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ACQUISITION, BUT NOT RETRIEVAL OF DELAYED ALTERNATION IS IMPAIRED BY KETAMINE

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ABSTRACT

Dissociative anaesthetics as ketamine and related drugs induce marked behavioral changes in rats, in particular behavioral stereotypies and learning impairments. In the present study the effect of ketamine on acquisition and retrieval of a delayed alternation task was investigated. Results indicate that ketamine (8mg/kg i.p.) impaired specifically acquisition, while retrieval was not affected. Thus, stereotypies competing with ongoing behavior and therefore interfere with learning, appear not to be causative to the acquisition deficit, since retrieval should be affected in the same way. A possible involvement of NMDA receptors in deficient acquisition is discussed.

INTRODUCTION

Ketamine, a cyclohexylamine, is used clinically as a potent anaesthetic component in man and several species of animals. The properties of ketamine are characterized by a superficial anaesthesia with maintenance of many protective reflexes, analgesia and weak muscle relaxation (Stumpf 1983). These properties of ketamine separate it from other general anaesthetics and have led to a classification as "dissociative anaesthetics" along with related compounds as phencyclidine (PCP)(Corsen and Domino

1966). Dissociative anaesthetics are further known to produce retrograde and anterograde amnesia of events around the surgical procedure (Greifenstein et al. 1958). This effect seems to be related to the blockade of glutamatergic transmission by dissociative anaesthetics. Glutamate is believed to be the major excitatory transmitter of the cerebral cortex and hippocampus (Fagg and Foster 1983). Its excitatory actions are mediated by at least three distinct receptor subtypes named for N-methyl-D-aspartate (NMDA), kainate and quisqualate (or AMPA), according to the most specific agonists at each of these receptor subtypes (Watkins and Evans 1981). Ketamine and PCP are non competitive NMDA receptor antagonists (Martin and Lodge 1986) and the NMDA receptor appears to be closely linked to learning and memory functions.

Aside this "cognitive" deficit this group of drugs induces severe psychotomimetic symptoms in humans, e.g. thought disorders, depersonalisation, mania (Luby et al. 1959, Domino 1964). These behavioral deficits could be partly paralled in experimental animals, since dissociative anaesthetics induce stereotyped behaviors as turning and sniffing in rats, which can be regarded as an experimental model of schizophrenia (Bischoff et al.1986). There is strong evidence that blockade of NMDA receptors is critically involved in generation of stereotyped behavior (Schmidt 1986) and a glutamatergic dysfunction may be

implicated in schizophrenia (Kim et al. 1980).

We employed in the present study a delayed alternation procedure in a T-maze which is sensitive to cognitive deficits (Wikmark et al.1973, Markowitsch and Pritzel 1977, Divac and Oeberg 1981) and investigated the effect of ketamine on two different conditions in this paradigm: the effect of ketamine on acquisition of this task by naive animals, and effects of ketamine on rats which are fully pretrained on this task (retrieval). The terms acquisition and retrieval refer to a specific kind of spatial learning. Spatial alternation seems to be a congenital explorative pattern of rodents, therefore requirements of this task may be well adjusted to the shifting strategies of this species. Further both conditions may reflect separate memory mechanisms which are to a different extent susceptible to ketamine treatment. Therefore a different effect of ketamine on both conditions may indicate an interference with memory-related systems and have implications to the amnestic activity of dissociative anaesthetics in humans. If stereotypies competing with ongoing behavior contribute to performance deficts seen following ketamine treatment, we expect a similar impairment under both conditions.

The range between minimal effective dose of ketamine and sensorimotor deficits is very small. The dose of ketamine used here was chosen low to avoid unspecific bahavioral

Statistics

The data are presented as means of errors (false arm entries)(+/-SEM) in ten choices per aday. The data were submitted to a two-way anaysis of variance (ANOVA) with groups and days as factors. Differeces were considered to be significant if the P-value is less than 0.05.

RESULTS

Experiment 1

Systemic administration of ketamine impaired acquisition of delayed alternation as shown in Fig 1. Analysis of variance (ANOVA) revealed a significant effect of group ($F(1,72)=12.56$, $p<0.025$), but no effect of days ($F(8,72)=2.02$, $p>0.05$). Ketamine treated animals made (except day 2) more errors than controls on the same day. Furthermore, total means of errors from all days tested of both groups differed clearly (controls: 2.6 errors, SEM+/-1.1; ketamine treated: 3,7 errors, SEM+/-2.7).

Experiment 2

As shown in Fig.2, ketamine treatment had no effect on retrieval of prelearned delayed alternation task. Anylysis of variance (ANOVA) showed no significant effects of groups $F(1,40)=4.08$ and days $F(4,40)=2.45, p>0.05$ respectively.

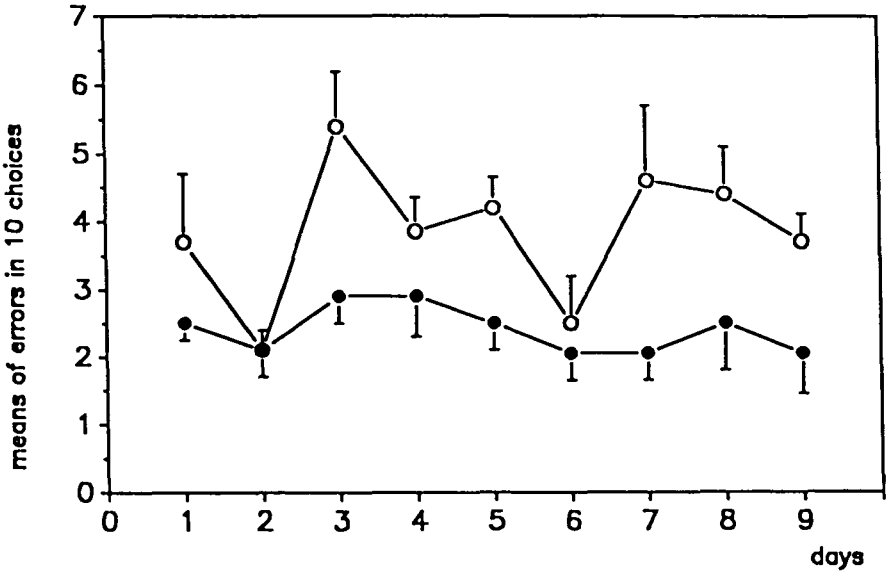

Fig.1 Effect of systemic administration of ketamine on acquisition of delayed alternation in a T-maze (experiment 1). Means of errors of ketamine treated animals (o, N=5, (mg/kg i.p.) and saline controls (●,N=5, 1ml/kg) (+/-SEM) in 10 choices on 9 consecutive days. Analysis of variance revealed a significant effect of groups ($F(1,72)=12.56, p<0.025$).

Therefore, total means of errors over all five days (controls: 2.2, SEM+/-0.25, ketamine treated: 2.6, SEM+/-0.12) and total mean of errors after pretraining differed only slightly. Prelearned delayed alternation appeared to be resistant against ketamine treatment at this dose.

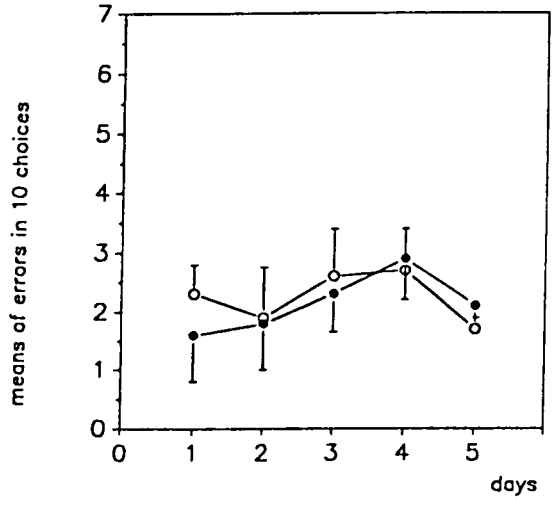

Fig.2 Effect of systemic administration of ketamine on retrieval of delayed alternation in a T-maze (experiment 2). Means of errors of ketamine treated animals (o, N=5, 8mg/kg i.p.) and saline controls (●, N=5, 1ml/kg i.p.) (+/-SEM) in 10 choices on 5 consecutive days. Analysis of variance (ANOVA) revealed no significant effect of groups ($F(1,40)=4.08, p>0.05$).

DISCUSSION

The present data indicate that systemic administration of ketamine produces a deficient acquisition of delayed alternation in a T-maze, while retrieval, e.g. a prelearned delayed alternation is unaffected.

Dissociative anaesthetics as ketamine and PCP are non competitive NMDA receptor antagonists and produce marked behavioral changes in rats, e.g. increased locomotion, stereotyped sniffing, swaying and falling (Koek et al.

1987). This is in accordance with findings that systemic administration of MK-801, a novel and highly specific non competitive NMDA receptor antagonist led to a similar behavioral activation and stereotypies (Clineschmidt et al. 1982, Bischoff et al. 1988). Interestingly, NMDA receptor blockade within the striatum by 2-amino-5-phosphonovaleriate (AP-5), a competitive antagonost mimiced the effects of systemic administration, e.g. produces stereotyped sniffing and enhanced locomotion (Schmidt 1986). Further, intrastriatal NMDA receptor blockade causes a similar acquisition deficit in a T-maze as observed here (Hauber 1988, Hauber and Schmidt 1989), which is attributed to an increased susceptibility to interfering external and internal stimuli. However, stereotypies competing with ongoing behavior and therefore interfere with learning seem not to be causative to the learning deficit observed here, since retrieval should be affected in a similar manner by processes of that kind.

In order to minimize unspecific beahvioral changes which may confound results, the dose of ketamine was chosen low in the present study (8mg/kg i.p.). Thus, a disruption of discrimination could not account for the acquisition deficit, since higher doses are required (30mg/kg) (Tang and Franklin 1983). Further, acquisition and retrieval should be affected in the same way. For the same reasons, this deficit is hardly due to a sensorimotor debility,

although ketamine was found to induce ataxic symptoms (Koek et al. 1987). In conclusion, it seems likely that the the learning deficit observed here is a result of a specific interaction of ketamine with memory-related systems. This view is supported by a study of Alessandri et al. (1988), where ketamine was reported to attenuate spatial learning in a hexagonal tunnel maze at a similar dose as used here.

The acquisition impairment may be the result of NMDA receptor blocking properties of ketamine. Ketamine and other dissociative anaesthetics as PCP are non competitive antagonists which act at the ion channel of the NMDA receptor (Martin and Lodge 1985) and there is convincing evidence of a glutamatergic involvement in memory related mechanisms (e.g. Morris et al. 1986). In addition, MK-801 was recently found to induce a similar impairment in the same task as used here (Bischoff et al. 1988). While glutamatergic transmission seems to be a causative factor in acquisition , this is not true for the retrieval condition in the present experiment. It is possible that learning can simply more easily disrupted than retrival of a learned response. On the other hand, Freed and Wyatt (1980) observed that glutamic acid diethyl esther (GDEE), a broad spectrum glutamic acid antagonist, disrupt selectively learning of a reinforced instrumental conditioning task, while retrieval was not deteriorated.

In context with our results this indicates that acquisition and retrieval may be qualitatively different processes with regard to neurotransmitter systems: NMDA receptors seem to be involved in mechanisms related with acquisition of information of this task and sensitive to treatment with NMDA antagonosts, while retrieval of consolidated informations appears not to be affected. This may partly reflect observations in humans, that dissociative anaesthetics produce amnesia around the surgical procedure (Greifenstein et al. 1958), but does not cause retrograde amnesia for events preceeding drug administration and chronic PCP abuse has been reported to cause a recent memory impairment (for refs.see Burns and Lerner 1981).

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