Evaluation Of Sub-Chronic Ketamine Treatment In A Rodent Model Of The Iowa Gambling Task

Bradley Jermy, Mohammed Shoaib

Institute of Neuroscience, Newcastle University, Newcastle, NE24HH, UK

Introduction

- The Iowa Gambling Task (IGT) is a choice-based task which assesses impulsivity, where patients must choose one of four options in order to optimise monetary gains.
- Choices that give large rewards are linked with large punishments or monetary losses and vice versa. Optimum gains are made by choosing small reward options the most and high-risk choices are associated with high levels of impulsivity and has been to shown to be higher in schizophrenics.
- This has been adapted to rodents with the rIGT by Zeeb et al (2009) where rodents must choose between four illuminated holes in order to gain maximum food pellets within a 30 minute period. The punishment is represented as a time-out period which has the indirect effect of reducing the number of pellets that can be gained (1) (see figure 1).
- Schizophrenia is associated with a wide-range of symptoms including cognitive deficits (2).
- Aberrant glutatmatergic transmission is thought responsible for these deficits, therefore ketamine (weak NMDA-receptor antagonist) can be used to model schizophrenia in rodents (3).
- Nicotine has been shown to improve attentional performance in patients with schizophrenia (4).

Aims and Hypotheses

- To assess the impact of sub-chronic ketamine exposure on ability of rats to make choices within the rIGT and therefore assess impulse behaviour.
- To determine whether nicotine can restore any alterations in choice produced by the sub-chronic ketamine exposure since it has been shown to improve cognition in other tasks (5).

References

1. Zeeb FD, Robbins TW, Winstanley CA. (2009) Serotonergic and dopaminergic modulation of gambling behavior as assessed using a novel rat gambling task. *Neuropsychopharmacology* **34**:2329-43
2. McGlashan TH. (1987) Testing DSM-III symptom criteria for schizotypal and borderline personality disorders. Arch Gen Psychiatry 44:143-8.
3. Adell, A. et al (2011) Is the acute NMDA receptor hypofunction a valid model of schizophrenia? Int J Neuropsychopharmacol. 7:1-12.
4. Ernst, M., Heishman, SJ., Spurgeon, L. London, ED. (2001) Smoking history and nicotine effects on cognitive performance. Neuropsychopharmacology 25: 313–319
5. Rushforth SL, Steckler T, Shoaib M (2011) Nicotine improves working memory span capacity in rats following sub-chronic ketamine exposure. Neuropsychopharmacology. 36:2774-81

Details of the rGT

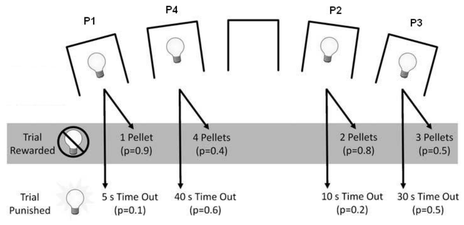

***Figure 1**. This diagram depicts the relative risk/reward of each choice associated with the illuminated holes in the rIGT. P2 is the optimal choice selection with P3 being the least optimal.*

Experimental Design

- Rats were trained to nose-poke into a hopper and then follow it up by nose-poking into an illuminated light which was then associated with a reward. Training was judged as being completed when the rats were repeatedly being successful in achieving 30 correct responses within a 10 second stimulus.
- Once training was complete, rats were randomly separated into two groups (n=12) with one group being treated with saline injections and the other group being treated with ketamine (30mg/kg IP). The rats underwent injections daily for 5 days.
- The rats then underwent a forced-choice version of the rIGT where each rodent experienced each choice contingency equally.
- The rats underwent one 30 minute session of the classic rIGT daily and choice selection was noted.
- Both groups of rats were each tested with a randomised sequence of nicotine doses (0, 0.05, 0.1, 0.2, 0.4) administered 10 min prior to rIGT sessions.
- Rats then carried out the IGT task once again and choice selection was assessed to determine the impact of nicotine on impulsivity.

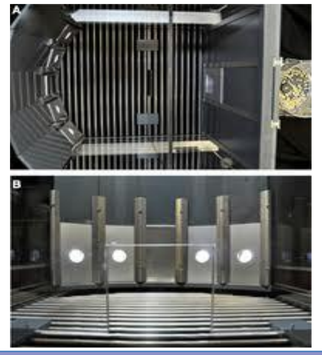

Figure 2.
(a) A top-down view of the skinner boxes used to carry out the rIGT showing the hopper delivery system (right) and the 4 illuminated choice holes (left). **(b)** a photo showing the 4 illuminated choice holes.

Results

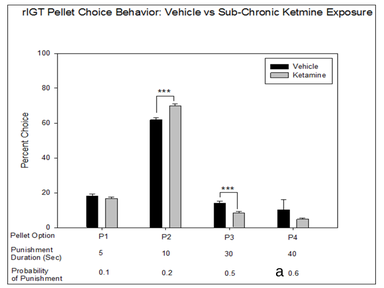

Figure 3. Sub-chronic ketamine treatment produced no significant differences between choice selection in the P1 and P4 selections. There was a significant increase ($p<0.001$) in the optimal selection (P2) with the ketamine treated rats compared to the vehicle group. There was also a significant decrease ($p<0.001$) in choosing for least optimal selection (P3) in the ketamine treated rats compared to the vehicle group.

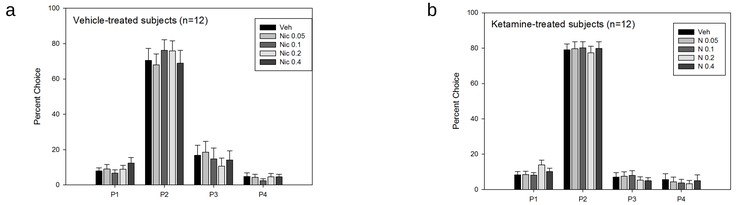

Figure 4. **(a)** Nicotine pre-treatment had no significant effect on choice selection in the rats in the vehicle group. **(b)** Nicotine pre-treatment also had no effect on choice selection in the ketamine treated group.

Conclusions

- Sub-chronic ketamine exposure increased optimal choice selection and decreased sub-optimal choice which is contradictory to published literature on impulsivity in patients with schizophrenia.
- The overall finding from this study suggests that the sub-chronic ketamine exposure decreases impulse behaviour in rats.
- Nicotine treatment had no effect on choice selection in control subjects and had no effect in restoring the altered baseline performance in the rIGT.