

Prolonged effect of an anesthetic dose of ketamine on behavioral despair

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Received 8 May 2001; received in revised form 18 September 2001; accepted 18 September 2001

Abstract

The present study investigated the effect of a single, anesthetic dose of ketamine, a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, on behavioral despair, an animal model of depression. Separate groups of male Wistar rats injected with an anesthetic dose of ketamine (160 mg/kg ip) and tested 3, 7, or 10 days later showed significantly less immobility in the second of two forced-swim tests compared to saline-injected controls. Ketamine- and saline-treated animals did not differ significantly in the swim tests with respect to other behavioral measures, namely diving, jumping, and head shakes. The present findings point to an ameliorative effect of ketamine on behavioral despair and support the view that NMDA antagonists may have a beneficial effect on depression. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Ketamine; NMDA antagonism; Behavioral despair; Forced swimming

1. Introduction

Ketamine, a dissociative anesthetic, is a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist (Kohrs and Durieux, 1998; White et al., 1982). Administration of ketamine and related NMDA antagonists has been shown to have a broad range of biochemical and behavioral effects in humans (Adler et al., 1998; Krystal et al., 1994; Moretti et al., 1984; White et al., 1982) and animals (Adamec et al., 1999; Aguado et al., 1994; Duncan et al., 1998; Dunn et al., 1989; Hammer and Herkenham, 1983; Lannes et al., 1991; Mickley et al., 1998; Verma and Moghaddam, 1996; Yamamoto et al., 1997). While these studies have mostly assessed short-term effects of subanesthetic doses of ketamine or related compounds, experiments in our laboratory have indicated a long-term effect of an anesthetic dose of ketamine in rats subjected to forced-swim tests in the behavioral despair model of depression (Porsolt et al., 1977, 1978). We found that sham-operated animals subjected to forced-swim tests approximately a week after ketamine anesthesia showed resistance to behavioral despair in that they did not display significantly increased immobility in the second swimming test.

Our findings seemed to warrant further study in that investigating the effect of ketamine on forced-swimming tests may shed light on the mechanism involved in the behavioral despair and may provide evidence for the potential beneficial effects of ketamine. NMDA receptors are implicated in the pathophysiology and NMDA antagonists may aid in the pharmacotherapy of depression (Papp and Moryl, 1994; Skolnick et al., 1996; Trullas and Skolnick, 1990). Furthermore, since ketamine is used in human (Reich and Silvey, 1989) and animal anesthesia (Van Pelt, 1977), it may be important to investigate its long-term effects on behavior. The following study therefore assessed the long-term effect of an anesthetic dose of ketamine in behavioral despair model of depression. The model, originally developed by Porsolt et al. (1977, 1978) is based on two forced-swim tests separated by 24 h. Rats display longer immobility in the second swim test compared to the first test.

2. Materials and methods

2.1. Subjects

A total of 55 male Wistar rats raised in our breeding colony, weighing 280–310 g at the start of the experiment,

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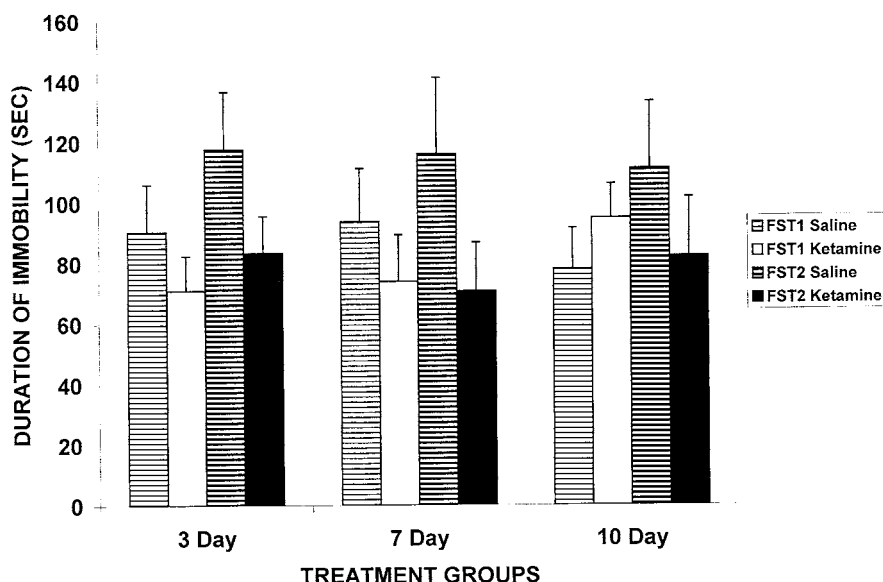


Fig. 1. Duration of immobility (mean $\pm$ S.E.M.) in two forced-swim tests (FST1 and FST2) conducted 24 h apart beginning 3, 7, or 10 days after a single ketamine (160 mg/kg ip) or saline injection. Each group had nine subjects except 7-day saline and ketamine groups ($n=8$ and 10, respectively) and 10-day saline group ($n=10$).

were used in the experiments. Animals were maintained on a 12-h light/12-h dark cycle with light onset at 07:00 h. Animals had free access to food and water. All testing was conducted between 10:00 and 16:00 h.

2.2. Procedure

Animals were injected either with ketamine hydrochloride (160 mg/kg ip, 50 mg/ml; Parke-Davis) or with an equivalent volume of physiological saline and individually tested in forced-swim tests beginning 3, 7, or 10 days after treatment. The procedures in the study were according to the NIH Guide for Care and Use of Animals.

2.3. Forced-swim tests

Animals were tested in two forced-swim tests separated by 24 h. In the first test, each animal was immersed in water for 15 min, followed 24 h later by a 5-min second swim test. For the swim tests, the subject was placed in a Plexiglas cylinder (45 cm height, 30 cm diameter) filled with 25 °C water to a height of 15 cm. After the test, the animal was placed under a lamp for 30 min for drying.

2.4. Behavioral coding and data analysis

Swim tests were recorded on videotape. The initial 5 min of the first test as well as the entire second test was analyzed. Specifically, for each test, total duration of immobility was measured. Immobility was defined as floating or remaining motionless without leaning against the wall of the cylinder. In addition, frequency of diving (involving total immersion of the body in water), jumping

(attempt at escape from the cylinder with at least the upper half of the body out of water), and head shakes were counted. Data were analyzed with a one-way analysis of variance (ANOVA).

3. Results

Fig. 1 shows duration of immobility (mean $\pm$ S.E.M.) in the two swim tests. ANOVA comparing immobility scores for the first swim test indicated no significant effect of treatment [$F(1,49)=0.41$, $P>.05$] or of day (day of testing after drug administration) [$F(2,49)=0.08$, $P>.05$] or a significant Treatment $\times$ Day interaction [$F(2,49)=1.10$, $P>.05$]. In the second swim test, ketamine-treated animals had significantly shorter duration of immobility than saline controls [$F(1,49)=5.30$, $P<.05$]. There was no significant effect for day of testing [$F(2,49)=0.07$, $P>.05$] nor a significant Treatment $\times$ Day interaction [$F(2,49)=0.09$, $P>.05$].

ANOVA also indicated that the increase in the duration of immobility in the second swim test compared to the first test was significantly smaller for the ketamine-treated animals than saline controls [$F(1,49)=9.39$, $P<.05$]. There was no significant difference between the groups due to day of testing [$F(2,49)=0.50$, $P>.05$] nor a significant interaction effect [$F(2,49)=0.94$, $P>.05$].

3.1. Other behaviors

Table 1 shows the frequencies (mean $\pm$ S.E.M.) of diving, jumping, and head shakes in the two swim tests. There was

Table 1

Frequencies (mean $\pm$ S.E.M.) of diving, jumping, and head shakes in two forced-swim tests (FST1 and FST2) conducted 24 h apart beginning 3, 7, or 10 days after a single ketamine (160 mg/kg ip) or saline injection

Test	Groups	Diving		Jumping		Head shakes	
		Ketamine	Saline	Ketamine	Saline	Ketamine	Saline
FST 1	3-day	3.3 $\pm$ 0.7	2.3 $\pm$ 0.6	5.5 $\pm$ 1.5	6.0 $\pm$ 1.8	34.1 $\pm$ 3.5	27.3 $\pm$ 3.4
	7-day	3.4 $\pm$ 0.8	3.0 $\pm$ 0.8	12.6 $\pm$ 2.9	5.1 $\pm$ 1.8	27.9 $\pm$ 2.1	24.6 $\pm$ 3.2
	10-day	2.2 $\pm$ 0.7	4.5 $\pm$ 0.9	5.3 $\pm$ 1.6	5.4 $\pm$ 1.7	28.4 $\pm$ 3.5	36.1 $\pm$ 5.4
FST 2	3-day	2.4 $\pm$ 0.8	1.2 $\pm$ 0.4	6.0 $\pm$ 2.3	5.2 $\pm$ 2.6	24.0 $\pm$ 3.0	18.8 $\pm$ 3.9
	7-day	1.7 $\pm$ 0.4	1.5 $\pm$ 0.5	6.9 $\pm$ 3.0	6.6 $\pm$ 3.1	12.8 $\pm$ 2.4	17.2 $\pm$ 3.3
	10-day	2.1 $\pm$ 0.7	2.5 $\pm$ 0.7	7.3 $\pm$ 2.1	6.4 $\pm$ 1.7	20.2 $\pm$ 3.3	26.3 $\pm$ 5.1

Each group had nine subjects except 7-day saline and ketamine groups ($n=8$ and 10, respectively) and 10-day saline group ($n=10$).

no significant main effect due to treatment or day of testing after injections or a significant Treatment $\times$ Day interaction for any of these behaviors ($P>.05$ in all cases).

4. Discussion

In the behavioral despair model, depression is defined as increased immobility observed in the second of two tests separated by 24 h (Porsolt et al., 1977, 1978). According to this criterion, our results suggest that an anesthetic dose of ketamine in male Wistar rats interferes with induction of behavioral despair for up to 10 days after its administration. The observed ameliorative effect of ketamine seems to be specific to behavioral despair and not due to a general arousal or hyperactivity in that other behaviors measured in the swim tests, namely diving, jumping, and head shakes, did not show a significant treatment- or time-dependent variability. This argument is bolstered by the fact that saline- and ketamine-administered animals showed similar levels of immobility in the first swim test and differed from each other significantly only in the second swim test.

The ameliorative effect of ketamine on behavioral despair lends support to the view that implicates an NMDA receptor-mediated involvement of glutamatergic system in the pathophysiology of depression (Papp and Moryl, 1994; Skolnick et al., 1996; Trullas and Skolnick, 1990). Our findings are also consonant with the report by Berman et al. (2000) that a single intravenous treatment with ketamine (0.5 mg/kg) induced significant improvement in depressive symptoms in humans that were evident for 72 h. The same study also reported a lasting effect of ketamine in mood improvement that returned to baseline levels only 1–2 weeks after treatment.

The prolonged beneficial effect of ketamine in the present study may be due to a long-term change in glutamatergic activation and its consequences. O'Neill and Sanger (1999) have shown that a single pretreatment with MK-801, an NMDA antagonist, induces an enduring sensitivity to the second administration of the same stimulant 4, 7, or 14 days later. It is possible that the anesthetic dose of ketamine in the present study may

have induced a prolonged change in the animal's responsiveness to forced-swim tests by altering neurochemical activity in the circuitry mediating immobility in the forced-swimming such as the frontal cortex, hippocampus, and the amygdala (Araki et al., 1985; Connor et al., 1997; Duncan et al., 1986; Jordan et al., 1994; Kawashima et al., 1990; Nowak et al., 1996; Przegalinski et al., 1997; Skolnick et al., 1996). Recent studies that have uncovered a long-term change in NMDA receptor activity in response to various antidepressant treatments suggest that altered glutamatergic activation may constitute the final common pathway for action of antidepressants in alleviating depressive behavior in rodents (Nowak et al., 1998; Skolnick et al., 1996; Trullas and Skolnick, 1990). These studies target the hippocampus and the frontal cortex, particularly the latter, as neural substrates involved in altered glutamatergic activation (Moghaddam, 1993; Nowak et al., 1996). Ketamine modulates dopaminergic and serotonergic levels in the brain, particularly in the frontal cortex (Duncan et al., 1998; Hammer and Herkenham, 1983; Lannes et al., 1991; Lindefors et al., 1997; Moghaddam et al., 1997), which have been implicated in behavioral despair and swim stress (Claustre et al., 1986; Connor et al., 1997; Detke and Lucki, 1996; Jordan et al., 1994). Moreover, microinjections of glutamate in the prefrontal cortex has been shown to aggravate learned helplessness in rats 1 and 72 h, but not 24 h, after drug administration (Petty et al., 1985). Since glutamatergic activation of the frontal cortex exacerbates learned helplessness, an animal model of depression that is related to behavioral despair (Willner, 1990), depression of glutamatergic activity in the frontal cortex as a consequence of ketamine administration may account for the present beneficial results.

Acknowledgments

We thank Dr. Gulsen Babacan-Yildiz, Zeynep Celen, Sevil Duvarci, Ozgun Gokce, Melis Inan, Gokce Ozkarar, and Ozgur Tataroglu for their technical assistance. This research was supported by Grant No. 99B704 to R.C. from the Bogazici University Research Fund.

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