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Dopamine Autoreceptor Antagonists: Effects on Sleep-Wake Activity in the Rat

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SVENSSON, K., P. ALFÖLDI, M. HAJÓS, G. RUBICSEK, A. M. JOHANSSON, A. CARLSSON AND F. OBÁL, JR. *Dopamine autoreceptor antagonists: Effects on sleep-wake activity in the rat.* PHARMACOL BIOCHEM BEHAV **26**(1) 123–129, 1987.—The effects of the putative dopamine (DA) autoreceptor antagonists cis-(+)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin, (+)-UH 232, and cis-(+)-5-methoxy-1-methyl-2-(n-propylamino)tetralin, (+)-AJ 76, on sleep-wake activity, EEG, and motor activity in the rat were studied. Both drugs induced a dose-dependent increase in wakefulness (W) and a reduction in non-REM sleep (NREMS). A definite tendency to a suppression of REM sleep (REMS) could also be observed. The results of spectral analysis indicated that EEG slow wave activity, a marker of sleep intensity, was particularly sensitive to the drugs. Slight differences between the two drugs were observed: (+)-AJ 76 seemed to be more efficacious than (+)-UH 232 in stimulating motor activity. (+)-UH 232 tended to suppress slow wave activity more strongly than (+)-AJ 76. It is suggested that the increase in W following administration of (+)-AJ 76 resulted predominantly from locomotor activation, while (+)-UH 232 might also act on dopaminergic mechanisms involved in the regulation of sleep.

Dopamine autoreceptors Dopamine antagonists EEG Sleep-wake activity Motor activity Rat

THE synthesis [10] and the in vivo pharmacology [22–24] of the putative dopamine (DA) autoreceptor antagonists cis-(+)-(1S,2R)-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin, (+)-UH 232, and cis-(+)-(1S, 2R)-methoxy-1-methyl-2-(n-propylamino)tetralin, (+)-AJ 76, were recently described. Both drugs produced a marked elevation of brain DA synthesis rate and turnover with only slight effects on the synthesis and turnover of serotonin (5-HT) and noradrenaline (NA) being noted. The apomorphine-induced decrease in DA synthesis rate in gamma-butyrolactone treated animals was completely blocked by (+)-UH 232 and (+)-AJ 76. In activity experiments using habituated animals, (+)-UH 232 and (+)-AJ 76 induced locomotor hyperactivity and weak stereotypies and antagonized the sedative effects of low doses of apomorphine. Locomotor stimulation was also observed in non-habituated rats; a slight hypomotility was noted only after the highest doses (52–204 μmol/kg) of (+)-UH 232. These effects contrast those produced by classical DA receptor antagonists, which are known to induce strong hypomotility and catalepsy. It was concluded that (+)-UH 232 and (+)-AJ 76 produce behavioural stimulation via a preferential antagonism on central DA autoreceptors, an action different from that of all known stimulants including, e.g., apomorphine and d-amphetamine.

Patients with Parkinson's disease suffer from sleep disturbances [1]. A low dose of the dopamine agonist apomorphine has been shown to induce sedation and sleep in human subjects [6], and this effect is absent in patients treated with L-DOPA for severe Parkinsonism [2]. These observations indicate that dopaminergic neurotransmission may contribute to the regulation of sleep-wake activity. Reviews of the results of the pharmacological experiments on animals led to the conclusion that DA in the central nervous system plays a role as a vigilance enhancing "instrument" [14]; the normal activity of DA neurons is required for motor behaviour, and thereby DA-mechanisms are involved in the maintenance of wakefulness [25].

The aim of the present experiments was to study the way in which the behavioural stimulation induced by (+)-AJ 76 and (+)-UH 232 affects sleep-wake parameters in the rat. Three different doses (3.2, 13 and 52 μmol/kg) of the drugs were tested; the lowest dose being a threshold dose for locomotor stimulation [22,23]. The sleep-wake activity was fol-

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lowed by means of recording the EEG and motor activity. In order to establish the drug effects on EEG slow wave activity (a measure of the function of sleep mechanisms) [3,4], EEG data were evaluated through spectral analysis.

METHOD

Male CFY rats (Szeged, Hungary) weighing 300–350 g were used. Under pentobarbital anaesthesia (50 mg/kg, IP), golden jewellery screws were implanted over the frontal and parietal cortices and over the cerebellum for EEG recording. The rats were allowed to recover for at least one week before the experiments.

The animals were raised in a light-dark cycle of 12 hours each (light on from 8:30 to 20:30), and at an ambient temperature of 21°C. The same conditions were maintained in the sound-attenuated recording chambers, which were equipped with loudspeakers providing low-level continuous noise. The rats were housed individually in Plexiglas cages in the experimental chamber with food and water continuously available. In order to habituate the animals to the recording conditions, the rats were connected to the flexible recording cables for 5 days before the experiments. The subcutaneous (SC) injection of the drugs or the solvent (saline) was timed 15 to 10 min before light onset. The animals received saline (SC) for 5 days and the sleep-wake activity, EEG and motor activity were recorded on day 5; these records were regarded as baselines. Test drugs were administered the following morning.

The (1S,2R)-(+)-enantiomers of cis-5-methoxy-1-methyl-2-(di-n-propylamino)tetralin hydrochloride, UH 232, and cis-5-methoxy-1-methyl-2-(n-propylamino)tetralin hydrochloride, AJ 76, were dissolved in saline (0.9% NaCl) and injected SC at a volume of 5 ml/kg. Both drugs were tested at the doses 3.2, 13 and 52 μmol/kg and each dose was administered to a group of 8 rats. Due to technical failures, one animal in the group injected with 13 μmol/kg (+)-UH 232 was discarded from the analysis of sleep-wake activity and EEG.

The EEG and motor activity were recorded on a paper chart (7.5 mm/sec). An electromagnetic transducer activated by cable movements was used to record motor activity. The vigilance states were scored in 40-sec intervals as wakefulness (W), non-REM sleep (NREMS) and REM sleep (REMS) according to conventional visual criteria, i.e., W: EEG theta activity plus motor activity; NREMS: synchronized EEG (slow waves and/or spindels) without motor activity; and REMS: highly regular EEG theta activity with occasional "activity" twitches. A 40-sec epoch was scored according to the predominant vigilance state. The percentage distribution of the vigilance states was calculated for 1 hour periods. Following analysis of variance, the paired *t*-test (two-sided) was used to evaluate the difference between the results on the drug day and the saline day.

EEG signals (filtering: below 0.53 Hz and above 30 Hz at 6 dB/octave) in the first 3 hours of the recording period were subjected to an analogue-to-digital conversion (sampling rate: 100 Hz), and fed into a computer for spectral analysis through the fast Fourier transformation. Power density values (μV^2/0.5 Hz) were computed for consecutive 2.5 sec periods. The power density spectra were averaged for 1 min periods, and the values were integrated for 2 Hz frequency ranges between 0.5 and 12 Hz, and for 4 Hz frequency ranges between 12.5 and 20 Hz. Finally, the mean power density values were calculated for the consecutive 1 hour periods. The differences between the results on the drug day and the saline day were expressed as percentages of the baseline power density values. Paired *t*-test (two-sided) was used to estimate the significance of the differences.

Effects on motor activity were quantified in the case of 13 μmol/kg of (+)-UH 232 and (+)-AJ 76. The motor activity (assessed as integrated activity counts (cable movements) per 30 sec) recorded in the first 2 hours was fed into a computer and the differences between the results on the drug day and on the saline day were evaluated by means of paired *t*-test (two-sided).

RESULTS

Effects on Sleep-Wake Activity

The baseline percentages of the vigilance states calculated for the 12 hours light period were similar in the groups injected with (+)-UH 232 (W: 25–29%; NREMS: 58%; REMS: 14–17%) or (+)-AJ76 (W: 28–31; NREMS: 55–57%; REMS: 13–15%).

The lowest dose (3.2 μmol/kg) of (+)-UH 232 increased W and reduced NREMS in hour 1; thereafter the percentage amounts of the vigilance states oscillated around the baseline values (Fig. 1, upper part). Increased doses of (+)-UH 232 enhanced the arousing effect; the rats were awake for 1 hour after 13 μmol/kg, and the increase in W was statistically significant 2 hours after 52 μmol/kg of (+)-UH 232. The changes in NREMS were opposite to those in W. REMS tended to be suppressed for 2 and 3 hours following administration of 13 and 52 μmol/kg of (+)-UH 232, respectively, however, statistical significance was not reached. A trend towards reduced REMS was observed throughout the 12-hour recording period after the highest dose of (+)-UH 232. A rebound-like compensatory increase in NREMS was noted 3 hours after administration of each dose of (+)-UH 232, although statistical significance was obtained only in the case of 52 μmol/kg.

The effects of (+)-AJ 76 on the sleep-wake activity resembled those of (+)-UH 232. The smallest dose (3.2 μmol/kg) of (+)-AJ 76 tended to increase W and decrease NREMS in hour 1, whereas REMS remained unaffected (Fig. 1, lower part). The increase in W and the reduction in NREMS persisted for 2 hours after the administration of 13 and 52 μmol/kg of (+)-AJ 76 and REMS was reduced for 3 hours following 52 μmol/kg. The NREMS suppression elicited by 13 and 52 μmol/kg of (+)-AJ 76 was followed by an increase in NREMS and the rebound-like changes in W were also obvious. After the initial decrease, the REMS percentages returned to baseline levels.

Analysis of EEG Spectra

As described by Borbély *et al.* [4], the power density spectra of the rat EEG (recorded through the same derivation as in our experiments) are interpreted as follows: the power density values in the low-frequency range (up to 6 Hz) are a measure of slow wave activity and a sensitive indicator of the slow wave sleep portion of NREMS. The theta activity characteristic of W and REMS is reflected by relatively high power density values in the 6 to 9 Hz frequency range, but these values may also be appreciably high in NREMS. Spindles, appearing primarily in shallow NREMS and less frequently for short periods of quiet W, and low-amplitude

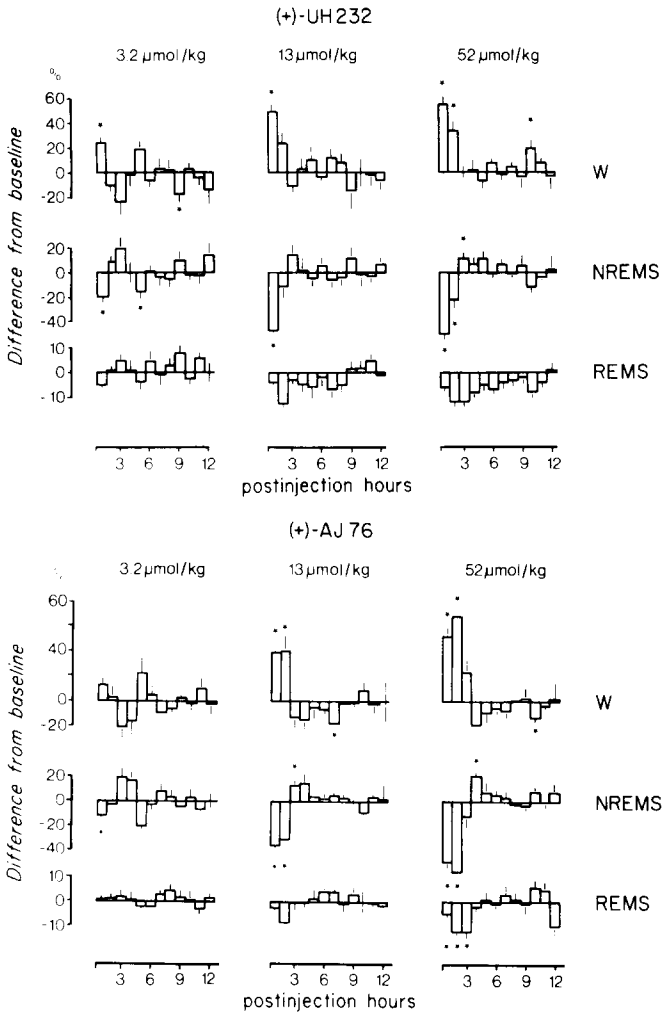

FIG. 1. Effects of (+)-UH 232 (upper part) and (+)-AJ 76 (lower part) on sleep-wake activity in the rat. W, NREMS and REMS denote wakefulness, non-REM sleep and REM sleep, respectively. The doses used were 3.2, 13 and 52 μmol/kg, n=8 (except 13 μmol/kg of (+)-UH 232: n=7). Shown are the mean deviations (±S.E.M.) from the baseline values expressed as % of the recording time for each hour in the 12-hour light period. Drugs were injected at light onset. Statistics: analysis of variance followed by paired *t*-test (two sided): $*p<0.05$ vs. baseline (saline control) values.

waves found occasionaly during W and shallow NREMS, relate to frequencies beyond 9 Hz. In accordance with this, it was earlier reported [4,26] that the highest power density values in the frequency range from 10 to 20 Hz are recorded in NREMS.

(+)-UH 232 and (+)-AJ 76 markedly reduced the slow wave activity. The two highest doses of these drugs also decreased the power density in the high-frequency range, whereas only slight changes in the power density values in the theta range (6–9 Hz) were noted (Fig. 2). This general picture varied somewhat with the two drugs and the doses used.

The lowest dose (3.2 μmol/kg) of (+)-UH 232 produced a marked reduction in the slow wave activity in hour 1. This reduction was apparent, though less pronounced, also in hour 2 (Fig. 2, upper part). The same dose of (+)-UH 232 increased the power density in the high-frequency range in hour 2 and 3, and there was also a trend towards increased slow wave activity in hour 3. Administration of 13 or 52 μmol/kg of (+)-UH 232 elicited decreases in both the slow wave and high-frequency activities in hour 1. The reduction in the power density in the low-frequency range was evident also in hour 2. An increase in the power density in the high-frequency range was noted in hour 3 after the two highest doses of (+)-UH 232. The middle dose of (+)-UH 232 increased the power density in the theta range (6–9 Hz) during the first two hours, whereas the highest dose of (+)-UH 232 was less effective in this respect.

A decrease in slow wave activity was noted after 3.2 μmol/kg of (+)-AJ 76 in hour 1 (Fig. 2, lower part). This effect was followed by a rebound-like enhancement in slow wave activity in hour 3. Both low and high-frequency activities were reduced in animals treated with 13 or 52 μmol/kg of (+)-AJ 76, and this reduction persisted for 2 hours after the highest dose. Enhancement of slow wave activity was observed after 13 μmol/kg of (+)-AJ 76 in hour 3. In contrast to (+)-UH 232, (+)-AJ 76 (3.2–52 μmol/kg) failed to significantly increase the power density in the high-frequency range during the 3-hours time interval. The theta activity was not affected by (+)-AJ 76, except for a slight decrease noted in hour 2 after the highest dose tested.

Effects on Motor Activity

The motor activity was measured in rats treated with 13 μmol/kg of (+)-UH 232 (Fig. 3) or (+)-AJ 76 (Fig. 4) and the results were compared to the activity measured on the saline day. Both drugs caused a pronounced behavioural stimulation, and concerning each 10 min interval, (+)-UH 232 and (+)-AJ 76 produced up to four and ten-fold increases in motor activity, respectively, compared to the saline control values (data not shown). The mean (±S.E.M., n=8) increase in motor activity was +243±50% ($p<0.05$) for (+)-UH 232 and +249±94% ($p<0.05$) for (+)-AJ 76 in hour 1. The increase in motor activity, compared to the saline control values, appeared to be even more pronounced in hour 2. However, only the motor hyperactivity induced by (+)-AJ 76 reached statistical significance: (+)-UH 232 (+712±626%); (+)-AJ 76 (+649±19%, $p<0.05$).

Observations of the gross behaviour revealed a pronounced motor stimulation combined with weak stereotypies (sniffing and rearing) after 52 μmol/kg of (+)-UH 232 and (+)-AJ 76. However, the latter effects were not quantified.

DISCUSSION

The putative DA autoreceptor antagonists, (+)-UH 232 and (+)-AJ 76, produced similar effects on the rat sleep-wake activity. (1) Both drugs induced a dose-dependent increase in W and a reduction in sleep, primarily in NREMS. (2) Spectral analysis suggested that the slow wave sleep portion of NREMS was particularly sensitive to the drugs. (3) A tendency to REMS suppression could be observed for both drugs. (4) In agreement with previous findings [22–24] obtained with a different technique, a pronounced increase in motor activity was noted after 13 μmol/kg of (+)-UH 232 and (+)-AJ 76.

It has been shown that variations in central DA metabo-

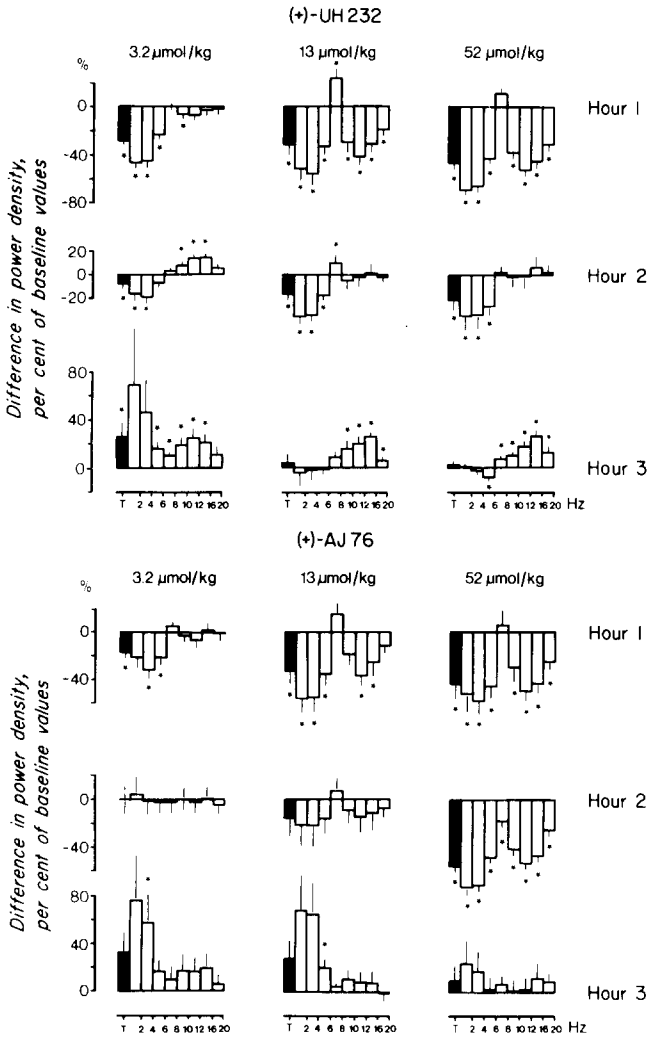

FIG. 2. Effects of (+)-UH 232 (upper part) and (+)-AJ 76 (lower part) on the rat EEG power density spectra. The changes in the power density values in the frequency bands are expressed as % deviations from the baseline values (means±S.E.M.) for each hour during the first 3-hour recording period. Black columns indicate changes in the total power (T); white columns indicate changes in the power density values in the frequency bands. Each frequency band is marked by its upper limit. Doses and number of animals: same as in Fig. 1. Statistics: paired *t*-test (two sided): $*p<0.05$ vs. baseline (saline control) values.

lism can be correlated with the sleep-wake activity, suggesting that dopaminergic mechanisms might be involved in sleep regulation [15]. The basic observations relating central dopaminergic mechanisms to the regulation of sleep-wake activity derives from experiments with DA receptor agonists, such as apomorphine. Low doses of agonists have been demonstrated to promote sleep, while high doses increase W [9, 11, 12, 16] and these effects can be blocked by DA receptor antagonists [6, 9, 16]. The biphasic effects on sleep corroborate the findings that a low dose of apomorphine causes behavioural depression, whereas high doses induce hyperactivity and stereotyped behaviour [8,20]. This phenomenon is considered to reflect stimulation of dopaminergic auto- and postsynaptic receptors after low and high doses of apomorphine, respectively [5]. On the other hand, classical DA receptor blockers, such as spiroperidol and haloperidol, are reported to increase slow wave sleep and decrease W [11,17]. As suggested earlier [5], a selective antagonism of dopaminergic autoreceptors would lead to an increased release of DA which, in turn, would result in an activation of postsynaptic DA receptors and thus behavioural stimulation. Low doses of DA receptor antagonists such as haloperidol have been shown to induce behavioural excitation in animals [7,21]. However, the results are not consistent and depend highly upon the models used [7], thus reflecting the high affinity of classical antagonists to both auto- and postsynaptic DA receptors. On the other hand, the DA receptor antagonists (+)-UH 232 and (+)-AJ 76 produced biochemical effects resembling those of, e.g., haloperidol. In activity experiments, however, the former compounds induced locomotor stimulation over a wide dose-range; weak stereotypies were noted only after high doses [22–24], thus suggesting a preferential DA autoreceptor antagonistic action of these agents (cf. Introduction).

The effects of (+)-UH 232 and (+)-AJ 76 on motor activity and sleep-wake activity were similar to those observed after a high dose of apomorphine, though the possibility of slight differences cannot be excluded. Thus, the increase in W noted after a high dose of apomorphine has a duration of about 1 hour [16] while the arousing effect of the highest doses of (+)-UH 232 and (+)-AJ 76 lasted for 2 hours. Furthermore, high doses of apomorphine produced marked stereotyped behaviour, whereas only occasional sniffing and rearing were noted after the highest dose of (+)-UH 232 and (+)-AJ 76 (this study and [24]).

The effects of (+)-UH 232 and (+)-AJ 76 on sleep-wake activity support the notion that postsynaptic DA activation (in this case produced indirectly by the two (+)-enantiomers) results in decreased sleep and increased W. Considering the evidently enhanced motor activity, it has been suggested that the increased W is predominantly due to a behavioural stimulation resulting from the activation of the nigrostriatal DA system [25].

However, the changes in motor activity cannot fully explain the changes in sleep-wake activity following drugs acting on DA mechanisms. Wauquier [25] pointed out that a reduction of behavioural activity does not necessarily lead to sleep. It seems therefore that, besides affecting motor activity through which the drugs interfering with DA transmission create favourable conditions either for W or sleep, these drugs also act on other mechanisms via inhibiting or promoting active sleep mechanisms. The latter effect has been attributed to DA systems not primarily involved in the generation of motor activity, probably the mesolimbic and mesocortical systems [25]. There are also other findings suggesting an influence of dopaminergic neurotransmission on sleep-wake mechanisms. Thus, Kafi and Gaillard [11] observed that the DA antagonist spiroperidol increased sleep without affecting motor activity (EMG) in rats. Gessa *et al.* [9] reported that antagonism of dopamine D-1 receptors by means of a high dose of SCH 23390 resulted in decreased locomotor activity with no effects on the EEG pattern being observed. In contrast, the selective D-1 receptor agonist SKF 38393 produced EEG desynchronization in rats while only slight effects on the behaviour were noted [19]. Finally, as a result of experiments on encéphale isolé cats, DA neurotransmission has been implicated in the generation of EEG spindle activity [13]. In fact, injection of low and high doses of DA into the

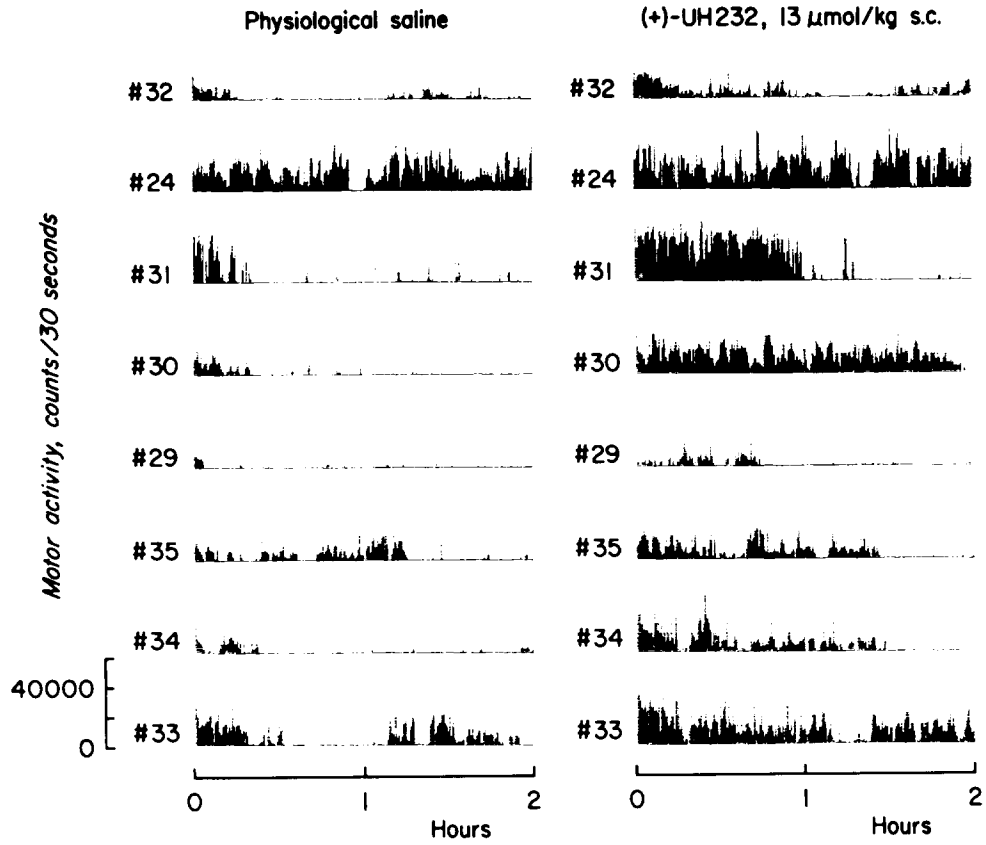

FIG. 3. Effects of (+)-UH 232 (13 μmol/kg) on rat motor activity. The results are expressed as integrated motor activity counts (cable movements) per 30 sec for the first 2-hour recording period following saline treatment (left part) or drug treatment (right part), n=8. The numbers (#) to the left of the recordings refer to the individual rats.

caudate nucleus increased and suppressed spindle activity, respectively, in gallamaine paralysed rats, thus indicating a direct EEG effect of DA [18].

Accepting that the increased motility is not the single mechanism responsible for the enhanced W following dopaminergic activation, it is worth noting that the effects of (+)-UH 232 and (+)-AJ 76 exhibited some, but slight differences. It has been shown that (+)-AJ 76 is more efficacious than (+)-UH 232 in stimulating motor activity [24]. In contrast, EEG slow wave activity (regarded as a marker of the function of sleep mechanisms [3]), appeared to be suppressed more strongly after (+)-UH 232 than after (+)-AJ 76. Slow wave activity was still significantly reduced in hour 2 following 13 μmol/kg of (+)-UH 232, while no significant alterations in motor activity and vigiliance states were observed at this time. In the case of (+)-AJ 76, the recovery from locomotor stimulation gave way to an immediate normalization of the percentages of the vigilance states (in fact, W and NREMS were back to normal levels sooner than was the locomotor activity after 13 μmol/kg of (+)-AJ 76), and the baseline level of slow wave activity was recovered or slow wave activity tended to increase. The inhibition of slow wave activity following the administration of (+)-UH 232 declined slowly, allowing only shallow NREMS initially. The possibility that a difference in pharmacokinetics of the two (+)-enantiomers account for the different effects on sleep-wake activity cannot be ruled out. However, the above findings may also indicate the presence of (at least partly) separate dopaminergic mechanisms, regulating motor activity and sleep-wake activity.

In summary, the preferential DA autoreceptor antagonists (+)-UH 232 and (+)-AJ 76 induce a dose-dependent increase of W and a suppression of sleep, effects that are comparable to those elicited by high doses of apomorphine. However, the mechanisms by which apomorphine and the former agents produce behavioural arousal are different. These observations support the view that dopaminergic neurons are involved in the regulation of the sleep-wake activity.

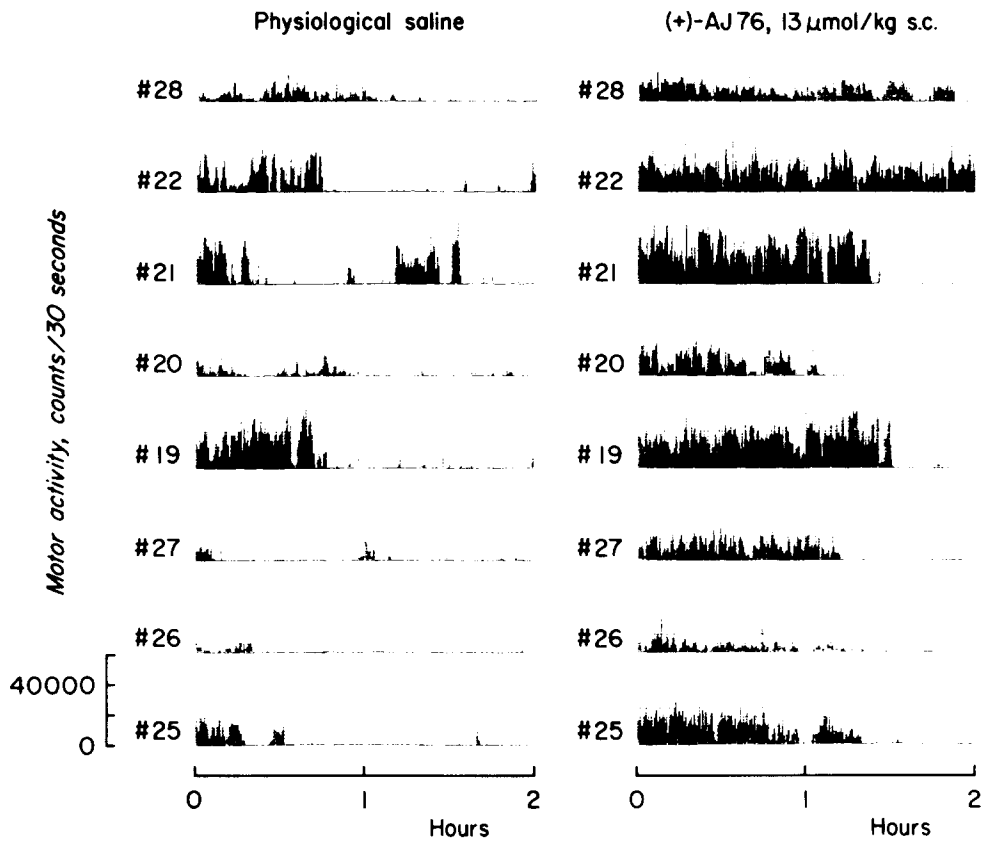

FIG. 4. Effects of (+)-AJ 76 (13 μmol/kg) on rat motor activity. For further information, see Fig. 3.

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REFERENCES

1. Askenazy, J. J. M. Sleep patterns in extrapyramidal disorders. *Int J Neurol* **15:** 62–76, 1981.
2. Bassi, S., M. G. Albizzati, L. Frattola, D. Passerini and M. Trabucchi. Dopamine receptors and sleep induction in man. *J Neurol Neurosurg Psychiatry* **42:** 458–460, 1979.
3. Borbély, A. A. A two process model of sleep regulation. *Hum Neurobiol* **1:** 195–204, 1982.
4. Borbély, A. A., I. Tobler and M. Hanagasioglu. Effects of sleep deprivation on sleep and EEG power spectra in the rat. *Behav Brain Res* **14:** 171–182, 1984.
5. Carlsson, A. Receptor-mediated control of dopamine metabolism. In: *Pre- and Postsynaptic Receptors*, edited by E. Usdin and W. E. Bunney. New York: Marcel Dekker, 1975, pp. 49–63.
6. Corsini, G. U., S. Manconi, M. Del Zompo, M. F. Piccardi, P. L. Onali, A. Mangoni and G. Gessa. Evidence for dopamine receptors in the human brain mediating sedation and sleep. *Life Sci* **20:** 1613–1618, 1977.
7. Costall, B., A. M. Domeney and R. B. Naylor. Stimulation of rat spontaneous locomotion by low doses of haloperidol and (−)-Sulpiride: importance of animal selection and measurement technique. *Eur J Pharmacol* **90:** 307–314, 1983.
8. Di Chiara, G., M. L. Porceddu, L. Vargiu, A. Argiolas and G. L. Gessa. Evidence for dopamine receptors mediating sedation in the mouse brain. *Nature* **264:** 564–566, 1976.
9. Gessa, G. L., M. L. Porceddu, M. Collu, G. Mereu, M. Serra, E. Ongini and G. Biggio. Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. *Eur J Pharmacol* **109:** 269–274, 1985.
10. Johansson, A. M., L.-E. Arvidsson, U. Hacksell, J. L. G. Nilsson, K. Svensson, S. Hjorth, D. Clark, A. Carlsson, D. Sanchez, B. Anderson and H. Wikström. Novel dopamine receptor agonists and antagonists with preferential action on autoreceptors. *J Med Chem* **28:** 1049–1053, 1985.
11. Kafi, S. and J. M. Gaillard. Brain dopamine receptors and sleep in the rat: effects of stimulation and blockade. *Eur J Pharmacol* **38:** 357–363, 1976.
12. Kafi-de St. Hilaire, S., J.-Y. Sovilla, S. Hjorth and J. M. Gaillard. Modifications of sleep parameters in the rat by (+)- and (−)-3-PPP. *J Neural Transm* **62:** 209–217, 1985.

13. Keane, P. E., J. M. Candy and P. B. Bradley. The role of endogenous catecholamines in the regulation of electrocortical activity in the encéphale isolé cat. *Electroencephalogr Clin Neurophysiol* **41:** 561–570, 1976.
14. Koella, W. P. Neurotransmitter and sleep—A synthesis. In: *Sleep '84*, edited by W. P. Koella, E. Rüther and H. Schulz. Stuttgart: Gustav Fischer, 1985, pp. 28–39.
15. Kovacevic, R. and M. Radulovacki. Monoamine changes in the brain of cats during slow-wave sleep. *Science* **193:** 1025–1027, 1976.
16. Mereu, G. P., E. Scarnati, E. Paglietti, B. Pellegrini Quarantotti, P. Chessa, G. Di Chiara and G. L. Gessa. Sleep induced by low doses of apomorphine in rats. *Electroencephalogr Clin Neurophysiol* **46:** 214–219, 1979.
17. Monti, J. M. The effects of neuroleptics with central dopamine and noradrenaline receptor blocking properties in the L-DOPA and (+)-amphetamine-induced waking EEG in the rat. *Br J Pharmacol* **67:** 87–91, 1979.
18. Okuyama, S., S. Hashimoto and H. Aihara. Effects on the caudate spindle in rats of dopamine microinjected into the caudate nucleus. *Neurosci Lett* **59:** 27–32, 1985.
19. Ongini, E., M. G. Caporali and M. Massotti. Stimulation of dopamine D-1 receptors by SKF 38393 induces EEG desynchronization and behavioral arousal. *Life Sci* **37:** 2327–2333, 1985.
20. Strömbom, U. Catecholamine receptor agonists: Effects on motor activity and rate of tyrosine hydroxylation in mouse brain. *Naunyn Schmiedebergs Arch Pharmacol* **292:** 167–176, 1976.
21. Strömbom, U. Antagonism by haloperidol of locomotor depression induced by small doses of apomorphine. *J Neural Transm* **40:** 191–194, 1977.
22. Svensson, K., S. Hjorth, D. Clark, A. Carlsson, H. Wikström, B. Andersson, D. Sanchez, A. M. Johansson, L.-E. Arvidsson, U. Hacksell and J. L. G. Nilsson. Novel stereoselective dopamine receptor antagonists with preferential action on autoreceptors. *J Neural Transm* **65:** 1–27, 1986.
23. Svensson, K., A. Carlsson, A. M. Johansson, L.-E. Arvidsson and J. L. G. Nilsson. A homologous series of N-alkylated cis-(+)-(1S,2R)-5-methoxy-1-methyl-2-aminotetralins: central dopamine receptor antagonists showing profiles ranging from classical antagonism to selectivity for autoreceptors. *J Neural Transm* **65:** 29–38, 1986.
24. Svensson, K., A. M. Johansson, T. Magnusson and A. Carlsson. (+)-AJ 76 and (+)-UH 232: central stimulants acting as preferential dopamine autoreceptor antagonists. *Naunyn Schmiedebergs Arch Pharmacol*, in press, 1986.
25. Wauquier, A. Dopamine: its active and permissive role in sleep-wakefulness. In: *Sleep' 84*, edited by W. P. Koella, E. Rüther and H. Schultz. Stuttgart: Gustav Fischer, 1985, pp. 14–16.
26. Young, G. A., G. F. Steinfels and N. Khazan. Cortical EEG power spectra associated with sleep-awake behavior in the rat. *Pharmacol Biochem Behav* **8:** 89–91, 1978.