Anesthetic Ketamine Impairs Rats’ Recall of Previous Information

The Nitric Oxide Synthase Inhibitor N-nitro-L-arginine Methylester Antagonizes This Ketamine-induced Recognition Memory Deficit

Antonios Boultadakis, M.D.,* Nikolaos Pitsikas, Ph.D.†

ABSTRACT

Background: There is poor experimental evidence concerning the effects of anesthetic doses of the noncompetitive N-methyl-D-aspartate receptor antagonist ketamine on rodents’ memory abilities. The current study was designed (1) to investigate the consequences of postraining administration of anesthetic ketamine (100 mg/kg intraperitoneally) on rats’ recognition memory and (2) to evaluate the ability of the nitric oxide synthase inhibitor N-nitro-L-arginine methylester (L-NAME; 1, 3, and 10 mg/kg intraperitoneally) to counteract the expected behavioral deficits produced by anesthetic ketamine. Finally, in an attempt to clarify if the expected memory impairments produced by anesthetic ketamine were related to the anesthesia, we also tested the effects of a subanesthetic dose of it (3 mg/kg intraperitoneally) on rats’ recognition memory.

Methods: The novel object recognition test, a procedure assessing recognition memory in rats, was selected.

Results: Posttraining administration of anesthetic (but not of subanesthetic) ketamine disrupted rats’ performance in the novel object recognition paradigm. The discrimination index (D) was decreased by ketamine from 0.415 (using saline) to 0.128, thus indicating that the anesthetic dose of ketamine impaired recognition memory. L-NAME (1–3, but not 10, mg/kg) reversed this memory deficit produced by ketamine; the D index of 0.128 using ketamine treatment was increased by 1 and 3 mg/kg L-NAME to 0.427 and 0.478, respectively.

Conclusions: The current results indicate that anesthetic ketamine impaired rats’ posttraining memory components (storage and/or retrieval of information) and that a nitric oxide component modulates its behavioral effects.

What We Already Know about This Topic

• The dissociative anesthetic ketamine has behavioral effects that may be mediated by nitric oxide, although whether nitric oxide mediates ketamine’s effects on memory is not known

What This Article Tells Us That Is New

• In rats, low, but not high doses of a nitric oxide synthase inhibitor prevented ketamine disruption of memory
• There was a temperature dependence of ketamine, with effect on memory at 25°C but not at 21°C

Conclusions: The current results indicate that anesthetic ketamine impaired rats’ posttraining memory components (storage and/or retrieval of information) and that a nitric oxide component modulates its behavioral effects.
nonselective nitric oxide synthase (NOS) inhibitor, N-nitro-
t-arginine methyl ester (L-NAME), antagonized ketamine-
induced analgesia; and the neuronal NOS inhibitor, 7-ni-
 troindazole, conferred protection against ketamine-induced
neurotoxicity in newborn rat forebrain culture. Microdi-
alyses studies has demonstrated that L-NAME counteracted
the increase induced by anesthetic ketamine of nitric oxide
oxidation products in the rat hippocampus. Finally, L-NAME
was able to reverse recognition and spatial memory
deficits produced by subanesthetic doses (3 mg/kg) of ket-
amine in rats.

After taking the described evidence into consideration, the
first aim of our study was to evaluate the effects of posttraining
administration of anesthetic ketamine on rats’ recognition
memory and to determine whether these effects were related to
the hypothermic properties of ketamine. Subsequently, the ef-
cacy of L-NAME (1, 3, and 10 mg/kg intraperitoneally) to
counteract the expected recognition memory deficits induced
by anesthetic ketamine was also assessed. The final aim of
the current study was to detect whether anesthesia is involved in the
expected cognitive impairments produced by ketamine. There-
fore, we evaluated, using the same experimental procedure
of the anesthetic study, the effects of a subanesthetic dose of
ketamine (3 mg/kg intraperitoneally) on rats’ recognition
memory. For these studies, the novel object recogni-
tion task was selected.

Materials and Methods

Animals

Male 3-month-old Wistar rats (Hellenic Pasteur Institute,
Athens, Greece), weighing 250–300 g, were used in this
study. The animals were housed in Makrolon cages (47.5-cm
long × 20.5-cm high × 27-cm wide), three per cage, in a
regulated environment (21°C ± 1°C; 50–55% relative hu-
midity; 12 h–12 h [lights on at 7 AM] light–dark cycle) with
free access to food and water. Experiments were conducted in
the room where only these animals were housed and occurred
between 9:00 AM and 3:00 PM.

Procedures involving animals and their care were con-
ducted in conformity with the international guidelines in
compliance with national and international laws and policies
(European Economical Community Council Directive 86/ 
609, JL 358, 1, December 12, 1987; National Institutes of
Health Guide for Care and Use of Laboratory Animals, Na-
tional Institutes of Health publication 85–23, 1985). The
current study was approved by the Animal Care and Use
Committee of the Medical School of the University of Thes-
saly, Larissa, Greece.

Drugs

Ketamine hydrochloride was dissolved in saline (NaCl, 0.9%)
and administered intraperitoneally at the anesthetic
dose of 100 mg/kg and at the subanesthetic dose of 3 mg/
kg in a volume of 1 ml/kg. L-NAME (σ, St. Louis, MO)
was dissolved in saline and administered intraperitoneally in
a volume of 1 ml/kg. Doses of L-NAME were chosen on the
basis of a previous study in which they were effective against
learning impairments and did not produce side effects.
Control animals received isovolumetric amounts of the vehi-
cle (NaCl, 0.9%).

Novel Object Recognition Test

Recognition memory was studied using a novel object recog-
nition paradigm modified from a procedure used in a previ-
sous study. The test apparatus has been described elsewhere.
Before testing, for 3 consecutive days, rats were allowed to
explore the apparatus for 5 min. Testing started the day after
the habituation phase. During testing, each animal received a
single daily 5-min “sample” trial (T1) for 2 consecutive days.
During T1, two identical samples (objects) were placed in
two opposite corners of the apparatus 10 cm from the side
wall. A rat was placed in the middle of the apparatus and was
left to explore these two identical objects. On day 3, a single
5-min “choice” trial (T2) was performed. During T2, a new
object (N) replaced one of the samples presented in T1.
Therefore, the rats were reexposed to two objects: the famil-
iliar (F) and the new (N). All combinations of objects were
used in a balanced manner to reduce potential biases because
of preferences for particular objects. To avoid the presence of
olfactory trails, the apparatus and the objects after each trial
were thoroughly cleaned.

Exploration was defined as follows: directing the nose
toward the object at a distance of 2 cm or less and/or touch-
ing the object with the nose. Turning around or sitting on
the object was not considered as exploratory behavior. The
times spent by rats in exploring each object during T1 and
T2 were recorded manually by using a stopwatch. From this
measure, a series of variables was then calculated: the total
time spent in exploring the two identical objects in T1 and
time spent in exploring the two different objects, F and N, in
T2. The discrimination between F and N during T2 was
measured by comparing the time spent in exploring the F
with that spent in exploring the N. Because this time may be
biased by differences in overall levels of exploration,a dis-
crimination index (D) was then calculated: D = (N − F)/
(N + F). D is the discrimination ratio and represents the
difference in exploration time expressed as a proportion of
the total time spent exploring the two objects in T2. In
addition, the motor activity of each animal, expressed as total
number of steps during each trial, was also recorded.

Experimental Protocol

To investigate whether the hypothermic properties of ketamine
had an effect on rats’ performance in this task, different groups
of animals received treatment in a room under standard ambient
temperature (21°C). Other groups received compounds in a
“warm” (25°C) room to avoid hypothermia and remained there
under these conditions for 2 h, starting immediately after injec-
tion. Room temperature was switched from 21°C to 25°C just

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before compound administration. The choice trial T2 was performed under standard environmental conditions (21°C) 24 h after treatment. Anesthetic state was defined as loss of righting reflex and movement.

The animals’ behavior was video recorded. Data evaluation was subsequently performed by experimenters who were unaware of the pharmacologic treatment. Figure 1 summarizes the experimental protocol.

**Experiment 1: Effects of Anesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/21°C)**

Rats were randomly divided into two experimental groups (10 rats per group), as follows: vehicle and ketamine, 100 mg/kg. Ketamine and vehicle were administered to the animals on day 2, just after T1, under standard regulated environmental conditions (21°C).

**Experiment 2: Effects of Anesthetic Ketamine and L-NAME on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/25°C)**

Rats were randomly divided into eight experimental groups (10 rats per group), as follows: vehicle + vehicle; vehicle + L-NAME, 1 mg/kg; vehicle + L-NAME, 3 mg/kg; vehicle + L-NAME, 10 mg/kg; vehicle + ketamine, 100 mg/kg; ketamine, 100 mg/kg + L-NAME, 1 mg/kg; ketamine, 100 mg/kg + L-NAME, 3 mg/kg; ketamine, 100 mg/kg + L-NAME, 10 mg/kg. Compounds were administered to the animals on day 2, just after T1, in a warm (25°C) room.

**Experiment 3: Effects of Subanesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/21°C)**

Rats were randomly divided into two experimental groups (8 rats per group), as follows: vehicle and ketamine, 3 mg/kg. Ketamine and vehicle were administered to the animals on day 2, just after T1, under standard regulated environmental conditions (21°C).

**Experiment 4: Effects of Subanesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/25°C)**

Rats were randomly divided into two experimental groups (8 rats per group), as follows: vehicle and ketamine, 3 mg/kg. Ketamine and vehicle were administered to the animals on day 2, just after T1, in a warm (25°C) room.

**Statistical Analysis**

Software (SigmaStat 3.0; Systat Software, Inc., Chicago, IL) was used for statistical analysis. Data are reported as mean ± SD. In experiments 1, 3, and 4, motor activity and total exploration time were analyzed by the two-way ANOVA with a split-plot design (between–within subjects). The first factor was treatment, and the second factor was trials. Discrimination index D data were analyzed with the Student paired t test. This statistical procedure was used for analyzing the significance of the difference between two means.

In experiment 2, motor activity and total exploration time were evaluated by the three-way ANOVA (two between and one within subjects). The first between-subjects factor was ketamine, and the second between-subjects factor was L-NAME. Trials was the within-subjects factor. Discrimination index D data were analyzed by using the two-way ANOVA. The first factor was ketamine, and the second factor was L-NAME. Post hoc comparisons were made by the Tukey t test. All P values are two tailed, and P < 0.05 was considered significant.

**Results**

The righting reflex was lost by rats within 8 min of receiving 100 mg/kg ketamine. Animals that received 100 mg/kg ketamine recovered from its anesthetic effects within 30 min of drug administration, independent of the environmental conditions (21°C or 25°C) and the dose of L-NAME.

**Experiment 1: Effects of Anesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/21°C)**

A two-way ANOVA, performed on motor activity data, showed a significant interaction between treatment and trials ($F_{2,59} = 4.741, P = 0.015$). In addition, a significant main effect of trials ($F_{2,59} = 3.413, P = 0.044$), but not of treatment ($F_{1,59} = 1.936, P = 0.18$, not significant [n.s.]), was also evident. Post hoc analysis conducted on these data indicated that the ketamine-treated rats displayed lower motility levels during T2 compared with the vehicle-treated animals and with their performance during the first and second T1 ($P < 0.05$, fig. 2A).
Analysis of total exploration times did not reveal a main effect of either treatment (F1,59 = 0.282, P = 0.60, n.s.) or trials (F2,59 = 0.415, P = 0.66, n.s.). A significant interaction between treatment and trials (F2,59 = 3.917, P = 0.029) was observed. Animals that received anesthetic ketamine explored significantly less during T2 with respect to the vehicle-treated rats (P = 0.05, fig. 2B).

Data for index D did not evidence any difference among the vehicle- and ketamine-treated animals (P = 0.806, n.s., fig. 2C). This indicates that all animals acquired this task similarly well.

**Experiment 2: Effects of Anesthetic Ketamine and L-NAME on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/25°C)**

Statistical analysis of the locomotor activity data did not demonstrate a significant three-way ketamine × L-NAME × trials interaction (F6,239 = 0.517, P = 0.79, n.s.) or a significant two-way interaction between ketamine and L-NAME (F3,239 = 1.089, P = 0.35, n.s.), ketamine and trials (F2,239 = 0.138, P = 0.87, n.s.), and L-NAME and trials (F2,239 = 0.463, P = 0.83, n.s.). A significant main effect of trials (F2,239 = 8.717, P < 0.001), but not of ketamine (F1,239 = 0.225, P = 0.635, n.s.) or of L-NAME (F3,239 = 0.189, P = 0.90, n.s.), was revealed. This main effect of trials demonstrated that all groups of animals had a lower motor activity during T2 with respect to their performance expressed during T1 (fig. 3A).

Overall analysis of total exploration times (fig. 3B) did not show a significant three-way ketamine × L-NAME × trials interaction (F6,239 = 0.696, P = 0.65, n.s.) or a significant two-way interaction between ketamine and L-NAME (F3,239 = 0.138, P = 0.394, n.s.), ketamine and trials (F2,239 = 0.789, P = 0.46, n.s.), and L-NAME and trials (F2,239 = 0.453, P = 0.84, n.s.). A significant main effect of trials (F2,239 = 8.717, P < 0.001), but not of ketamine (F1,239 = 0.502, P = 0.48, n.s.) or of L-NAME (F3,239 = 1.981, P = 0.118, n.s.), was evidenced. This main effect of trials indicate that all animals, irrespective of the type of treatment, explored much less on trial T2 than that on trial T1.

![Figure 2](image2.png)

**Fig. 2.** Novel object recognition test. Vehicle and ketamine (100 mg/kg) were injected intraperitoneally under standard environmental conditions (21°C) just after the second T1 on day 2. The histogram represents the mean ± SD of 10 rats per treatment group. (A) Total motor activity. *P < 0.05 versus the same group of rats within T1; †P < 0.05 versus the vehicle group within T2. (B) Total exploration time. *P < 0.05 versus the vehicle group within T2. (C) Discrimination index D.

![Figure 3](image3.png)

**Fig. 3.** Novel object recognition test. Vehicle, ketamine, and L-NAME were injected intraperitoneally under warm environmental conditions (25°C) just after the second T1 on day 2. The histogram represents the mean ± SD of 10 rats per treatment group. (A) Total motor activity. (B) Total exploration time. (C) Discrimination index D. *P < 0.05 versus all the other groups (except the ketamine plus L-NAME group, 10 mg/kg); †P < 0.05 versus all the other groups (except the ketamine plus vehicle group).
Concerning D data, a significant main effect of ketamine \((F_{1,79} = 8.601, P = 0.005)\) and of L-NAME \((F_{3,79} = 3.194, P = 0.029)\) and a significant interaction between ketamine and L-NAME \((F_{3,79} = 3.184, P = 0.029)\) were revealed. Post hoc analysis showed that animals treated with ketamine + vehicle and ketamine + L-NAME \((10 \text{ mg/kg})\) were unable to discriminate between the familiar and the novel object compared with the rest of the groups (including ketamine + L-NAME \([1 \text{ mg/kg}]\) and ketamine + L-NAME \([3 \text{ mg/kg}]; P < 0.05\), fig. 3C).

**Experiment 3: Effects of Subanesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/21°C)**

A two-way ANOVA of motor activity results (fig. 4A) demonstrated a nonsignificant interaction between treatment and trials \((F_{2,47} = 2.238, P = 0.125, \text{n.s.})\) and a nonsignificant main effect of treatment \((F_{1,47} = 1.871, P = 0.19, \text{n.s.})\). A significant main effect of trials \((F_{2,47} = 19.668, P < 0.001)\) was observed. The main effect of trials in the absence of a significant interaction between ketamine and trials suggests that both vehicle- and ketamine-treated animals displayed lower locomotor activity levels during T2 compared with those expressed during T1.

An analysis of total exploration times did not evidence a main effect of either treatment \((F_{1,47} = 1.647, P = 0.220, \text{n.s.})\) or trials \((F_{2,47} = 1.892, P = 0.17, \text{n.s.})\) or a significant interaction of groups \(\times\) trials \((F_{2,47} = 0.162, P = 0.851, \text{n.s.}, \text{fig. 4B})\).

D index evaluation did not show any effect of treatment, indicating that all animals acquired this task similarly well \((P = 0.930, \text{n.s.}, \text{fig. 4C})\).

**Experiment 4: Effects of Subanesthetic Ketamine on Rats’ Performance in the Novel Object Recognition Test (Temperature Ambient/25°C)**

Overall analysis of motor activity data showed a nonsignificant interaction between treatment and trials \((F_{2,47} = 1.034, P = 0.37, \text{n.s.})\) and a nonsignificant main effect of treatment \((F_{1,47} = 2.483, P = 0.14, \text{n.s.})\). A significant main effect of trials \((F_{2,47} = 5.909, P = 0.007)\) was evidenced, indicating that all animals, regardless of treatment, displayed lower motility levels during T2 with respect to those expressed by these rats during T1 (fig. 5A).

Statistical analysis of the total exploration times demonstrated a significant interaction between treatment and trials \((F_{2,47} = 3.477, P = 0.045, \text{fig. 5B})\). In addition, a significant
main effect of trials ($F_{2,47} = 8.398, P = 0.001$), but not of treatment ($F_{1,47} = 0.0362, P = 0.85$, n.s.), was also evidenced. Post hoc analysis revealed that the ketamine-treated animals displayed lower exploratory activity compared with the vehicle-treated rats during T2 ($P < 0.05$). Moreover, the ketamine-treated rats explored less during T2 compared with their performance expressed during T1 ($P < 0.05$).

Data for index D did not show any effect of treatment, suggesting that either control or ketamine-treated rats acquired this task similarly well ($P = 0.824$, n.s., fig. 5C).

**Discussion**

There were no differences in motor activity and in total exploration time between different groups of rats during T1, as would be expected because compounds were not current during the sample phase. Posttraining administration of anesthetic ketamine did not disrupt animals’ performance in the novel object recognition task when anesthesia was induced under standard conditions (21°C), indicating that it did not affect rats’ recognition memory abilities.

On the contrary, animals that received anesthetic ketamine at a room temperature of 25°C displayed an impaired performance with respect to that expressed by the vehicle-treated rats. A single posttraining injection of 1 and 3 mg/kg L-NAME antagonized the ketamine-induced performance deficits in this recognition memory paradigm. In agreement with previous reports, L-NAME at a dose of 10 mg/kg was ineffective at counteracting recognition memory impairments caused by ketamine. Because this lack of effect was observed after short-term treatment, it is not attributable to tolerance. In addition, L-NAME, at 30 mg/kg, previously disrupted rats’ performance in the novel object recognition test. Collectively, these findings indicate that L-NAME exerts a biphasic effect on recognition memory. One possible hypothesis to explain this result is that L-NAME acts through different mechanisms operating at different doses. For instance, we cannot exclude that L-NAME, at this low-dose range, might interfere with the cyclic guanosine monophosphate system, which is considered the main signal transduction pathway of nitric oxide, rather than with NOS activity. Moreover, neuroprotective effects were obtained when inhibition of nitric oxide production was only mild and transient, whereas an aggravating action was associated with conditions of strong and long-lasting inhibition. Therefore, small changes in local nitric oxide concentration may be a key factor in determining its biologic action.

Ketamine and L-NAME influenced rats’ performance during retention, seemingly reflecting a modulation of posttraining mnemonic processes (storage and/or retrieval of information).

To clarify whether amnesia produced by anesthetic ketamine was related to anesthesia, we tested, under the current experimental conditions, the effects of subanesthetic ketamine (3 mg/kg) on rats’ performance in the novel object recognition task. This dose of ketamine has disrupted rats’ recognition memory, and this deficit has been reversed by L-NAME. Subanesthetic ketamine, independently of room temperature during treatment, did not impair animals’ performance in this behavioral paradigm. These results suggest that the anesthetic state is critical for the induction of amnesia by ketamine.

According to other reports, the dual effects displayed by ketamine in the current study on recognition memory between the anesthetic and subanesthetic doses may be dependent on the dosage used. Along this line, ketamine exerts a biphasic dose-dependent action on glutamate and dopamine release in prefrontal cortex and striatum. Low doses of ketamine (10, 20, and 30 mg/kg) increased glutamate and dopamine outflow, whereas high doses of ketamine (200 mg/kg) decreased these concentrations. Furthermore, we cannot rule out issues related to the pharmacokinetics of subanesthetic and anesthetic ketamine. The disrupting effect of anesthetic ketamine on recall of previous information might be dependent on a longer duration of action of it with respect to that of the subanesthetic dose.

The current findings on subanesthetic ketamine are apparently in contrast to previous research, in which the same dose (3 mg/kg) of it impaired rats’ recognition memory. The experimental design of that study was consistently different from that used in the current experimentation. In the previously mentioned study, treatment and experimentation were performed only under standard environmental conditions (21°C). Drug administration under the warm condition (25°C) was never performed. Animals were subjected to a single 2-min sample trial T1 and immediately after received 3 mg/kg ketamine. Subsequently, an intertrial interval of 1 h was given and finally a single 2-min choice trial T2 was performed.

Conversely, in the current study, we were obliged to consider that 24 h are required for the complete recovery of rats’ sensorimotor functions after application of anesthetic ketamine. Thus, a novel experimental protocol, with respect to that used in our former study, was utilized. Results obtained in different methodological procedures may explain this discrepancy.

Compounds were administered systemically; thus, it cannot be excluded that nonspecific factors (i.e., attentional, sensorimotor, and motivational) might have influenced animals’ performance. Animals that received ketamine and/or L-NAME showed lower concentrations of motility during T2, compared with their performance expressed during T1, in which treatment was not applied. In addition, motor activity expressed by the anesthetic ketamine-treated rats, under standard environmental conditions, was lower during T2, regarding their control cohorts. The exploratory activity of animals treated with anesthetic ketamine and/or L-NAME was also decreased throughout the trials. Rats that received subanesthetic ketamine, at a room temperature of 25°C, displayed lower total exploration concentrations during T2 than those shown by these animals during T1. Moreover,
these animals explored less during T2 with respect to their control counterparts.

The current results are in contrast to previous reports in which ketamine (either subanesthetic or anesthetic) and L-NAME did not reduce the previously mentioned parameters.9,14,16 The described controversy might depend on differences in experimental settings (i.e., the different experimental protocol used in the current experiments vs. those used in previous studies).

In this context, under standard environmental conditions, ketamine did not impair rats’ cognitive performance. In addition, when anesthesia was induced at 25°C, treatment with L-NAME did not antagonize this anesthetic ketamine-induced hypomotility and reduction of exploration; instead, it counteracted recognition memory deficits. Moreover, animals that have received L-NAME alone displayed recognition memory abilities similar to those expressed by their vehicle-treated counterparts. This pattern of results implies that the effects of compounds on rats’ cognitive performance were unrelated to the extent of motility and exploratory behavior.

Pretraining administration of anesthetic ketamine (100 mg/kg) did not disrupt rats’ performance in the novel object recognition task when it was administered under standard environmental conditions (21°C).9 Conversely, animals that received ketamine at room temperature (25°C) showed an impaired performance compared with that expressed by their control counterparts. In that study, it was observed that the body temperatures of rats that received anesthetic ketamine under standard conditions were significantly lower (2°C) compared with those receiving vehicle. On the other hand, when either vehicle or anesthetic ketamine was administered in a warm room (25°C), no differences in body temperature were observed among the various experimental groups. It seems likely that the mild hypothermia exerted by anesthetic ketamine provided protection of animals’ performance on the novel object recognition test.9 In line with this view, a similar temperature decrease (2°C) may significantly reduce ischemic damage.24

The current results obtained in a procedure assessing recall of previous information confirm and extend the previously mentioned findings concerning the hypothermic profile of anesthetic ketamine. This protective effect of mild hypothermia cannot be explained only by the decrease of cerebral metabolic rate. It is not yet elucidated how ketamine exerts its protective action. Mild hypothermia delays the initial release of excitable neurotransmitters and reduces the absolute rate of excitatory neurotransmitter release during ischemia.25,26 This mechanism might be a plausible explanation for the beneficial effects of anesthetic ketamine on excitotoxic neuronal damage.27 Clearly, further studies are required to clarify this important issue.

The true role of anesthetic ketamine on posttraining stages of memory formation is debated. Posttraining treatment with this N-methyl-D-aspartate receptor antagonist impaired the performance of mice in a fear-conditioning procedure6 and in the T-maze task.7 Nevertheless, other studies have not supported this proposition. Posttraining administration of anesthetic ketamine did not disrupt the performance of mice in the passive avoidance test6 and did not impair the memory abilities of rats in the autoshaping paradigm.8 The current results are in accordance with former studies6,7 and support a role of ketamine in posttraining memory processes. The previously described controversial findings on the role of anesthetic ketamine might depend on differences in experimental settings: the type of animal model and the behavioral pattern investigated.

The mechanisms by which anesthetic ketamine produces its adverse behavioral effects have been attributed, at least in part, to the blockade of the N-methyl-D-aspartate receptor28 and to its agonistic properties on the γ-aminobutyric acid type A receptor.29,30 Furthermore, anesthetic ketamine inhibited both the α7 and the α4β2 subunits of neural nicotinic acetylcholine receptors that are localized in the hippocampus and are implied in cognition.3,31 Finally, a recent study32 demonstrated that the inhibition of the extracellular signal–regulated kinase signal transduction pathway may be involved in the cognitive impairments produced by anesthetic ketamine in the 21-day-old rat.

The involvement of nitric oxide on pharmacological effects mediated by anesthetic ketamine was evaluated with the nonselective NOS inhibitor L-NAME. To our knowledge, the current findings provide the first demonstration that L-NAME reversed anesthetic ketamine-induced recognition memory deficits, suggesting that this NOS inhibitor is implied in the behavioral effects of this dissociative anesthetic. The current data are also consistent with previous results showing that L-NAME, at the same dose range, counteracted delay-dependent impairments34 and reversed performance deficits produced by subanesthetic doses (3 mg/kg) of ketamine in the novel object recognition task in the rat.14

A potential issue when using NOS inhibitors relates to its hypertensive properties. Therefore, it is difficult to quantify how and at what extent these cardiovascular effects might have specifically affected animals’ cognitive performance. Reportedly, NOS inhibitors injected peripherally induce a nearly maximal hypertensive effect at 10 mg/kg, a dose that, in the current study, did not disrupt animals’ performance.33 Thus, behavioral consequences due to a potential L-NAME–induced hypertensive effect can likely be excluded. Furthermore, the probability that the effects exerted by L-NAME on animals’ cognitive performance were related to a potential action of it on rats’ body temperature can probably be excluded because a series of studies34,35 indicated that L-NAME did not alter rodents’ body temperature.

The mechanisms underlying L-NAME antagonism of anesthetic ketamine-induced behavioral effects is not yet clarified and is still a matter of investigation. In this context, NOS inhibitors, including L-NAME, previously antagonized ketamine-induced analgesia33 and conferred protection against ischemic neuronal damage.27 This may suggest that the mechanisms underlying L-NAME antagonism of anesthetic ketamine-induced behavioral effects are different from those involved in the protection against ischemic neuronal damage.
neuronal cell loss caused by ketamine. In line with this view, neurochemical data demonstrated that application of L-NAME counteracted the increase of nitric oxide plasmatic concentrations that were produced by anesthetic ketamine in the rat hippocampus. Although important differences in experimental settings exist between these studies and our findings, these results further support a role for nitric oxide on ketamine’s effects.

Finally, L-NAME abolished the psychotomimetic effects of subanesthetic doses of the N-methyl-D-aspartate receptor antagonist phencyclidine by reducing the phencyclidine-induced increase in cyclic guanosine monophosphate production in the medial prefrontal cortex of the mouse brain. Additional research will be needed to elucidate this issue.

In summary, studies presented herein indicate that post-training administration of anesthetic, but not subanesthetic, ketamine disrupted recall of previous information in the rat. This deficit seems to be related to the anesthetic state produced by ketamine and the environmental conditions during treatment. The NOS inhibitor L-NAME antagonized this recognition memory impairment, suggesting that a nitric oxide component modulates the effects exerted by anesthetic ketamine on cognition. Our findings might be of interest because ketamine is widely used as a pediatric anesthetic in children and in veterinary surgery.

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Anesthetic Ketamine, L-NAME, and Recognition Memory

ANESTHESIOLOGY REFLECTIONS

The “Reckless” Humphry Davy of J. A. Paris

In 1831 in his two-volume biography, The Life of Sir Humphry Davy, physician John Ayrton Paris, P.R.C.P., F.R.S. (1785–1856) portrayed Davy as not only the discoverer of nitrous oxide analgesia but also as a hypomanic genius who stormed through chemical laboratories conducting five or more laboratory experiments simultaneously. Snapping off glassware from one experiment to start the next, Davy was “perfectly reckless of his apparatus; breaking apart to meet some want of the minute.” Paris observed, “With Davy, rapidity was power.” Even a past-president of the Royal Society, Sir Joseph Banks, openly questioned whether Davy was “too lively to fill the Chair of the Royal Society with that degree of gravity which it is most becoming to assume.” (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.