Investigating the role of Methylglyoxal as a $GABA_A$ Agonist through Glyoxalase 1 Manipulation

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Introduction

- Cocaine use disorder (CUD) affects over 1 million people in the US. However, there are no FDA approved treatments for CUD
- Methylglyoxal (MG) is an endogenous byproduct of glycolysis
  - When MG accumulates it causes degradation of proteins, cytotoxicity and mutagenesis
  - High levels of MG are often related to diabetes and diabetic neuropathy
- Glyoxalase 1 (Glo1) is part of the glyoxalase system and is the main catabolic pathway for MG
- Studies have shown that MG accumulation through Glo1 inhibition mitigates the symptoms of psychiatric disorders such as anxiety(McMurray, 2016) and depression (McMurray, 2018). Studies have also shown Glo1 inhibition can reduce self administration of alcohol in mice (McMurray, 2018) and rats (de Guglielmo, 2018)
- MG has been shown to act as a competitive partial $GABA_A$ agonist (Distler et. al, 2012)
- A study by Morris et. al (2008) showed that co-administration of a well established $GABA_A$ agonist, midazolam, potentiates the locomotor activation of cocaine

Methods

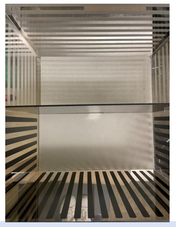
- 120 male/female C57BL/6J mice (n=9-11/sex/drug) for each drug
- 10 mg/kg cocaine HCl dissolved in 0.9% Saline solution
- 1 mg/kg Oxycodone HCl dissolved in 0.9% Saline
- 0, 12.5, 25, and 50 mg/kg pBBG dissolved in 8% DMSO+80Tween+ 0.9% Saline

Open Field Test

- One day test in an open clear box for 30 min.
- Pre-treated with pBBG, 1.5-hrs prior to start of test
- I.P. injection of either oxycodone/cocaine immediately prior to test

Conditioned Place Preference

- Two chamber box with visually and physically distinct sides
- 30 min. pretest following saline I.P injection
- 4 days of training where they either receive saline/drug on one side for 30 min.
- Test day where they have free access for 30 min following a saline injection and 1.5-hour pre-treatment with pBBG



Results

Co-Administration of Cocaine and pBBG Potentiates Locomotor Activation

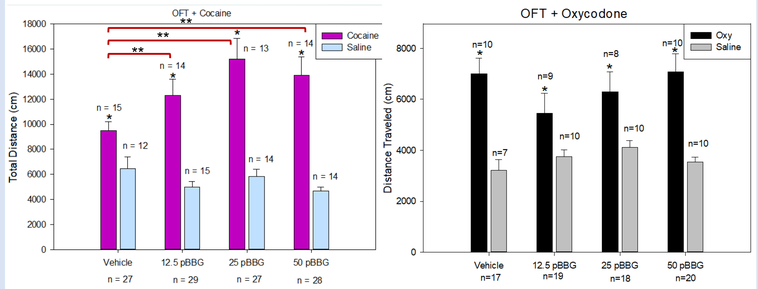


Figure 1 Open Field test in C57BL/6J mice with cocaine(a) and oxycodone(b). The x-axis represents the distance traveled in a 30-minute test and the y-axis are the four different doses of pBBG: 0, 12.5, 25, and 50 mg/kg. Panel (a) shows a trend of increasing cocaine activation with increasing pBBG dose. Panel (b) shows no difference of cocaine activation at any dose. * and ** shows p<0.05

GLO1 Knockdown on B6 Background Show Increased Cocaine Locomotor Activation

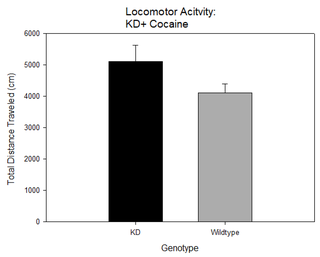


Figure 2 Locomotor activity measured from a conditioned place preference test to cocaine in GLO1 KD mice on a B6 background. The y-axis represents the distance traveled in a 30-minute test. The y-axis shows the genotype, knockdown (black) and wildtype littermates (grey). KD animals show a trendline (p<0.88) increase of cocaine activation compared to WT littermates. N=13-15/genotype

Inhibition with pBBG Does Not Block Reward Seeking Behavior

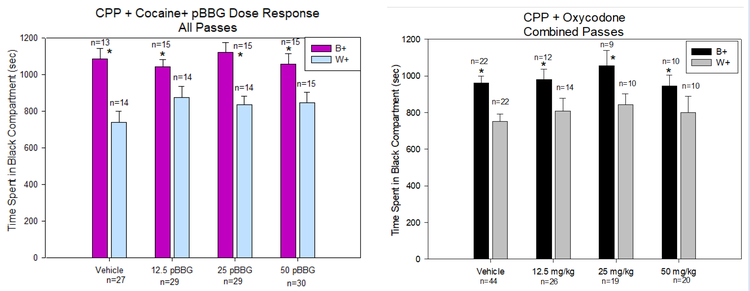


Figure 3 Conditioned place preference in C57BL/6J mice with cocaine (a) and oxycodone(b). The x-axis represents time (s) spent in the drug paired compartment, in this case black. The y-axis are the four different doses of pBBG: 0, 12.5, 25, and 50 mg/kg. Both panels show a conditioned place preference to cocaine (a) and oxycodone (b) which is not affected by pBBG at any dose. * shows p<0.05

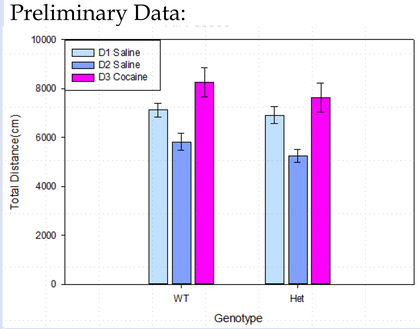
Conclusion

- Increased locomotor activation caused by a substance has been related to substance sensitization
- pBBG on its own does not affect locomotor activity
- Co-administration of the Glo1 inhibitor, pBBG, which leads to accumulation of MG and subsequentially increases $GABA_A$ activation, with cocaine potentiates the locomotor activation typically seen with cocaine use
- Due to the similar effect of pBBG to other traditional $GABA_A$ agonist on locomotor activation, we can more confidently conclude that MG is in fact acting as a $GABA_A$ agonist as well

Future Directions

- Since the animals used for the OFT were not naïve animals, as they were previously used for CPP, future experiments will repeat the experiment with novel animals
- The OFT will be repeated with GLO1 overexpressing animals on a FVB background to test

Preliminary Data:



3-day open field test in GLO1 overexpressors on a FVB background with cocaine. The y-axis shows the distanced traveled in a 30-minute test and the x-axis shows the genotypes. According to this preliminary data wildtype animals behave similarly on all three days of the experiment. N=35-40/genotype

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