Effects of GRIK3 receptor knock-out on the development and expression of cocaine locomotor sensitization in rats: sex differences.

Vanessa B. Adamson[1], Sarah A. Korthauer[1], Natalie E. Zlebnik[2], F. Kent Hamra[3], Marilyn E. Carroll[2]

[1]Undergraduate Program in Neuroscience, Univ. of MN, Minneapolis, MN 55455, (adams944@umn.edu, korth029@umn.edu)

[2] Department of Psychiatry, Univ. of MN, Minneapolis, MN 55455 [3] UT Southwestern Medical Center, Dallas, TX

Background and Rationale

The GRIK3 gene encodes gluek3, which is a kainite-type glutamate receptor that can function as a ligand-activated ion channel in mammals and is speculated to be linked to many psychiatric illnesses such as alcohol dependence, schizophrenia, bipolar disorder.

It is hypothesized that GRIK3 receptors may contribute to susceptibility to cocaine addiction and may influence changes in the induction and expression of locomotor sensitization after repeated cocaine exposure in rats.

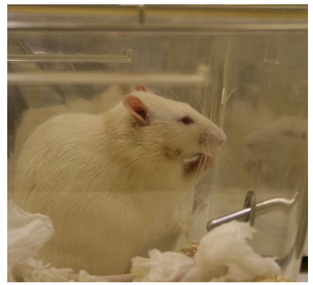
Sensitization to a drug occurs when a greater response is elicited by the same drug dose, and animals show this through increased locomotor activity (DiFranzia and Wellman 2007). Although these rats are not self administering cocaine, neuroadaptions for addiction influence reward systems to be sensitized to drugs and stimuli associated with the drug (Robinson and Berridge 2001). Therefore, by placing rats in a locomotor track and recording beam breaks ever ninety degrees, we can measure response to cocaine and evaluate for sensitization.

Objective

To investigate the effects of GRIK3 receptor knockout on cocaine locomotor sensitization in rats. We hypothesized that homozygous and heterozygous knock-out animals would show potentiated sensitization to cocaine compared to wild-type littermates.

Methods

A



B

Figure 1. Rats of wild-type, homozygous or heterozygous genotypes (B) entered a locomotor (A) track each session for 45 minutes. Movement was measured with infrared laser beams located every 90 degrees about the track.

Table 1. Outline of sensitization procedure.

	Habituation/Novelty seeking control	Sensitization procedure	Drug-free period	Sensitization test
Trt	**S**	**C C C C C C C C**		**S C**
Day	**1**	**2 3 4 5 6 7 8 9**	**10 - 24**	**25 29**
Loco testing	Yes	Yes	No	Yes
Duration (days)	1	8	14	2
Session Length (mm)	90	90	N/A	90

S = Saline (given 45 min into session)
C = Cocaine (15 mg/kg) (given 45 min into session)

Results

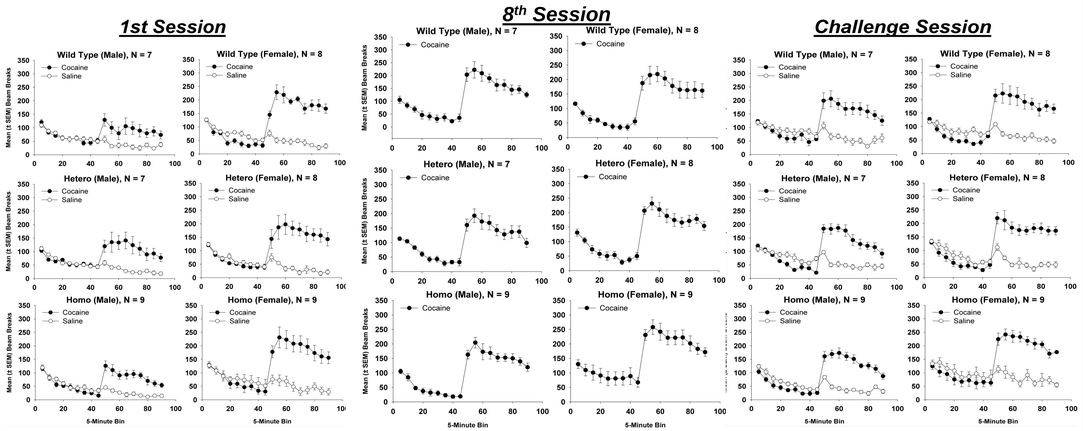


Figure 2. First Session of Sensitization: There is a trend for females to have a greater activity levels than males under cocaine sessions. There was no significant difference in activity during saline sessions for males or females.

Figure 3. Last Sensitization Session: There was no significant phenotypic effect in males. However there was an induction effect from the 1st session to the 8th session. This was not the same in females. Females had a phenotypic effect where the homozygous rats had higher levels of activity compared to wild-type rats. There was no sign of an induction effect in females.

Figure 4. Challenge Session after 15-day Rest: The challenge session was run on two days after a 15-day rest period. The level of locomotor activity for males and females in the challenge session resembles the activity levels in the 8th day of the sensitization session. There was no induction and expression effect in females, but there was an expression effect in males.

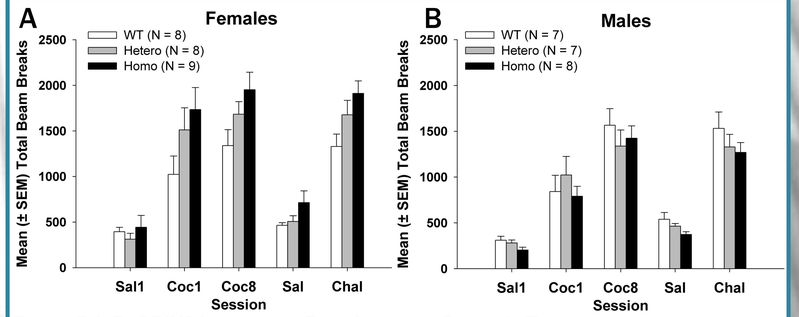


Figure 5 A-B. GRIK3 Locomotor Rats Averaged Data: (A) There is a ceiling effect between coc1, coc8 and challenge as no significant differences were found. However there were subtle differences in phenotypes, homozygous being the most active on the track. (B) Effect of induction and expression; males had greater beam breaks during cocaine session 8 when compared to cocaine session 1 and sensitization was still apparent regardless of phenotype after a 15-day rest period.

Conclusions

- Differences in locomotor activity patterns showing induction and expression of sensitization to cocaine may explain why certain humans are at a higher risk for drug dependence
- No phenotypic effect in male rats
- Average locomotor activity in homozygous females was greater than the average locomotor activity for wild type females.
- Cocaine sensitization for female rats had a ceiling effect across induction and expression.
- Cocaine sensitization was apparent in males of all phenotypes after a 15-day rest period.
- In general, female rats displayed higher locomotor activity than males.
- Gender and phenotypic differences may contribute to different levels of locomotor activity as seen in induction and expression of sensitization to cocaine.

References

DiFranzia JR, Wellman RJ. Sensitization to nicotine: How animal literature might inform future human research. Nicotine and Tobacco. 2007. 9(1): 9-20

Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction. 2001. 96: 103-114

Acknowledgements

We would like to acknowledge the help of Amy Saykao, Seth Johnson, Justin Anker, Anna Nelson, and the rest of the Carroll lab with their help in this project. Supported by Grant R01 DA003240.