Ketamine Administration During Waking Increases Delta EEG Intensity in Rat Sleep

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Ketamine is known to increase the metabolic rate of limbic brain structures. We exploited this action to test a hypothesis of the homeostatic model of delta sleep: that an increase in the waking metabolic rate of plastic neuronal systems would increase delta electroencephalographic (EEG) intensity in subsequent nonrapid-eye-movement (NREM) sleep. In separate experiments, we gave intraperitoneal injections of ketamine to Sprague-Dawley rats of either 15, 25, or 50 mg/kg (0.055, 0.091, 0.18 mmol/kg) three times, at approximately hourly intervals, during the dark (waking) period; the last dose was given 4 to 5 hours before onset of the light (sleep) period. After ketamine, both NREM duration and delta EEG intensity (amplitude and incidence) increased significantly over control (saline injections) levels. The magnitude of this increase places it among the largest pharmacologically induced stimulations of delta sleep yet observed. The interpretation of this effect is complicated by the fact that ketamine produces widespread metabolic changes throughout the brain and it also acts on several receptor classes. However, since ketamine's major action is noncompetitive blockade of the cation channel gated by the N-methyl-D-aspartate receptor, our data join recent observations that suggest that excitatory amino acid receptor systems are involved in sleep regulation. ***[Neuropsychopharmacology 9:41–48, 1993]***

KEY WORDS: *Sleep; EEG; Delta; Period/amplitude analysis; Ketamine; NMDA receptors; Rat*

This experiment was undertaken to test a prediction derived from the original homeostatic model of human slow-wave sleep (Feinberg 1974). One component of this model holds that an increase in the waking metabolic rate of plastic neuronal structures will increase the intensity of delta electroencephalogram (EEG) in subsequent nonrapid-eye-movement (NREM) sleep. This component was based on indirect evidence. Children have higher rates of cerebral metabolism (Kennedy and Sokoloff 1957; Chugani et al. 1987), presumably as a result of more intense plastic neuronal activity. They also have, proportionally, a higher incidence and amplitude of delta waves during NREM sleep. (Elsewhere, we have shown that the ontogenetic curves for human cortical metabolic rate and delta wave amplitude parallel that for synaptic density; all three brain variables show a steep decline over late childhood and adolescence [Feinberg et al. 1990b]. Although synaptic reorganization [toward fewer but more effective synapses] is a major part of brain reorganization during the second decade of life, we speculate that this is only one component of a process in which neurons lose relative equipotentiality and become "committed" to specific roles in neural networks. In this revised model, both delta amplitude and waking metabolic rate are proportional to the number of uncommitted neurons [Feinberg et al. 1990a]).

Deoxyglucose studies of the brain effects of ketamine and its structural analogs, 1-(1-phenylcyclohexyl) piperidine (PCP) and MK-801, suggested a more direct, albeit limited test of the intensity hypothesis. These drugs increase glucose utilization in plastic structures in the rat brain (hippocampus, cingulate and entorhinal cortex) and decrease uptake in sensory and other

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cortical areas (Meibach et al. 1979; Crosby et al. 1982; Hammer and Herkenham 1983; Weissman et al. 1987; Kurumaji et al. 1989). Recognizing that the interpretation of any sleep changes would be complicated by the multiple actions of ketamine on both brain metabolism and neurotransmitter systems, we nevertheless administered ketamine to rats as an experimental "first approach" to the hypothesis that the intensity of delta EEG in NREM sleep depends in part on the metabolic rate of plastic neuronal systems during waking.

MATERIALS AND METHODS

Electrodes were implanted under pentobarbital (65 mg/kg, 0.26 mmol/kg) and methoxyflurane anesthesia into Sprague-Dawley rats (n = 10) each weighing between 300 to 350 gm for chronic EEG recording. Cortical EEG was recorded from stainless-steel screws implanted through the skull over the frontoparietal cortex. Hippocampal EEG was recorded from a stereotactically placed bipolar electrode, except for three animals where hippocampal theta was measured from midline cranial screws. Electromyograms (EMG) were recorded from stainless-steel wires embedded in the nuchal muscles.

Two or more weeks after surgery, the rats were habituated to the recording cable on one or more occasions lasting at least 12 hours. A commutator and counterbalance for the cable's weight allowed each rat to move freely about its cage. An experimental session consisted of 3 consecutive days: a 24-hour period for further adaptation during which the animals were attached to the cable in the recording cage with the equipment turned off; a 24-hour recording period in which they received three intraperitoneal (IP) injections of saline given at about the same time intervals as the corresponding ketamine dosage; and a 24-hour recording period in which they received three IP ketamine HCl injections of either 15 (n = 5), 25 (n = 4) or 50 mg/kg (n = 5) [0.055, 0.091, or 0.18 mmol/kg]. One rat was studied under both the 15 and 25 mg/kg doses, one rat was studied under both the 25 and 50 mg/kg doses, and one rat was studied under all three doses so that the 10 rats provided 14 saline–ketamine comparisons. The injections were given during the dark (wake) period under dim red illumination. A 12-hour light/dark cycle was maintained for at least 2 weeks prior to the study. For those animals who received more than one dose, at least 1 week separated the experiments.

The actual duration of ketamine's metabolic effects is not known. In an effort to produce a sustained increase in limbic metabolism, we gave three IP ketamine injections, waiting for the behavioral effects of each injection to disappear before giving the next. For each animal, the saline trials preceded the ketamine injections. We used this order rather than counterbalancing because we did not know whether any ketamine effects on sleep would induce compensatory reactions during the subsequent saline condition. This schedule raises the possibility that the sleep EEG changes we observed after ketamine were actually due to ongoing habituation. However, the apparent dose dependence of our findings (see below), and the fact that we have not found such habituation effects on delta in other studies with 48 hours of baseline recording renders this possibility quite remote.

Cortical and hippocampal EEG and nuchal EMG were amplified and recorded with a polygraph (Grass Model 78; Quincy, MA). The 1/2 amplitude low-frequency filters were set at 0.3 Hz for the EEG signals and 3 Hz for the EMG. The amplified signals were digitized and analyzed online with PASS PLUS, a commercially available microcomputer program (Delta Software; St. Louis, MO) that uses the zero-cross and zero-first derivative algorithms that we have applied to the EEG of human sleep for over 18 years; their reliability and validity have been established (Feinberg et al. 1978, 1980).

Zero-cross integrated amplitude (IA) in cortical and hippocampal EEG and in nuchal EMG was summed for each 10-second epoch and plotted separately on the computer monitor; 360 10-second epochs (1 hour) were displayed on a standard monitor. These graphic displays were scored visually into NREM sleep, REM sleep, and waking using the traditional criteria for vigilance states in the rat with one addition: REM was identified by a precipitous decline in hippocampal 0 to 3 Hz EEG, in addition to the increase in theta. Scoring a 12-hour record required about 2 hours with this method; for an illustration and further description of this method of computer-assisted visual sleep state scoring, see Campbell and Feinberg (1993).

The statistical analyses we employed addressed two questions. First, did ketamine (all doses together) alter subsequent sleep EEG, especially delta measures? This question was tested with a repeated-measures analysis of variance (ANOVA) using Program BMDP 2V (Dixon et al. 1990) with time (hour of light period) and condition (ketamine versus saline) as repeated measures (within factors). This analysis also tested for linear and quadratic trends in NREM sleep across the light period.

Second, we addressed the question of dose dependence. Originally, we had hoped to conduct a pure within-S dose–response study, with each animal receiving all three doses. We did not achieve this aim due to electrode failures. As a consequence, we were unable to perform a within-S ANOVA or a pure between-S ANOVA. We nevertheless applied BMDP Program 2V, using saline values as a covariate, time as a repeated

measure, and dose as a between-S grouping. In this analysis, animals who receive more than one dose were rated as separate subjects. This limitation is discussed further below.

RESULTS

Immediate Effects of Ketamine

The behavioral responses to 25 and 50 mg/kg were virtually immediate. They consisted of head swinging and increased locomotion followed by ataxia. Dark-period sleep following the higher doses was reduced (see below). The effects on waking EEG were as described by French and Domino (1988). For 15 mg/kg, the behavioral and EEG responses were delayed in onset, weaker (sometimes unapparent), and shorter lived. The third and last ketamine dose was injected an average of 3 hours 55 minutes, 4 hours 34 minutes, and 4 hours 59 minutes (for the 15, 25, and 50 mg/kg doses) before the onset of the light (sleep) period. The behavioral effects persisted for durations roughly proportional to the dose, averaging 26, 43, and 88 minutes after the third injections. Thus, onset of the light (sleep) period occurred, on average, 3 hours 33 minutes, 3 hours 49 minutes, and 3 hours 25 minutes after the behavioral effects induced by 15, 25, and 50 mg/kg were no longer evident.

Effects of Ketamine on NREM and REM Durations

The sleep measures were analyzed by hour for the first 11 hours of the light (sleep) period. Data for the 12th hour were lost because of limited disk space at the time the study was initiated.

To illustrate graphically the effects of ketamine on sleep, we combined the data for all 10 rats who received ketamine (COMB); if a rat received more than one dose, only the results for the highest dose were included. The COMB group includes three rats who received 15 mg/kg, two who received 25 mg/kg, and five who received 50 mg/kg. Statistical analyses are presented in Table 1 for the main sleep variables.

Figure 1A and B show NREM and REM durations (in minutes) under ketamine and saline conditions for hours 1 to 11 of the light period for the COMB group. Analysis of variance (Table 1) revealed that total NREM sleep was increased significantly by ketamine. Figure 1A suggests that the ketamine effect on NREM sleep occurred in the second half of the sleep period. For hours 1 to 6 the difference between ketamine and saline was small (5.1%) whereas for hours 7 to 11 it was substantial (22.1%) and significant (post-hoc paired $t = 3.02$; $p < .02$). Because almost all of the ketamine stimulation of delta intensity occurred in the first 6 hours of sleep (see below), this result suggests that ketamine first increased NREM sleep intensity and then its duration.

There were no significant effects of ketamine on REM sleep duration at any dose. Although Figure 1B suggests that ketamine suppressed REM sleep in the first part of the sleep period for the COMB group, a post-hoc *t*-test for hours 1 to 4 was not significant.

Effects of Ketamine on Cortical Delta (1 to 4 Hz) EEG within NREM

Here we present results for NREM cortical delta (1 to 4 Hz) EEG measured by the zero-cross component of PASS PLUS. We analyzed four waveform measures: IA, which for delta frequencies is almost exactly proportional to spectral power as measured with the Fast Fourier Transform (FFT) (Ktonas and Gosalia 1981; Feinberg 1989; Uchida et al. 1992); time, occupied by 1 to 4 Hz (almost entirely determined by wave incidence); average sample amplitude (ASA = IA/time in 1 to 4 Hz); and mean frequency of waves within 1 to 4 Hz.

Figure 2A to D plots the results for cortical 1 to 4 Hz EEG in NREM sleep by hour of the light period for the COMB group. Compared to the saline controls, sleep following administration of ketamine showed significant increases in the amplitude and density of delta and a decrease in 1 to 4 Hz mean frequency.

Thus, administration of ketamine during waking increased the average amplitude of delta waves (ASA) and the rate of delta wave production (IA/minute and time/minute of NREM). As NREM duration itself increased after ketamine, there were strong and significant (Table 1) increases above saline levels in *total* IA (39%) and total time occupied by delta EEG (32%).

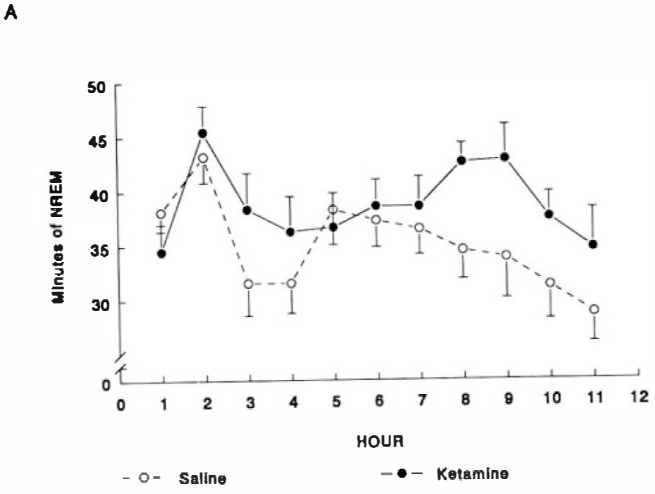
Table 1 also shows that, as predicted by the original homeostatic delta model (Feinberg 1974) and as found in subsequent studies of rat sleep by others (Bergmann et al. 1987; Trachsel et al. 1988), delta amplitude and density showed significant declining trends across sleep. Mean frequency within 1 to 4 Hz increased as amplitude declined. The inverse relation of EEG frequency and amplitude has long been known. In the NREM EEG of human sleep, amplitude has been shown to vary inversely as a power of frequency (Feinberg et al. 1984).

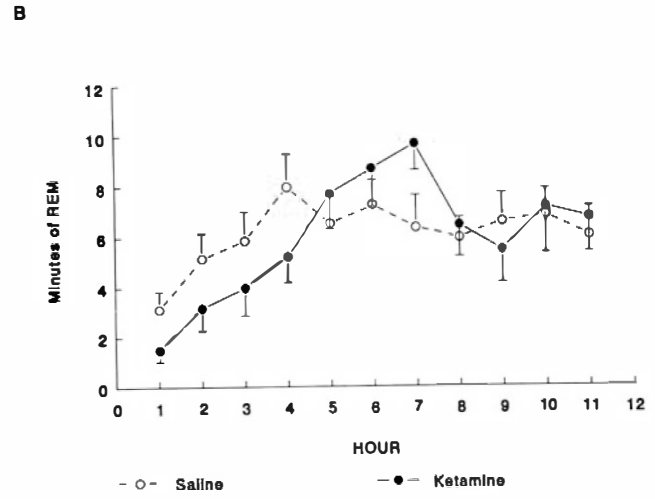
Each delta measure exhibited a highly significant linear trend across the light period. Tests for curvature (quadratic trend) were significant for some measures. A more detailed analysis of normative delta trends across NREM sleep of both the light and dark periods is presented in Campbell and Feinberg (1993). Ketamine altered the across-NREM trend of ASA, time in delta/minute and IA/minute (time × condition interaction; Table 1).

Table 1. Repeated-Measures ANOVA[1] for NREM and REM Durations and Delta (1 to 4 Hz) EEG Measures within NREM: Effects of Condition (Saline vs. Ketamine) and Trend Analysis Across Hours of the Light Period

	Condition	Time[2]			Interaction
			(Linear)	(Quad)	(Time × Cond)
	F (1, 9)	*F* (10, 90)	*F* (1, 9)	*F* (1, 9)	*F* (10, 90)
Sleep durations					
NREM min	14.4**	2.7*	4.3	2.1	1.4
REM min	0.16	6.4***	19.1**	21.8***	1.1
Delta measures					
Avg sample amp	7.94*	18.2***	19.8**	50.3**	4.8*
Time in delta/min	22.3***	76.2***	150.8***	0.42	4.5**
Total time in delta	22.1***	12.9***	63.8***	0.5	1.3
IA/min	9.7*	21.2***	25.3***	26.9***	3.9*
Total IA	18.0**	9.2***	16.6**	0.16	1.3
Mean delta freq.	35.9***	27.8***	47.8***	33.6***	1.6

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[1] BMDP 2 V with 2 repeated measures or within factors (con and time).
[2] Cubic component was not significant for any of the variables listed.
p Values for time and interaction are Huynh-Feldt *p* values that adjust for sphericity.





Dose–Response Effects of Ketamine

Figure 3 points to strong dose dependence of the main delta measures. However, because we did not have a sufficient number of animals receiving each dose to carry out a pure between S's ANOVA, the evidence for dose dependence in Table 2 must be considered suggestive rather than conclusive.

Table 2 suggests that ketamine's dose-response relations were significant for the two main measures of delta intensity, ASA and time/minute of NREM sleep. Although IA/minute is the product of ASA and time/minute, its dose-response effects did not quite reach statistical significance ($p = .055$). However dose-response relations for total IA were statistically significant as were those for total time occupied by delta. Dose effects for mean frequency did not reach statistical significance.

Comparison of Ketamine Effects (50 mg/kg) on Delta Sleep with Those Produced by 24 Hours of Total Sleep Deprivation

The behavioral excitement caused by ketamine produced a significant loss of NREM sleep during the dark

Figure 1. Mean (and SEM) minutes of NREM **(A)** and REM **(B)** sleep in each hour of the light period for rats who received three injections of ketamine (COMB group, $n = 10$) or saline during the dark (waking) period. Ketamine significantly increased NREM sleep in the second half of the light period (see text). The ANOVA revealed no significant effect of ketamine on REM sleep. The apparent suppression of REM sleep in hours 1 to 4 was not significant with a post-hoc *t*-test.

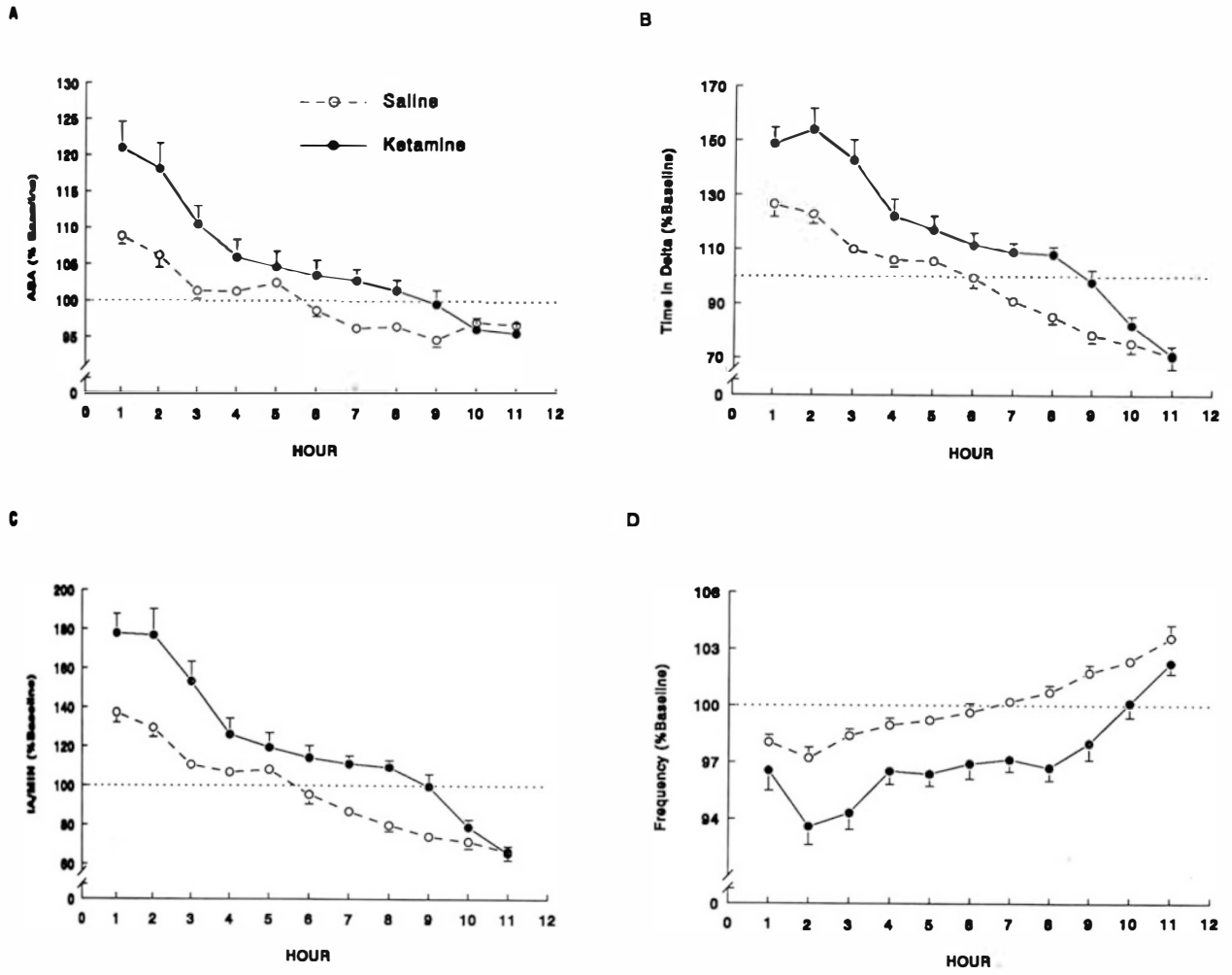


Figure 2. Effects of ketamine and saline on delta (1 to 4 Hz) waveform characteristics in NREM sleep during hours 1 to 11 of the light period (COMB group, $n = 10$). Because of the typically wide interindividual variation in rat EEG, all values are expressed as a percent of the 11-hour saline mean (shown by the dotted line at 100%). Absolute values can be approximated by multiplying the graphed value by the saline mean and dividing by 100. **(A)** Average sample amplitude, a measure of the average amplitude of delta waves (saline mean = 76.2 μV). **(B)** Seconds occupied by 1 to 4 Hz waves/minute of NREM sleep (saline mean = 14.5 sec). **(C)** Integrated amplitude (the period-analysis measure most closely related to power density with spectral analysis) (saline mean = 1150 μV × sec). **(D)** Average frequency of waves within the 1 to 4 Hz frequency band (saline mean = 2.89 Hz).

period. After 50 mg/kg ketamine, the animals averaged 74 minutes of NREM during the dark period as compared with 235 minutes after saline, a net loss of 161 minutes or slightly less than 3 hours. This NREM sleep loss could have produced the delta increase during the light period.

We evaluated this possibility by comparing the ketamine stimulation of delta with that produced by sleep deprivation. The maximum duration of sleep deprivation under 50 mg/kg of ketamine would have been 8 hours, since the first injection was 8 hours prior to light-period onset. We compared the data on 50 mg/kg ketamine with results in our laboratory for 24 hours of total sleep deprivation ($n = 5$ in each study). Tobler and Borbely (1986) found a correlation between amount of sleep deprivation and the increase in delta power during the recovery period. Thus, our 24-hour deprivation data should overestimate the effect of the maximum 8-hour sleep deprivation caused by ketamine. We used gentle handling rather than forced locomotion to accomplish the deprivation because handling is less stressful to the rat and results in more normal postdeprivation behavior (Franken et al. 1991). The same methods of scoring and analysis were applied in the deprivation and ketamine experiments.

Figure 4 compares the effects on delta amplitude of the 50-mg/kg ketamine condition with those produced by 24 hours of deprivation. The initial increase in delta IA/minute was similar in the two conditions, but the ketamine effect was far more sustained. As a

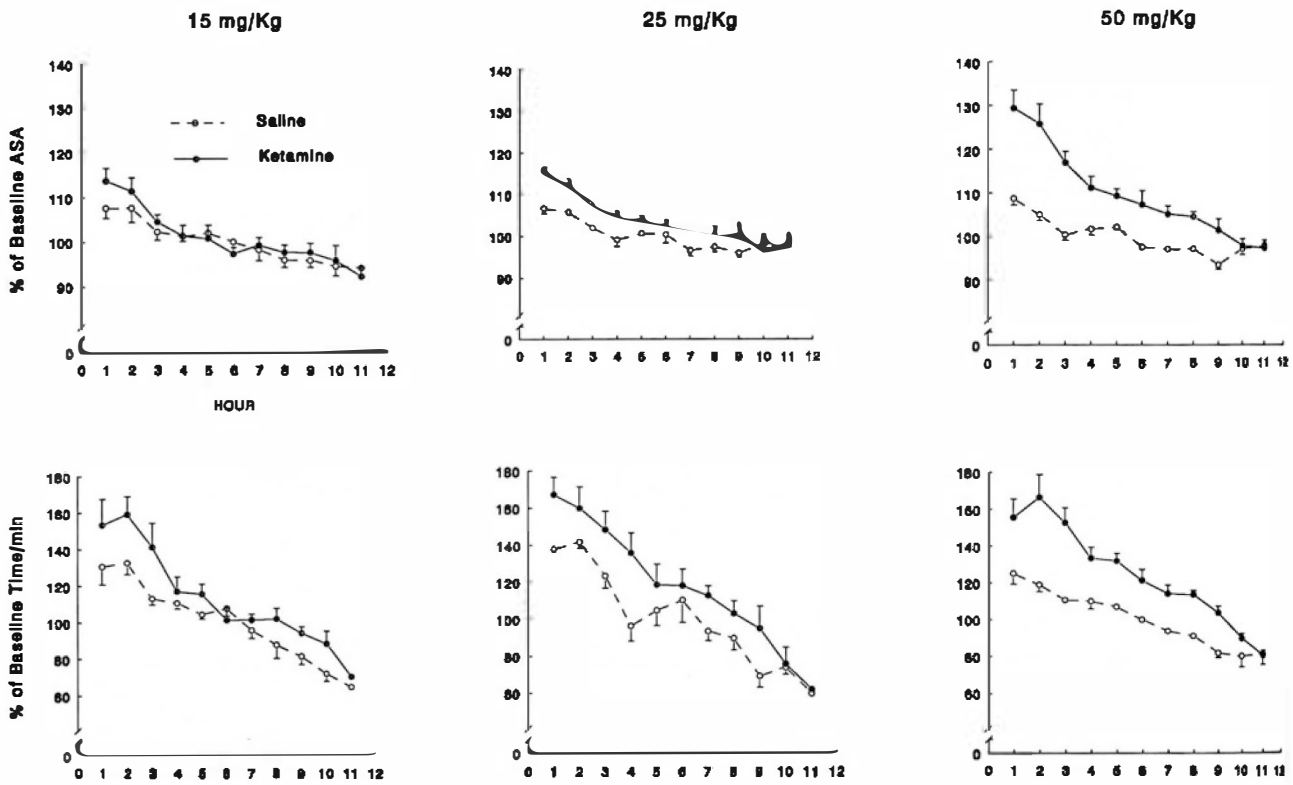


Figure 3. Dose effects of ketamine on average sample amplitude (top row) and density of delta waves/minutes of NREM sleep (bottom row). As in Figure 2, the data for each measure are plotted as percentages of the 11-hour saline mean. Both measures of delta intensity appear to show significant dose effects with ANOVA (Table 2). However, because of limitations in statistical design (see Methods) this apparent dose dependence requires confirmation.

consequence, the average (11 hours) increase in IA/minute above control values after ketamine (34%; from 899 ± 217 to 1200 ± 256 uV × sec/min) was nearly three times as large as that produced by deprivation (12%; from 1252 ± 415 to 1399 ± 467 uV × sec/min). Therefore, although it is possible that sleep loss following the ketamine injections made some small contribution to the delta increase, it could not have been responsible for the bulk of the effect.

DISCUSSION

The number of substances claimed to play a role in NREM sleep regulation is quite large and this literature has been thoroughly reviewed by Borbely and Tobler (1989) and Inoue (1989). Neither of these extensive reviews describes a pharmacologically induced increase in delta intensity of the magnitude found here with ketamine.

Although ketamine affects multiple receptor systems, one of its most important actions is a noncompetitive blockade of the cation channel gated by the NMDA receptor system. It is this blockade that is thought to underly its metabolic effects, which it shares with the more specific channel blocker MK-801. It is therefore of interest that other lines of evidence suggest that excitatory amino acid (EAA) systems may be involved in sleep regulation. Direct brain administration of EAA agonists and antagonists alters sleep-related electrophysiology (Armstrong-James and Fox 1988; Stutzmann et al. 1988; Juhasz et al. 1990; Milasius et al. 1990). Glutamate-like immunoreactivity has been found in many hypothalamic nuclei (van den Pol 1991) and recent evidence (Cahill and Menaker 1989; Ohi et al. 1991) suggests that EAAs serve as presynaptic transmitters for the retinal input to the suprachiasmatic nuclei. It has long been suspected that the hypothalamus plays a role in sleep regulation, as it does in organismic homeostasis generally. More directly, the suprachiasmatic nuclei are known to control the circadian activity cycle of rodents. The finding here that ketamine blockade of the NMDA-gated cation channel stimulates NREM sleep and delta intensity adds to the evidence that implicates EAA systems in sleep regulation.

The results of our experiment are consistent with, but can provide only limited support for, the "intensity" hypothesis of the homeostatic model of delta sleep. Although this hypothesis predicted the results we obtained, it is quite possible that the causal factors were

Table 2. Repeated-Measures ANOVA[1] for Dose Response of Ketamine Effects on Delta EEG within NREM

Variable	*F* (dose in mg/kg)	50 vs 15[2]	50 vs 25[2]	25 vs 15[2]
Avg sample amp	5.15*	SIG	NS	NS
Time in delta/min	10.83**	SIG	SIG	NS
Total time in delta	11.85**	SIG	SIG	NS
IA/min	3.90			
Total IA	8.17**	SIG	SIG	NS
Mean delta freq.	3.21			

* $p < 0.05$.
** $p < 0.01$.
[1] BMDP 2V (Dixon et al. 1990) with time as a repeated measure, dose as a grouping factor, and saline value as a covariate.
[2] Bonferroni multiple comparison test for significance at $\alpha = 0.05$.
SIG, significant; NS, not significant.

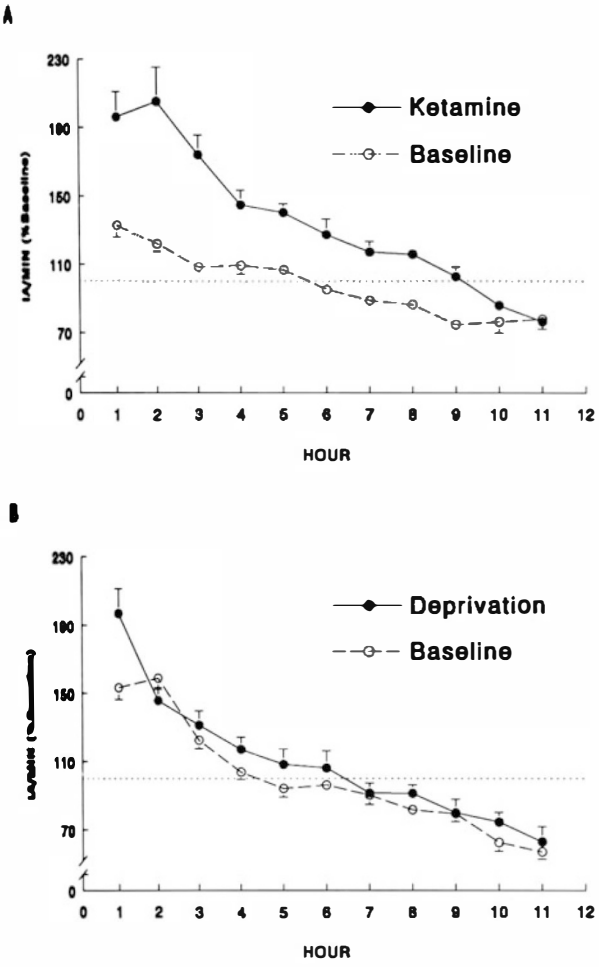


Figure 4. A comparison of the effects on delta IA/minute in NREM sleep in the light period of 50 mg/kg of ketamine and 11 hours of total sleep deprivation ($n = 5$ rats in each experiment). All values are expressed as a percentage of the 11-hour mean of the control condition (shown by dotted line at 100%). Deprivation was carried out with gentle handling. This figure shows that the ketamine effects on delta intensity are not attributable to the sleep loss that followed the ketamine injections (see text).

other than augmented limbic metabolism or EAA perturbation. For example, the delta stimulation may have resulted from an hitherto unknown, long-lived effect of ketamine or its metabolites on sleep systems rather than being a consequence of altered waking limbic metabolism. Moreover, since ketamine produces a complex pattern of metabolic change throughout the brain, the delta stimulation may result from metabolic perturbations in nonlimbic structures. It is also possible that the delta effect is mediated by ketamine actions on non-NMDA receptors such as sigma opioids, which depress rather than stimulate limbic metabolism (London et al. 1988). These possibilities can be tested experimentally.

One must also recognize that an increase in delta EEG amplitude and density does not necessarily indicate that *physiologic* sleep processes have been stimulated. Evidence for such stimulation requires that the appropriate behavioral change also occurs. This consideration has been neglected in pharmacologic studies of sleep. In the present case, one would need to show that arousal threshold after ketamine has been increased with a time course that parallels the increase in delta intensity. Drugs that meet both behavioral and EEG criteria could point to a new class of hypnotics.

One final methodologic point is worth noting. The rationale of our study was to alter brain chemistry and metabolism during waking and then to examine the effects on subsequent sleep. This paradigm is seldom employed in current sleep research. The findings here suggest that it is a useful approach to the basic pharmacology of sleep.

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