The Role of TUF 1 in Anxiety and Memory

William von Hohenberg

Introduction

TUF1 is a novel protein that is robustly expressed in limbic and hypothalamic regions of the brain and has been shown to play a role in the formation of fear memories. The high degree of homology found for Tuf1 suggest across different species suggests a conserved function related to modulation of learning and affective states (*1*).

Given these findings, we hypothesized that Tuf1 may also modulate sensorimotor gating and expression of fear and anxiety to a noxious environment. An elevated plus maze and open field test was used to test anxiety and pre-pulse inhibition (PPI) was then used to measure sensorimotor gating *(2)*. These experiments will help evaluate the validity of the TUF 1 mouse model as an accurate representation of human anxiety and memory.

Methods

Elevated plus maze:

The elevated plus-maze comprised two open arms and two closed arms attached to a central hub. The apparatus was supported 82 cm above the ground. Mice were placed into the central hub facing one of the open arms and allowed to move freely for 5 minutes. Time spent in closed vs. open arms was recorded using Topscan *(3)*.

Open Field Test:

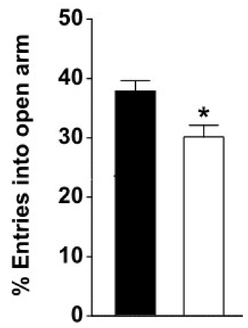
Animals were placed in arenas 60 cm across. Each session was recorded and analyzed offline using TopScan software. The horizontal and vertical activity of the test subjects was measured and recorded. Time in the center of the boxes were also measured and compared with time spent in the periphery as a preliminary measure of anxiety. Data was analyzed with independent sample t-tests.

Prepulse Inhibition:

Each prepulse inhibition trial consisted of a prepulse and pulse stimulus. First, a white 22 kHz noise (i.e. the prepulse) was presented for 120ms. Then 100ms following the prepulse, animals were exposed to a second noise stimulus at 120dB (i.e. the pulse) *(3)*. Inhibition of the startle response was calculated as the percent change from pulse alone trials (i.e. {[pulse alone trial – prepulse and pulse trial] / pulse alone} *100). The final raw data were analyzed using a mixed factorial ANOVA.

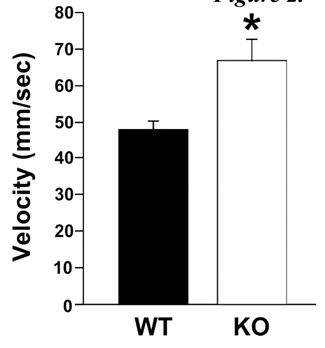
Results

Figure 1.



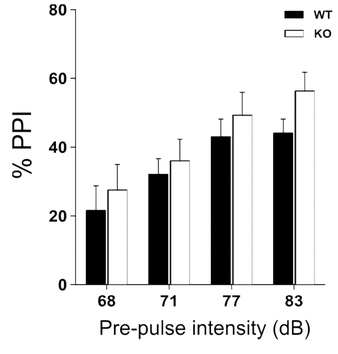
- The tuf-1 KO mice exhibited decreased novelty and exploratory behavior in the elevated plus maze test.
- The number of entries by *tuf1*-KO mice into the open arms was significantly less than their WT counterparts.

Figure 2.



- Locomotor activity expressed as velocity indicates that *tuf1*-KO mice move significantly faster than WT mice.
- However, this increased locomotor activity is independent from the presence of generalized anxiety demonstrated in Fig. 1.

Figure 3.



- The *tuf1*-KO mice display similar pre-pulse inhibition to an auditory stimulus as WT.
- Increasing inhibition of the startle response to the higher pre-stimulus intensity in both *tuf1*-KO and WT indicates that auditory processing and sensorimotor gating mechanisms are not effected by deletion of the the TUF1 gene. However, the slightly higher inhibition in KO mice may indicate that the TUF1 gene influences sensorimotor gating in an epistatic manner.

Conclusion

Deletion of the TUF 1 gene lead to a change in behavioral phenotype indicating that the gene plays some function in the regulation of anxiety and exploratory behavior. In the elevated plus maze the decreased number of entries of the KO mice to the open arms suggests the presence of generalized, non-cue specific anxiety. Although KO mice displayed normal levels of sensorimotor gating there was a trend of increased inhibition as a result of the TUF 1 gene knockout. Prepulse inhibition test is often used in human to assess sensorimotor gating and serves as an indicator of neuropathology in a variety of diseases. The TUF 1 KO mouse model appears to be an accurate representation of affective dysfunction. However, more research needs to be conducted in order to better understand the molecular and psychological effects of the TUF 1 in brain physiology.

References

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