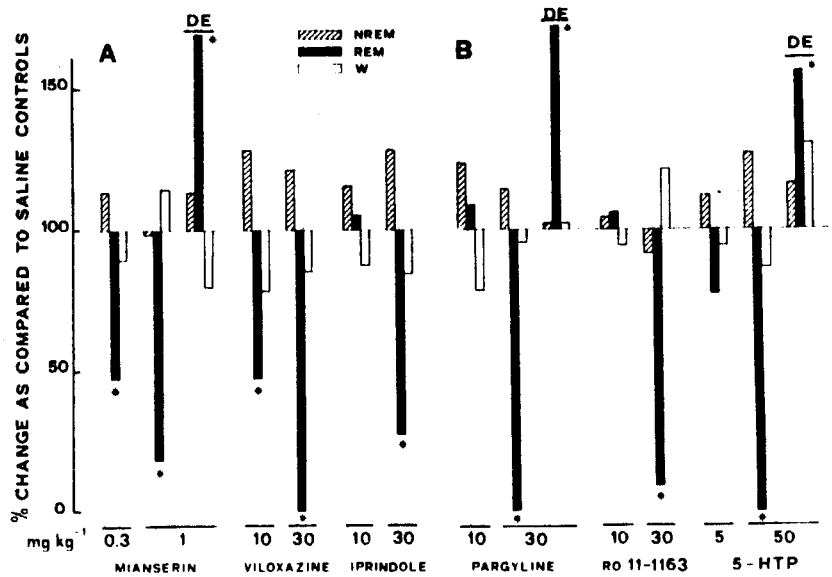

Fig. 3. Effects of antidepressants with atypical pharmacological profiles (A), and of MAO inhibitors and 5-HTP (B), on the amount of NREM sleep, REM sleep and wakefulness, expressed as percentage of controls (100%). Graphic presentation is the same as in Figure 2.

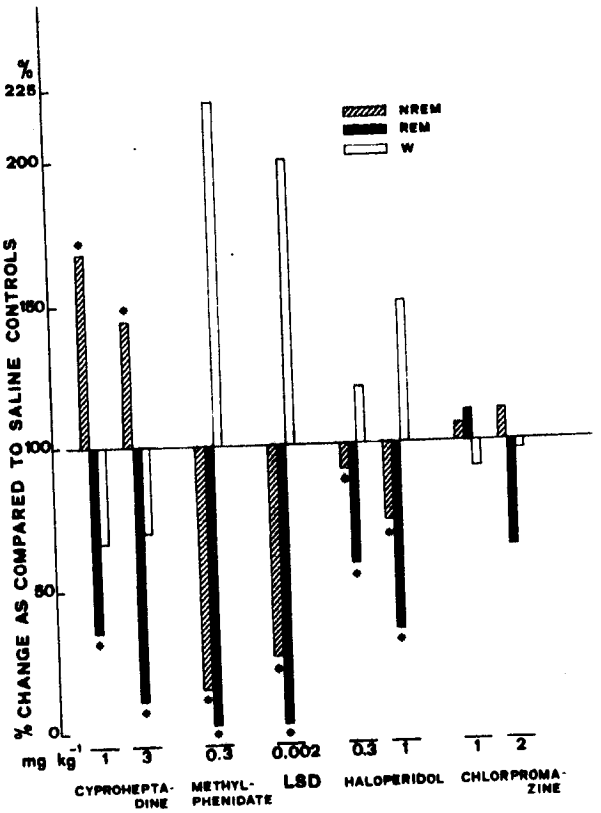

Fig. 4. Effects of miscellaneous compounds on the amount of NREM sleep, REM sleep and wakefulness, expressed as percentage of controls (100%). Graphic presentation given as in Figure 2.

compound, LSD (2 μg kg^{-1}), suppressed REM sleep and profoundly reduced NREM sleep (Fig. 4). These doses of both drugs did not induce any signs of overt excitation.

Of the two neuroleptics investigated, the phenothiazine, chlorpromazine, had no effect at 1 mg kg^{-1}. After the dose of 2 mg kg^{-1}, which already produced a moderate ataxia, a non-significant depression of REM sleep was observed (Fig. 4). The butyrophenone, haloperidol, reduced significantly both REM sleep, and to a smaller extent, NREM sleep at the minimum effective dose (0.3 mg kg^{-1}). A dose of 1 mg kg^{-1} produced similar, but more pronounced effects (Fig. 4). In contrast to chlorpromazine, haloperidol did not produce changes of the motor behaviour in the doses which significantly affected SWC.

DISCUSSION

With the method used in this study for the quantitative assessment of SWC in cats the acute effects of a relatively large number of drugs and doses can be evaluated. A shortcoming of the method is the restriction of recording to 6 hr per day, since any possible drug effects or compensatory mechanisms occurring between the 6th and 18th hr after drug application remain undetected. The absence of rebound phenomena with most drugs may, therefore, not reflect their real capacity to depress REM sleep without a rebound effect.

All compounds reported here depressed REM sleep in appropriate doses. Since these drugs belong to classes with widely differing psychotropic activities, suppression of REM sleep might appear to be a non-specific drug effect. This assumption is, however, not valid if the effects which these drugs exerted at the lowest doses that significantly altered SWC are considered. These doses were much lower than those used in most previous sleep studies in cats (Hishikawa, Nakai, Ida, and Kaneko, 1965; Delorme, 1966; Wallach, Winters, Mandell and Spooner, 1969; Baldy-Moulinier, Dapres and Passouant, 1969), and, most importantly, separated the drugs into four distinctly different classes: (1) those that selectively depressed REM sleep (antidepressants, MAO inhibitors, 5-HTP); (2) those which reduced both REM and NREM sleep (methylphenidate, LSD); (3) those depressing REM sleep, but increasing NREM sleep (cyproheptadine); and (4) neuroleptics (haloperidol, chlorpromazine), which had weak or no significant effects on sleep parameters.

(1) *Drugs which selectively depress REM sleep*

The characteristic property of the compounds of this group is to suppress REM sleep at doses which had no significant effects on NREM sleep. The reduction by minimum effective doses of REM sleep was mainly due to a shorter duration of individual REM phases and not to a decreased number of episodes.

indicating that these drugs act by impairing the animal's capacity to maintain sleep rather than by preventing the initiation of these phases. Doses higher than minimum effective ones altered the brain electrical activity in all states of SWC, i.e. amplitudes of cortical and hippocampal waves increased. No attempt was made in this study to quantify these changes of the EEG.

(a) *Imipramine-like antidepressants and newer derivatives with potential antidepressant activity*

The tertiary amines, clomipramine, imipramine and amitriptyline were more potent in depressing REM sleep than the secondary amines, desipramine, nortriptyline, Ro 03-5939 and maprotiline; there was a 30 fold difference in the potency between the two extremes, clomipramine (0.1 mg kg^{-1}) and maprotiline (3 mg kg^{-1}). Similar, but less marked effects were found by Baxter and Gluckman (1969).

According to the present state of knowledge, the action of imipramine-like antidepressants most relevant for their therapeutic activity seems to be the inhibition of the neuronal reuptake of monoamine transmitters (Carlsson, 1970; Biel and Bopp, 1974), the tertiary amines being more potent inhibitors of 5-HT, and the secondary amines more potent on NA uptake. The relative order of potencies of imipramine-like drugs as REM sleep depressants suggests that the mechanism of REM sleep control is more sensitive to agents that affect the dynamics of 5-HT transmission than to those acting preferentially on NA systems. This striking relationship has previously been observed in studies of PGO waves in the cat (Ruch-Monachon, Jalfre and Haefely, 1976), which are a characteristic phasic component of REM sleep. This study thus confirms the hypothesis that REM sleep and PGO waves are under a tonic inhibitory influence of 5-HT and NA neurons, as both phenomena are augmented by drugs and procedures that reduce the activation of 5-HT and/or NA receptors and suppressed by agents which increase the activation of these receptors (Ruch-Monachon *et al.*, 1976; Brooks and Gershon, 1977).

Most of the imipramine-like drugs found to depress REM sleep here were reported to have similar effects in man (Toyoda, 1964; Ritvo, Ornitz, La Franchi and Walter, 1967; Dunleavy, Brězinová, Oswald, MacLean and Trinker, 1972; Passouant *et al.*, 1972). The lack of systematic dose-response studies in man, however, makes it impossible to correlate the relative potencies of these drugs in man and in the cat. Nevertheless, the existence of such a correlation is very likely, since clomipramine was found to be the most potent drug in reducing REM sleep in healthy volunteers and depressive patients (Dunleavy *et al.*, 1972; Passouant *et al.*, 1972).

(b) *Mianserin, iprindole and viloxazine*

These 3 drugs, which are claimed to possess antidepressant activity in man but which differ from imipramine-like compounds in their pharmacological profile, also selectively reduced REM sleep.

Mianserin was the most potent of these and at least as potent as amitriptyline. Some authors denied any significant effect of mianserin on the uptake of monoamines (Goodlet, Mireylees and Sugrue, 1977). A recent study, however, shows mianserin to have 1/10 the potency of desipramine in blocking neuronal uptake of NA and to enhance the release of NA in field-stimulated brain slices presumably by blocking presynaptic noradrenergic α-receptors (Baumann and Maître, 1977). These two effects, and the observed increase by mianserin of the 5-HT release from brain synaptosomes (Raiteri, Angelini and Bertollini, 1976) would explain the marked REM sleep depressant effect of mianserin. Blockade of noradrenergic autoreceptors could also account for the lack of reversal by mianserin of the behavioural depressant effect of reserpine (van Riezen, Behagel and Chafik, 1975), which is a classical animal screening test for antidepressant activity. Data on the effect of mianserin on REM sleep in man were not available to us.

Iprindole selectively depressed REM sleep at the high dose of 30 mg kg^{-1}, whereas Baxter and Gluckman (1969) found no significant reduction of REM sleep in cats after doses as high as 40 mg kg^{-1}. In man, iprindole did not affect REM sleep (Dunleavy *et al.*, 1972; Passouant *et al.*, 1972). Iprindole had little effect on the uptake of monoamines and did not alter the turnover of brain monoamines (Leonard and Kafoe, 1976), but potentiated the pressor effect of sympathomimetic amines and antagonized the reserpine induced effect to some extent (Gluckman and Baum, 1969). Viloxazine reduced REM sleep at the relatively high dose (10 mg kg^{-1}) and abolished it at 30 mg kg^{-1}, which, however, induced a long-lasting epileptoid activity. In human volunteers, the drug was found to reduce REM as well as NREM sleep (Brězinová, Adam, Chapman, Oswald, and Thomson, 1977). In conceptual agreement with the above findings, viloxazine was reported to enhance the excitatory as well as the inhibitory effects of NA and 5-HT applied microiontophoretically near rat cortical neurones (Jones and Roberts, 1978).

(c) *MAO inhibitors*

The non-hydrazide MAO inhibitors, pargyline and Ro 11-1163, the former being considered an irreversible inhibitor, the latter having a short duration of action (Keller, Burkard, Kettler and Da Prada, 1978), were equipotent in their selective abolition of REM sleep. Similar findings with other MAO inhibitors were reported by Jouvet, Vimont and Delorme (1965). The exact mode of action of MAO inhibitors on monoaminergic transmission is still unknown. Their effect on REM sleep could result from a retardation of the metabolic inactivation of 5-HT and/or NA released into synapses, or from the inhibition of neuronal and/or extraneuronal uptake of the monoamines due to a rise of their intragranular and extragranular

concentration. The REM sleep suppressant effect of MAO inhibitors in depressed patients is well known and correlated with the therapeutic improvement (Akindele, Evans and Oswald, 1970; Wyatt, Fram, Kupfer and Snyder, 1971).

(d) *5-HTP*

The direct precursor of 5-HT, L-5-HTP, given together with benzerazide in order to prevent the formation of 5-HT in peripheral tissues, had no effect at 5 mg kg^{-1}, but abolished REM sleep at 50 mg kg^{-1} without inducing any side effects. Non rapid eye movement sleep was not affected significantly, confirming findings of Ursin (1976), but not of Delorme (1966) who observed a pronounced increase of NREM sleep, admittedly without injecting inhibitor of decarboxylase. The therapeutic value of 5-HTP in depression is a matter of controversy (van Praag, Korf, Dols and Schut, 1972; Matussek, Angst, Benkert, Gmür, Papousek, Rüther and Woggon, 1974; Sano, 1977).

(2) *Drugs suppressing both REM and NREM sleep*

The amphetamine-like central stimulant, methylphenidate, virtually abolished both states of sleep at the minimum effective dose (0.3 mg kg^{-1}) without producing any visible excitation. It appears, therefore, that methylphenidate at this dose affected the mechanisms controlling all states of vigilance, as was described by Jewett and Norton (1966) for a low dose of amphetamine (0.25 mg kg^{-1}).

An effect very similar to that of methylphenidate was observed after a small dose of LSD (2 μg kg^{-1}), which also did not induce signs of psychomotor stimulation. Hobson (1964) and Brooks (1975) found essentially similar results to ours with the exception that NREM sleep was not so dramatically decreased in their studies. The actions of LSD in the brain are very complex; evidence for both a stimulant and blocking effect on 5-HT receptors (Anden, Corrodi, Fuxe and Hökfelt, 1968; Boakes, Bradley, Briggs and Dray, 1970) and stimulant effect on dopamine receptors (Pieri, Pieri and Haefely, 1974) has been provided. It seems reasonable to assume that stimulation of DA receptors is primarily responsible for the increase of wakefulness (Jouvet, 1972), while the potent stimulant action on 5-HT receptors might underlie the suppression of REM sleep, the latter finding being supported by strong inhibitory effect of LSD on PGO waves (Ruch-Monachon *et al.*, 1976; Brooks, 1975).

(3) *Depression of REM sleep with concomitant increase of NREM sleep*

At the dose of 1 mg kg^{-1}, cyproheptadine markedly reduced REM sleep and enhanced NREM sleep; after 3 mg kg^{-1} REM sleep was virtually abolished. Although both mianserin and cyproheptadine are peripheral 5-HT antagonists, only for the latter drug a central 5-HT antagonistic effect was found in the hippocampus (Segal, 1976). Both cyproheptadine and mianserin slightly increased PGO waves induced by a reserpine-like drug Ro 4-1284 within a narrow dose range, indicating a weak blockade of NA and/or 5-HT receptors (Ruch-Monachon *et al.*, 1976). The mechanism, by which cyproheptadine depresses REM and augments NREM sleep, remains unexplained. There are no data on the effects of cyproheptadine on sleep in man.

(4) *Haloperidol and chlorpromazine*

Haloperidol slightly, but significantly depressed REM and NREM sleep. Doses higher than 1 mg kg^{-1} were previously shown to decrease REM sleep and to increase slow wave sleep in cats (Monti, 1968). The effect of haloperidol is probably not due to a specific interaction with mechanisms subserving the vigilance, they seem rather to result from other central actions of the drug. In keeping with this assumption, inconsistent effects on REM sleep were observed after haloperidol in humans (Nakazawa, Kotorii, Kotorii, Ohshima and Hasuzawa, 1977).

Chlorpromazine did not produce significant changes of SWC at doses of 1 and 2 mg kg^{-1}, although ataxia occurred at these minimum effective doses. The effects of chlorpromazine on sleep seem to depend on the dose and species, as indicated by divergent results reported in the literature. While Hishikawa *et al.* (1965) obtained effects similar to the results reported here, Jewett and Norton (1966) observed a depression of REM sleep and an increase of slow wave sleep with doses of 5 and 7.5 mg kg^{-1} which, however, produced ataxia and adrenolytic effects. In man, chlorpromazine was reported to decrease, and, less often, to increase REM sleep (Hartmann, 1978). The two neuroleptics are, therefore, easily differentiated from antidepressants by their rather unspecific effects on SWC.

This study shows that the only drugs which selectively depressed REM sleep at minimum effective doses and multiples thereof are imipramine and imipramine-like compounds, MAO inhibitors, 5-HTP, as well as three drugs with an antidepressant action in man but pharmacological properties different from imipramine-like drugs, viz. mianserin, viloxazine and iprindole. The mechanisms by which imipramine-like compounds, MAO inhibitors and 5-HTP affect REM sleep seem to be clearly related to the monoaminergic control of this phenomenon. There is evidence that mianserin also increases noradrenergic synaptic transmission, albeit by a mechanism different from that of imipramine-like drugs, and that viloxazine and iprindole in still another yet unknown way potentiate the synaptic effects of NA. Considering these facts and the finding that electroconvulsive shock also selectively decreases REM sleep in cats (Kaelbling *et al.*, 1968), it may be concluded that selective depression of REM sleep in cats at behaviourally inactive doses appears at present to be the animal test which has the highest predictive value for a therapeutic activity in depression. Recent findings of a reduced

REM sleep latency and increased REM sleep density in depressed patients (Kupfer, 1978) and the beneficial effect of REM sleep deprivation in depression already mentioned (Vogel, 1975) suggest that reduction of REM sleep may be causally implicated in the mode of action of presently known antidepressant treatments. The assessment of selective REM sleep depression in the cat should, therefore, become an integral part of the preclinical pharmacology of antidepressant drugs.

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