Ketamine Induced Deficits in Working Memory with Relevance to Schizophrenia

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INTRODUCTION

Schizophrenia is a chronic debilitating brain disorder, which affects approximately one percent of the adult population worldwide. The symptoms of schizophrenia are commonly divided into three broad classes: positive symptoms, negative symptoms, and cognitive disturbances (Kay, et al., 1987). The positive symptoms of schizophrenia include hallucinations, delusions, and disorganized thinking, while the negative symptoms include affective flattening, social withdrawal, and an inability to plan and carry out future activities. The cognitive disturbances exhibited in schizophrenia include deficits in spatial reference and working memory as well as difficulties with focus and attention (Lewis et al., 2007). Several models have been proposed as to the etiology of schizophrenia, one of which proposes the hypofunction of a discrete class of excitatory receptors (NMDA) on primarily inhibitory circuits in the brain. This change in signaling is argued to give rise to a loss of coordinated network activity throughout the brain resulting in deficits observed in schizophrenia (Figure 1). Data for this model is based on postmortem alterations in inhibitory circuits and the ability of drugs that block the function of the NMDA receptor (NMDA antagonists) to produce deficits similar to those seen in schizophrenia populations (Coryle, 2012). The ability of these NMDA antagonists to produce psychosis similar to what is observed in schizophrenia has led to their extensive use in studying the mechanisms responsible for the disorder. Previous studies in our laboratory have demonstrated the ability of ketamine, an NMDA receptor antagonist, to produce deficits in rodent’s spatial and emotional learning and memory consistent with observations in schizophrenic populations (Bolton et al., 2012; Sabbagh et al., 2012). In these investigations, it was also shown that ketamine administration was sufficient to induce alterations in inhibitory circuits in the brain that are commonly implicated in schizophrenia (Sabbagh et al., 2013). In the present study, we examined the extent to which the same administration of ketamine produced deficits in rodent’s spatial reference and working memory performance in the radial arm maze task. As working memory deficits are a core pathological feature of schizophrenia, these investigations seek to further the validity of the ketamine model as it relates to the etiological origin of schizophrenia.

EXPERIMENTAL PROCEDURE

Drug Administration

Twenty male Sprague-Dawley rodents (n=20) weighing between 250 and 275g from Taconic Farms (Albany, NY) were used in this project. Animals were divided into two groups and received injections of saline (n=10) or 8mg/kg ketamine (n=10) daily, thirty minutes prior to behavioral testing. Injections began on the first day of behavioral testing and continued throughout completion of the experiment.

RESULTS

Radial Arm Maze

The radial arm maze (Med Associates Inc., St. Albans, VT) consisted of a clear center platform with a white base, 35.6 cm in diameter, 35.6 cm in height, with a width of 40.6 cm. Eight arms, 45.7 cm in length, extended radially outwards from the center platform, with metal food trays at the end of the arms for food pellet baiting (Figure 2). The arms consisted of a white base with clear plastic walls allowing the animal to visualize distal spatial cues on the walls. Four spatial cues were placed along the walls of the testing room to help orient the animal.

Trials were recorded using a video tracking system (Smart, San Diego Instruments, San Diego, CA) recorded from a Sony Handycam camera connected to a Cobalt instruments computer. For each trial, the animal’s latency to complete and speed were tracked and recorded using the video tracking system. For each animal, arm entries were tracked and recorded by a trained experimenter.

Statistical Analysis

The effect of treatment on performance in the radial arm maze was analyzed using a repeated measures analysis of variance (RM-ANOVA). A repeated measures analysis of variance was performed for the latency and speed of animals in the radial arm task.

No deficits were seen in the amount of reference memory errors made between ketamine and saline groups across the ten days of training with the ketamine group showing an increase in total number of working memory errors relative to control (F1,18=38.343, p<.001). The ketamine group displayed a significant increase in latency (C) across days compared to the control group (F1,18=3.37, p=0.083) or speed (D) (F1,18=4.12, p=0.041) between the groups.

CONCLUSION

- Administration of 8 mg/kg ketamine produced deficits in rodent’s working memory performance in a radial arm maze task.
- No deficits were seen in the amount of reference memory errors made between ketamine and saline groups.
- These findings are consistent with reports of schizophrenia populations of which working memory deficits are a core pathological feature.
- Future directions include examining tissue collected from animals run in the radial arm maze for histo-pathological alterations consistent with schizophrenia. These include alterations in parvalbumin containing GABAergic cells as well as a variety of markers for NMDA.

REFERENCES