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**The Effect of the NMDA  
Noncompetitive Antagonist  
Ketamine on  
Serial Learning in Rats**

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**Abstract**

*Past research has demonstrated that N-methyl-D-aspartate (NMDA) receptor antagonists disrupt the acquisition of a variety of spatial and non-spatial tasks. In the present investigation, the effects of the NMDA antagonist, ketamine, were examined in a task with minimal spatial demands. Twenty-six male Long-Evans rats, approximately 5 months of age at the beginning of training, served as the subjects. Before training began, all rats were reduced to 85% of their free feeding weight and maintained with this 15% reduction throughout training. After injections of ketamine or saline, rats were trained to respond in a runway to a nonmonotonic serial pattern consisting of 14-, 0-, 3-, or 7-pellets, respectively. Saline rats were capable of tracking the rewarded and non-rewarded elements of the series while the ketamine rats were markedly impaired. Specifically, analysis of the running times revealed a significant drug group  $\times$  elements interaction,  $F(3, 36) = 3.01, p < .05$ . Examination of the interaction with Tukey  $\alpha$  revealed that the saline rats ran significantly faster to the three rewarded elements of the series than the 0-pellet element ( $p_s < .05$ ). Conversely, ketamine-treated rats had similar running times to all elements of the series ( $p_s > .05$ ). The results are discussed in terms of NMDA-receptor involvement in the task acquisition.*

The effects of lipophilic substances with known N-methyl-D-aspartate (NMDA) antagonistic properties have only recently been assessed (Wesierska, Marcias-Gonzalez, & Bures, 1990). Most competitive NMDA antagonists are polar compounds unable to

penetrate the blood-brain barrier and, as a consequence investigators have turned to noncompetitive antagonists such as phencyclidine (PCP) and ketamine, a cyclohexylamine (Hauber & Schmidt, 1990).

The NMDA receptor is one of three distinct receptor subtypes that appear to mediate the effects of the neurotransmitter glutamate (Hauber & Schmidt, 1990). It has been suggested that glutamate is the principal excitatory neurotransmitter in the cerebral cortex and hippocampus (Fagg & Foster, 1983) and may participate in a variety of learning and memory functions (Hauber & Schmidt, 1990). Dissociative anesthetics used as part of a surgical procedure appear to disrupt glutamatergic transmission and produce both retrograde and anterograde amnesia of events preceding and following surgery (Jansen, 1990).

A number of investigations have demonstrated that NMDA antagonists impair spatial performance in the Morris water maze (Morris, Anderson, Lynch, & Baudry, 1986; Wesierska et al., 1990) or radial maze tasks (Kesner, Hardy, & Novak, 1983; McCann, Rabin, & Winter, 1987). Similar impairments have been demonstrated with nonspatial tasks (Tonkiss, Morris, & Rawlins, 1988). Impairments appear to be the result of disruption of long-term potentiation, affecting the acquisition of or working memory elements of a task rather than the retrieval or reference memory elements (Wesierska et al., 1990).

Serial pattern learning is one methodology useful for the assessment of acquisition deficits after lesions or pharmacological manipulations (Compton, 1993; Compton, Dietrich, & Smith, 1995). In rodents, learning is reflected by anticipatory responding, which is inferred from differences in times taken to run to a goal area as a function of differing quantities of 45 mg food pellets (Compton, 1993).

The purpose of the present experiment was to examine the effect of ketamine on the acquisition of a nonmonotonic serial pattern. Further, because the minimal effective dose known

to affect learning and sensorimotor deficits is small, the animals were also assessed for differences in activity that could interfere with the acquisition process.

### **Method**

#### **Subjects**

Fourteen male hooded rats (Long-Evans derived), weighing 250-300 g and approximately 5 months of age at the beginning of testing, served as the subjects. An additional 12 male rats of comparable age and weight were used to determine the effect of ketamine on general activity. All animals were housed individually and maintained under a 12 hr light-dark cycle with lights on at 7:00 p.m. (local time) and a room temperature of  $22^{\circ}\text{C} \pm 3^{\circ}$ . Eight days before training began all animals were weighed and reduced to 85% of their free-feeding weights and maintained at this 15% reduction throughout training with ad lib access to water. All animals were treated in accordance with the "Ethical Principles of Psychologists and Code of Conduct" (American Psychological Association, 1992) under the supervision of the Georgia College Animal Care and Use Committee.

#### **Apparatus**

An enclosed runway 185 cm in length, with a 25 cm goal box and a 15 cm start box, served as the apparatus. Start and goal boxes were separated by manually operated guillotine doors and all sections were covered with hinged Plexiglas. Raising the guillotine door at the junction of the start box and runway activated one timer (Lafayette, 62225/40) accurate to 0.01 s, which was stopped when the rat interrupted a photobeam 15 cm into the goal box. The goal box contained a removable ceramic dish which was baited with predetermined quantities of 45 mg Noyes pellets.

#### **Pretraining and Experimental Training**

Following a brief period of hand taming to acclimate the rats to handling,

each rat was randomly assigned to the ketamine or saline groups and permitted to explore the runway for two 5 min periods. In addition, all rats were allowed to consume seven 45 mg food pellets in the goal box.

After the exploration period, experimental training began and lasted for 30 days. Animals were transported to the testing room in squads of six. Fifteen minutes before training, the ketamine animals received daily intraperitoneal (ip) injections of 15 mg/kg ketamine HCL (Ketaset, Fort Dodge, IA) and the control animals were injected with a similar volume of 0.09% saline. In no case did the injection volume exceed 1 ml/kg in drugged or control animals. All animals received two daily trials consisting of two repetitions of a 14-, 0-, 3-, and 7-element nonmonotonic pattern. Within each squad, all animals underwent the first trial before any animal experienced the second trial. The intertrial interval (ITI) was approximately 30 min and the inter-element interval (IEI) was approximately 20 s. Each subject was confined in the goal box until all pellets were consumed, or on 0-pellet elements, for 30 s. Animals were placed in the goal box and a 60 s running time was recorded if an animal failed to reach the goal box within a 60 s period.

The last 5 days of training were collapsed and analyzed using a two-way 2 x 4 (Groups x Elements) ANOVA, with Groups treated as a between-subjects factor and Elements (14, 7, 3, & 0) treated as a within-subjects factor. Within each group, Tukey tests were used to analyze significant differences between elements of the series.

### **Results**

Figure 1 is a presentation of the mean running times (s) for the ketamine and saline groups to each element of the series. Analysis of variance applied to the data revealed the following significant effects ( $ps < .05$ ). A significant main effect of Elements was obtained,  $F(3, 36) = 3.01$ , was found. A breakdown of this interaction using Tukey *a* tests ( $p < .05$ )

indicated that the saline animals ran significantly faster on the three rewarded elements of the series than on the 0-pellet element. Conversely, in the ketamine group, similar running times to all elements of the series were detected ( $ps > .05$ ).

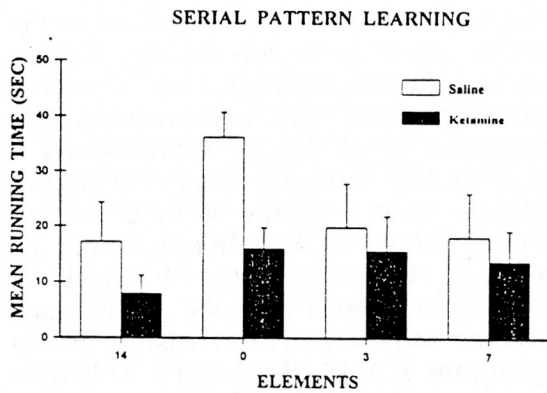


Figure 1. Mean running times for the ketamine and saline groups to each element of the series collapsed over the last 5 days of training.

In order to ascertain whether the observed tracking deficits in the ketamine animals were due to hyperactivity, 12 naive animals were injected with ketamine or saline followed 15 min later by six 5 min exposure periods (5 min/day) in a stabilimeter cage. The data are summarized in Figure 2. In order to meet assumptions of ANOVA, all data were transformed ( $X = \log_{10}$ ; Winer, 1971) before analysis. A significant main effect of Day,  $F(5, 50) = 2.90$ , and, more importantly, a significant Group x Day interaction,  $F(5, 50) = 3.79$ , were

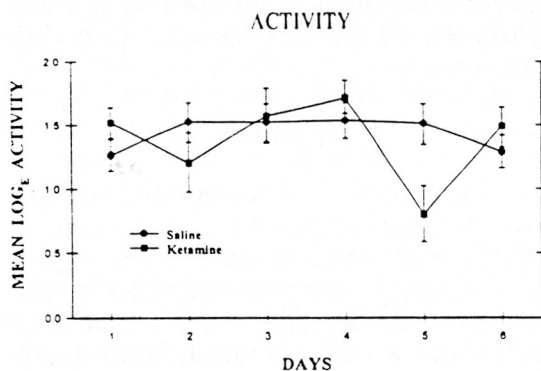


Figure 2. Activity counts as measured by a stabilimeter cage on each of 6 days of testing.

obtained. Decomposition of this interaction with Tukey *a* tests revealed that group differences were present only on Day 5 of the assessment period (see Figure 2).

### Discussion

Depending on dose (Irifune, Shimizu, & Nomoto, 1991) ketamine can induce locomotor activity and ataxia in rodents (Marietta, Way, Castagnoli, & Trevor, 1977; Morris et al., 1986), although the exact locus of this effect remains to be elucidated (Irifune et al., 1991). Because differences in activity generally were not observed, acquisition deficits as the result of hypermotility are unlikely. The reason for the decline in general activity on Day 5 of general activity assessment is unknown.

While more research needs to be completed, the results suggest that the learning deficit observed in the ketamine rats was the result of a specific interaction of ketamine with mnemonic processes. This proposal is consistent with previous investigations where ketamine-related memory impairments were reported in a hexagonal tunnel maze (Alessandri, Welzl, & Battig, 1988), delayed alternation (Hauber & Schmidt, 1990), and latent learning in a Morris water task (Wesierska et al., 1990).

In the present investigation, the results are suggestive of an acquisition-impairment due to the NMDA receptor-blocking characteristics of ketamine. There is considerable support for a glutamatergic role in the acquisition of a variety of spatial and non-spatial tasks (e.g., Barnes, 1988; Tonkiss et al., 1988). Ketamine acts at ion channels of the NMDA receptor complex (Earley, Burke, Leonard, Gouret, & Junien, 1990) and LTP induction is governed by the glutamatergic NMDA receptor complex (Izquierdo et al., 1993). In fact, the NMDA receptor complex is concentrated in the field CA1 and dentate gyrus regions of the hippocampus (Monaghan & Cotman, 1985). Although LTP is dependent on both glutamatergic NMDA and opiate receptors, NMDA receptors do appear to mediate the acquisition of



information (Bostock, McKay, Fong, & Min, 1992). While the present methodology provides a mechanism for assessment acquisition deficits after NMDA blockade, the results did not provide the means to determine if the deficits were due to underlying effects on mnemonic processes or simply a performance-based deficit (Keith & Rudy, 1990). Which of these two explanations is correct can be elucidated through future research.

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