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UC Health

Glutamate Receptor Expression After Traumatic Brain Injury In A Rat Model Of Depression

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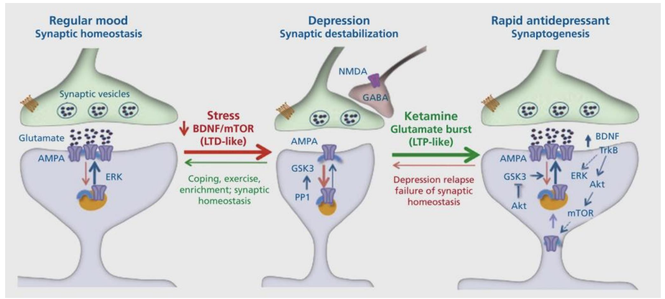
Background

•Over 68 million people per year experience a traumatic brain injury (TBI) worldwide, with significant morbidity resulting from injury-related cognitive deficits.
•TBI patients with a pre-existing mental illness such as depression, anxiety, or other mood disorder display symptoms of altered recovery compared to those without mental illness.
•Wistar-Kyoto rats display significant deficits on cognitive and motivational tasks indicative of a depressed phenotype. Our study utilizes these animals to determine the effect of pre-injury depression on TBI.
•Glutamate signaling is an emerging new target for patients with depression. Our study evaluates how glutamate signaling is altered three weeks after TBI in a pre-injury model of depression

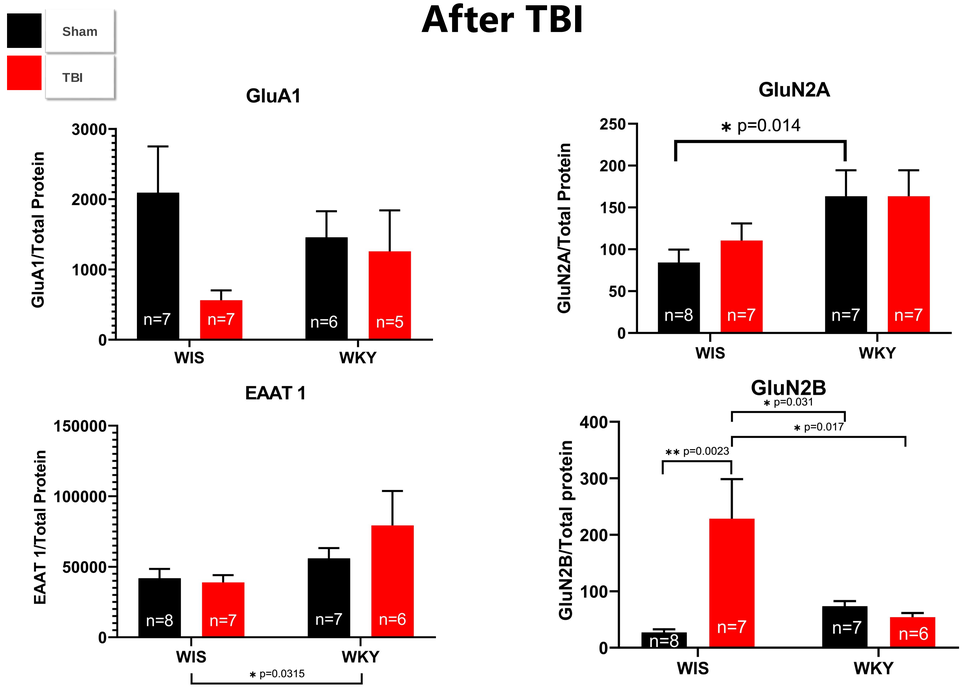


Duman, R 2014

Hypothesis

•We hypothesized that alterations in glutamate receptor subunit expression would be apparent after TBI, with differential changes seen in the depressed Wistar Kyoto (WKY) animals as compared to the control Wistar (WIS) strain.

Differential Glutamate Receptor Expression Changes After TBI



Conclusions

- **WKY rats displayed significant decreases in baseline activity consistent with a depressed phenotype.**
- **No significant differences were seen in AMPA receptor subunits, although WIS animals showed a trend towards decrease GluA1 expression after TBI.**
- **GluN2B expression drastically increased after TBI in WIS but not in WKY.**
- **EAAT 1 receptor concentration was different between strains but did not differ with TBI.**
- **Pre-injury depression, as in the WKY strain, may diminish typical glutamate receptor subunit expression changes seen weeks after TBI**

Acknowledgements

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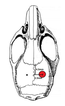
References

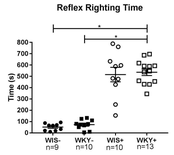
Duman, R. S. (2014). Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues in clinical neuroscience*, *16*(1), 11.

Methods

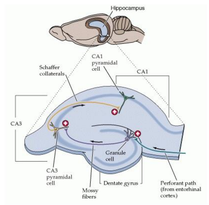
Adult male WIS and WKY rats were randomly assigned to naïve (n), sham (-), or TBI (+) groups.

Moderate TBI was administered through a craniectomy over the right parietal cortex via lateral fluid percussion injury at an average pulse-pressure of 2.11ATM. Sham groups received craniectomy but no injury pulse; naïve groups did not receive craniectomy or injury. Injuries were confirmed by measuring reflex righting time (RRT) immediately after injury or sham, showing that injured animals exhibited significantly longer righting times ($p < 0.001$) and there were no differences between injury severity in WIS versus WKY animals.



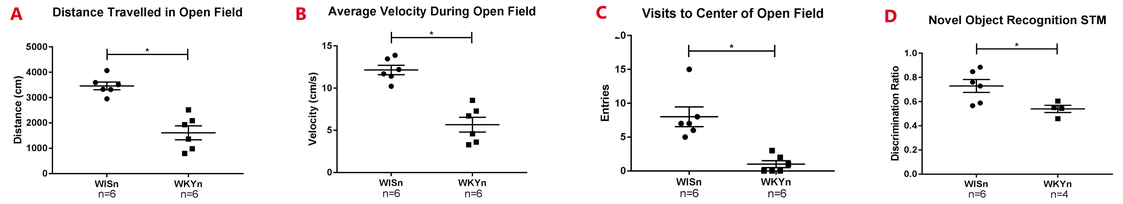


We used ipsilateral homogenized dentate gyrus tissue for immunoblotting to determine protein levels of αamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunits, GluA1 and GluA2, N-methyl-D-aspartate (NMDA) receptor subunits, GluN2A and GluN2B, and the astrocytic glutamate transporters EAAT 1 and EAAT3 21 days after TBI. Western blot data were analyzed using two-way ANOVA, with significance indicated by $p < 0.05$.



Antibody	Catalog #	Company	Conc.	Host
GluR1	75-327	UC Davis	1:500	Mouse
GluR2	75-002	UC Davis	1:500	Mouse
NR2A	75-288	UC Davis	1:250	Mouse
NR2B	75-097	UC Davis	1:250	Mouse
EAAT 1	14501	CST	1:500	Rabbit
EAAT 2	NB100-1869	NOVUS	1:500	Rabbit

Assessment of Baseline Activity



Naïve WIS and WKY rats were tested on Open Field (OF) and Novel Object Recognition tasks to determine baseline activity and cognitive ability. **A-C.** On all measures, WIS rats explored the OF more and exhibited less anxious behavior compared to WKY rats ($p < 0.01$). **D.** WIS rats performed significantly better than WKY rats on a short-term memory (STM) task ($p = 0.0277$).