Kynurenine Aminotransferase II Knockout Mice Mimic Depression with Psychomotor Retardation

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INTRODUCTION

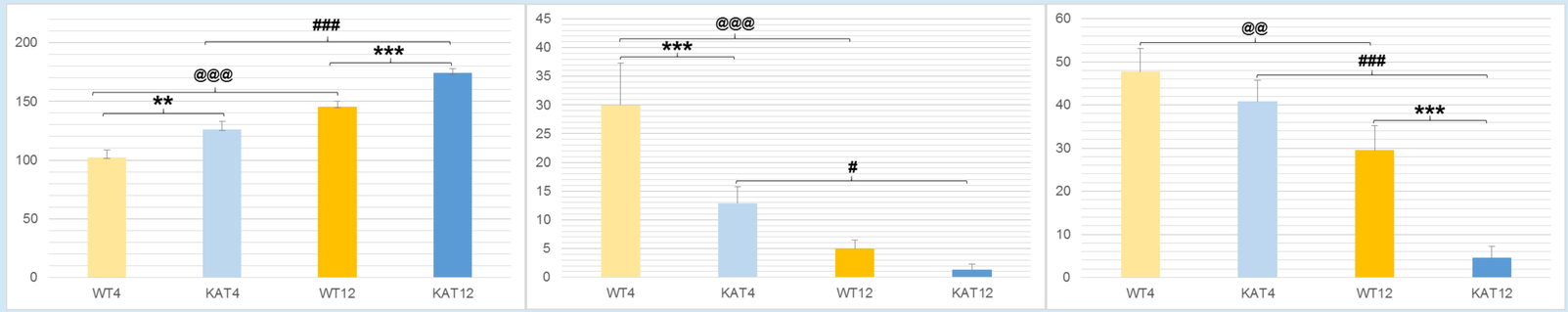
- Major depressive disorder (MDD) is characterized by multifarious symptoms and alteration of the tryptophan (Trp)-kynurenine (KYN) metabolic system was observed in patients with MDD
- Kynurenine/α-aminoadipate aminotransferase (KAT II) is a mitochondrial enzyme of the Trp-KYN system, encoded by the *aadat* (aka *kat2*) gene, which converts KYN to kynurenic acid
- The consequence of the KAT II gene knockout upon behaviors remains inconclusive
- We assayed the negative emotional and motor domains of *kat2*$^{-/-}$ mice male mice at age of 4 weeks and 12 weeks, by animal models of depression, anxiety, and motor impairment

METHODS

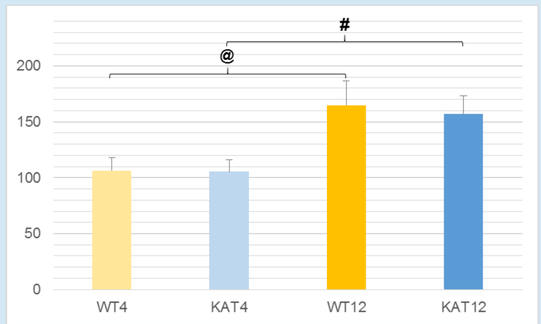
- Behavioral sampling was carried out with modified forced swim test (FST), light-dark box (LDB) test, and open field (OF) test at 4 and 12 weeks of age in C57BL/6N (wild-type, WT) and *kat2*$^{-/-}$ male mice (n = 10-14)
- The Committee of Animal Research at the University of Szeged (I-74-1/2022); the Scientific Ethics Committee for Animal Research of the Protection of Animals Advisory Board (XI./95/2020)

RESULTS

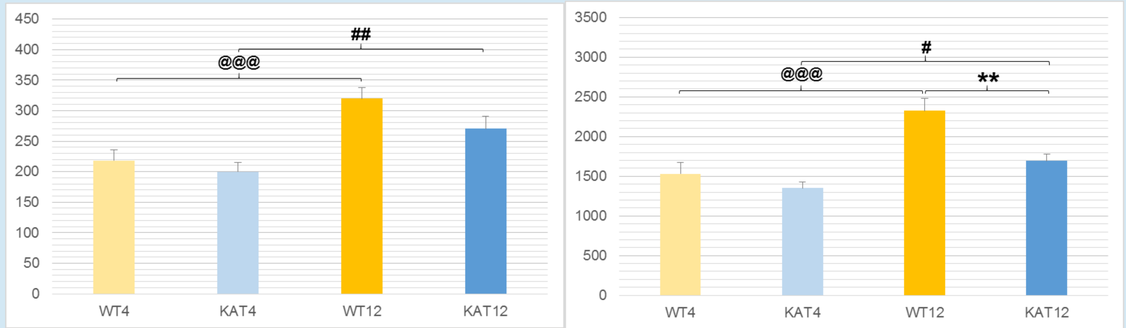
Modified FST showed significantly higher depression-like behaviors at 4 and 12 weeks in *kat2*$^{-/-}$ mice than the wild-type and in an age-dependent manner. In the LDB test both strains spent significantly more time in the light at week 12 than week 4. In the OF test both strains entered significantly more time into the center zone at week 12 than week 4 and *kat2*$^{-/-}$ mice showed significantly shorter ambulation time than the wild-type at week 12. WT4: 4-weeks old wild-type; KAT4: 4-weeks old *kat2*$^{-/-}$; WT12: 12-weeks old wild-type; KAT12: 12-weeks old *kat2*$^{-/-}$; *: significant differences between wild-type and *kat2*$^{-/-}$ strains in the same age-group; @: significant differences between wild-type age-groups; #: significant differences between *kat2*$^{-/-}$ age-groups; mean+SEM; * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001



Time spent with immobility (s; left), climbing (s; middle) and swimming (s; right) in modified forced swim test



Time spent in the lighted compartment in light-dark box test (s)



Number of entries into the lighted center zone (left) and ambulation distance (cm; right) in open field test

CONCLUSION

- We show here that *kat2*$^{-/-}$ mice exhibit increasing depression-like behavior, accompanied with decreasing anxiety and motor activity in an age-dependent manner
- The *aadat* gene knockout influences behavioral domains in such a manner that the transgenic strain potentially serves as an animal model of MDD subtype, depression with psychomotor retardation

CORRESPONDENCE, ACKNOWLEDGEMENT AND REFERENCES

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