Does Ketamine Really Modulate Glutamate?

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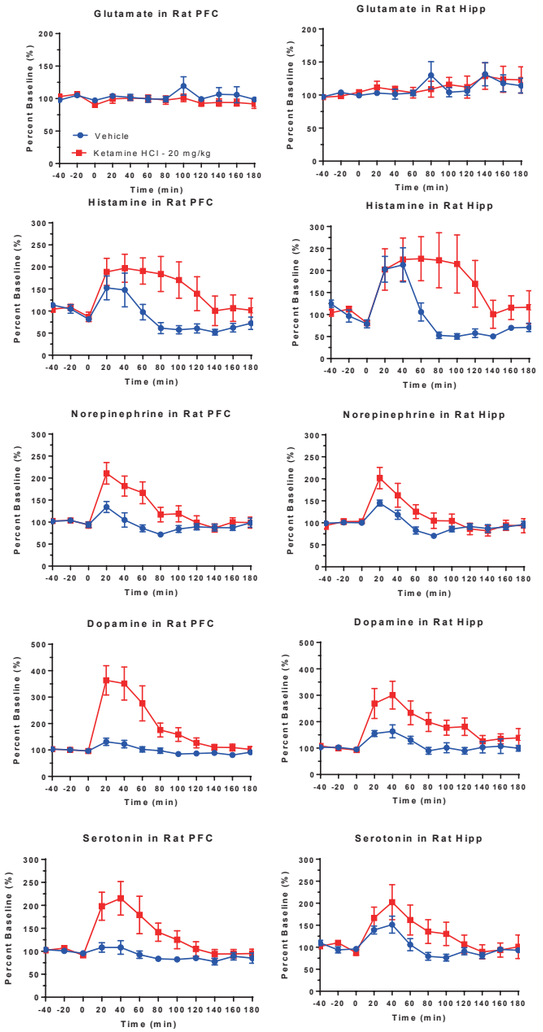
1 Introduction

The noncompetitive NMDA receptor antagonist ketamine has been shown to elicit psychotic action in humans, exacerbate symptoms in schizophrenic patients, and more recently has been shown to have potential in treating depression. It is hypothesized that these actions may be regulated by ketamine's action on glutamate (glu), as has been previously demonstrated using *in vivo* microdialysis in the prefrontal cortex of rodents (Lorrain *et al.* 2003, Moghaddam *et al.* 1997). In addition, it has also been demonstrated that ketamine increases dopamine (DA) activity (Moghaddam *et al.* 1997). However, we have historically been unable to attain a reproducible ketamine-induced release of glutamate using both *in vivo* microdialysis and biosensors. Thus, in the current set of experiments we utilized *in vivo* microdialysis to examine the effects of different dose of ketamine on neurotransmitter release in the prefrontal cortex and hippocampus of mice and rats. Consistent with our previous findings, we were unable to see an increase in glutamate levels of either species using 10 and 20 mg/kg of ketamine. Interestingly, we were able to observe a significant increase in dopamine levels, as previously reported as well as an increase in both serotonin (5HT) and norepinephrine (NE). Some of these monoaminergic changes were more pronounced in the hippocampus as compared to the prefrontal cortex. These results challenge existing reports of the mechanism by which ketamine exerts its actions, and provide additional support for the neuroactive mechanisms of ketamine functioning through monoaminergic pathways.

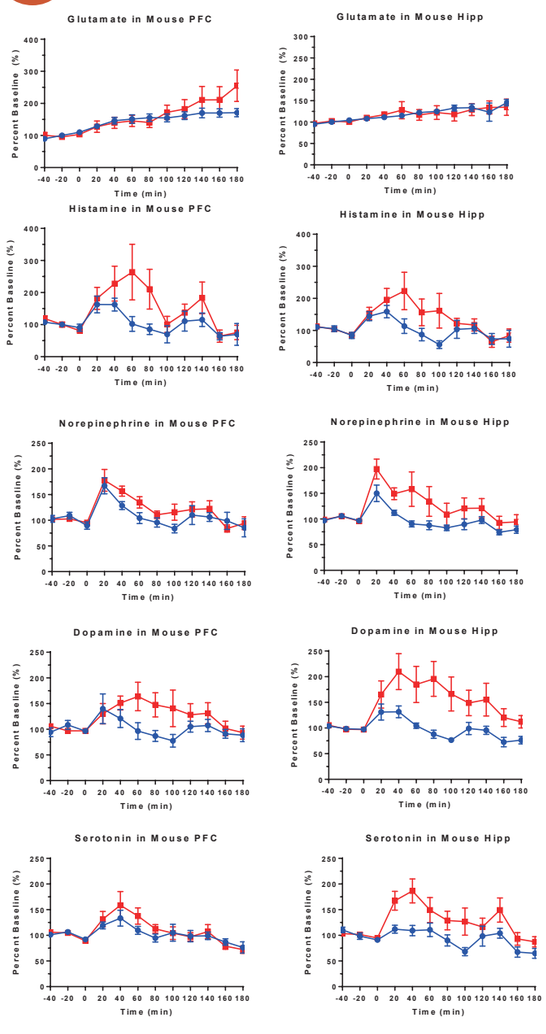
2 Materials and Methods

- Mice and Rats (n = 6/group) were anesthetized using isoflurane (2%, 800 mL/min O_2).
- The animals underwent stereotaxic surgery where I-shaped microdialysis probes (polyacrylonitril membrane, BrainLink, the Netherlands) were inserted into the PFC and hippocampus (3 mm exposed surface for Hipp and 2 mm exposed surface for the PFC).
- Experiments were performed one day after surgery.
- On the day of the experiment, the probes were perfused with aCSF containing 147 mM NaCl, 3.0 mM KCl, 1.2 mM $CaCl_2$ and 1.2 mM $MgCl_2$, at a flow rate of 1.5 µL/min.
- Microdialysis samples were collected for 30 minute periods by an automated fraction collector into polystyrene mini-vials containing 15 µL of 0.02M formic acid (FA) and 0.04% ascorbic acid in ultrapurified H_2O.
- Ketamine (20 mg/kg, Sigma) was administered IP at time = 0.
- Microdialysis samples were derivatized using SymDaq® and analyzed for the levels of DA, NE, 5HT, Glu, GABA, and Gly by LC MS/MS.

3 Results (Rat)



4 Results (Mouse)



5 Summary/Conclusions

- Ketamine (20 mg/kg) does not increase the levels of extracellular **glutamate** in either the PFC or hippocampus of rats or mice
- Ketamine (20 mg/kg) does not increase the levels of extracellular **GABA** in either the PFC or hippocampus of rats or mice
- Levels of **histamine** were significantly increased by ketamine administration in the PFC and Hipp of both mice and rats.
- **Dopamine, serotonin, and norepinephrine** levels were differentially regulated in the rat PFC as compared to mouse PFC such that ketamine administration resulted in significant elevations of all 3 transmitters in the PFC of rats with little to no effect on the PFC release of DA, NE, 5HT in mice.
- Monoamine levels (**DA, 5HT, and NE**) were elevated following ketamine administration in the hippocampus of both mice and rats
- Here we demonstrate that ketamine reproducibly increases the release of monoamines in the PFC and hippocampus in rats and mice whilst having no effect on glutamate release. Therefore, when examining the potential mechanism by which ketamine exerts its actions one must look at the effects on monoamines compared to amino acids. The lack of a response on glutamate in our hands could explain the variability reported on ketamine's actions in a variety of rodent behavior assays. These studies warrant further exploration into the discrepancies on ketamine's *in vivo* effects.