Changes in basal and fluoxetine-induced adult neurogenesis and depression-related behaviors in transgenic S100B over-expressing mice

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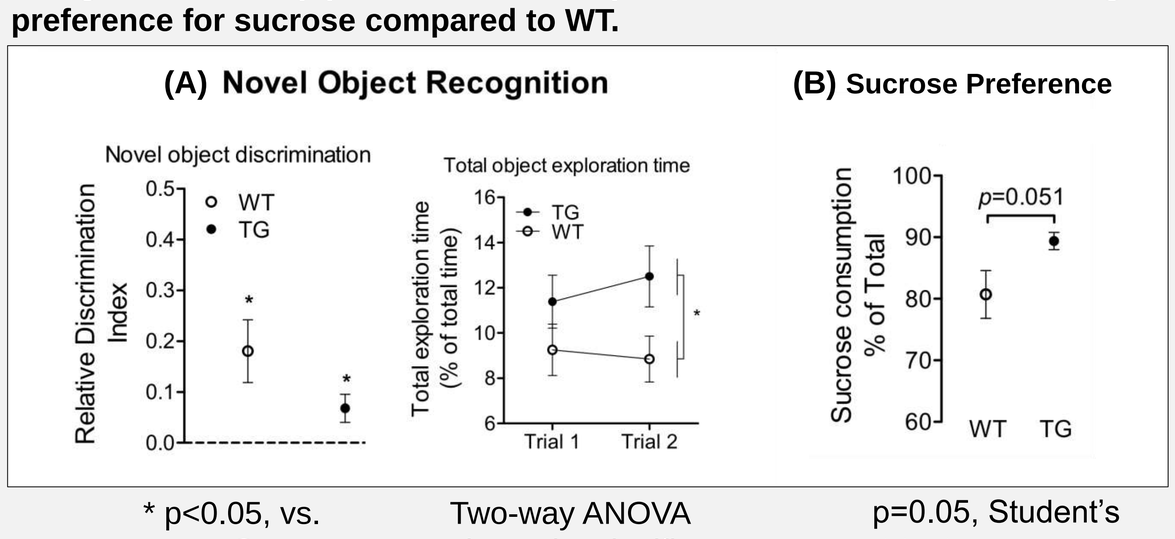
Main findings:

- Compared to wild type (WT), S100B overexpressing (TG) mice showed higher baseline levels of cell proliferation.
- There were no significant differences between genotypes in baseline levels of ongoing neurogenesis, cell survival, and in the neurogenic response to chronic fluoxetine treatment.
- These results correlate with behavioral performance in the novelty-induced hypophagia test (a task sensitive to neurogenesis), in which there were no differences between genotypes in either vehicle or chronic fluoxetine treated mice.
- TG mice had higher sensitivity to the acute effects of fluoxetine in the tail suspension test.

Background

- The S100 calcium binding protein B (S100B) has neurotrophic effects and its secretion appears to be mediated by 5-HT1A receptors and by treatment with drugs that increase serotonin transmission [1, 3].
- In hippocampal neurons, serotonin-mediated S100B release has neurotrophic effects, and intraventricular S100B infusion in adult rats leads to higher cell proliferation in the dentate gyrus, after ischemia [2].

Figure 1: (A) Performance of untreated WT and TG mice in the novel object recognition task. (B) In the sucrose preference test, TG show a higher preference for sucrose compared to WT.



* p<0.05, vs. zero, One sample t-test

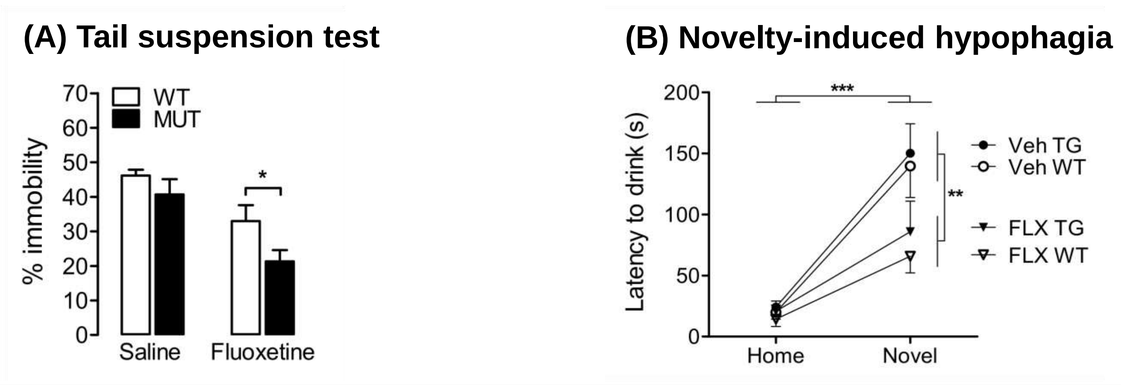
Two-way ANOVA showed a significant effect of genotype

p=0.05, Student's t-test

Aims

- To test whether S100B is involved in the neurogenic response to fluoxetine, we measured adult neurogenesis and depression related behavior in transgenic S100B over-expressing mice **(TG,)** treated chronically with fluoxetine

Figure 2: (A) TG show higher behavioral response to <u>acute</u> fluoxetine, in the tail-suspension test. (B) Behavioral response to <u>chronic</u> fluoxetine treatment in the novelty-induced hypophagia test.



Two-way ANOVA showed a significant effect of treatment and genotype

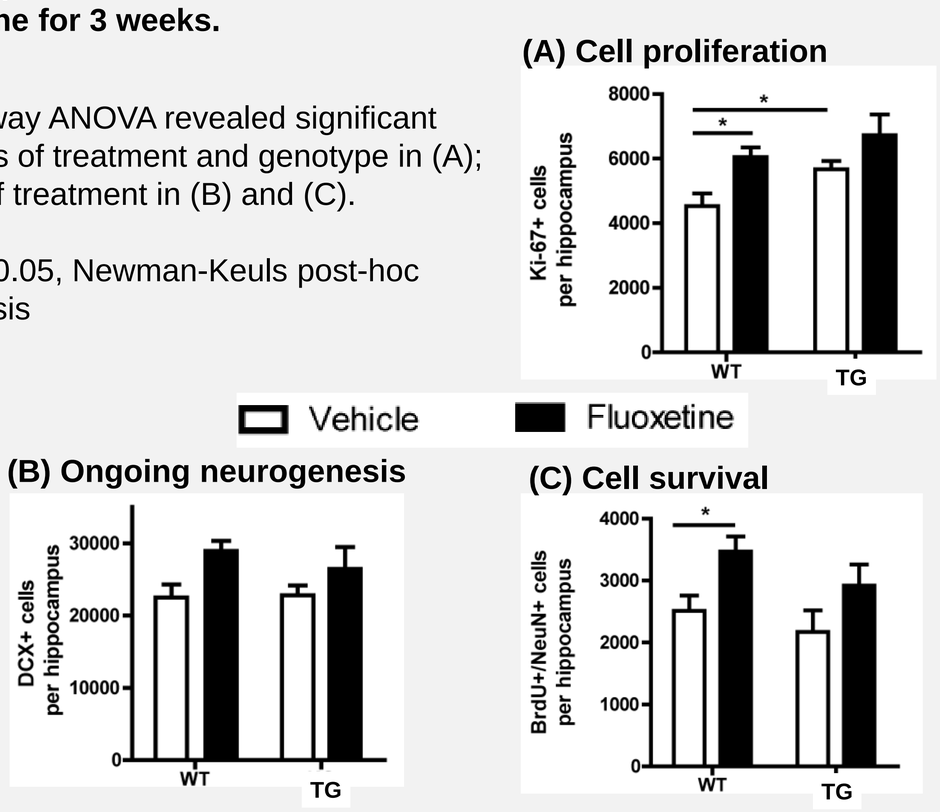
* - p<0.05, Newman-Keuls post-hoc analysis

Repeated measures ANOVA showed a significant effect of cage environment (***p<0.001).
In the novel cage environment, there was a significant overall effect of drug treatment (**p<0.01)

Figure 4: Bar graph of the number (A) Ki-67, (B) Doublecortin (DCX), and (C) BrdU - positive cells in WT and S100B TG mice treated with vehicle or fluoxetine for 3 weeks.

Two-way ANOVA revealed significant effects of treatment and genotype in (A); and of treatment in (B) and (C).

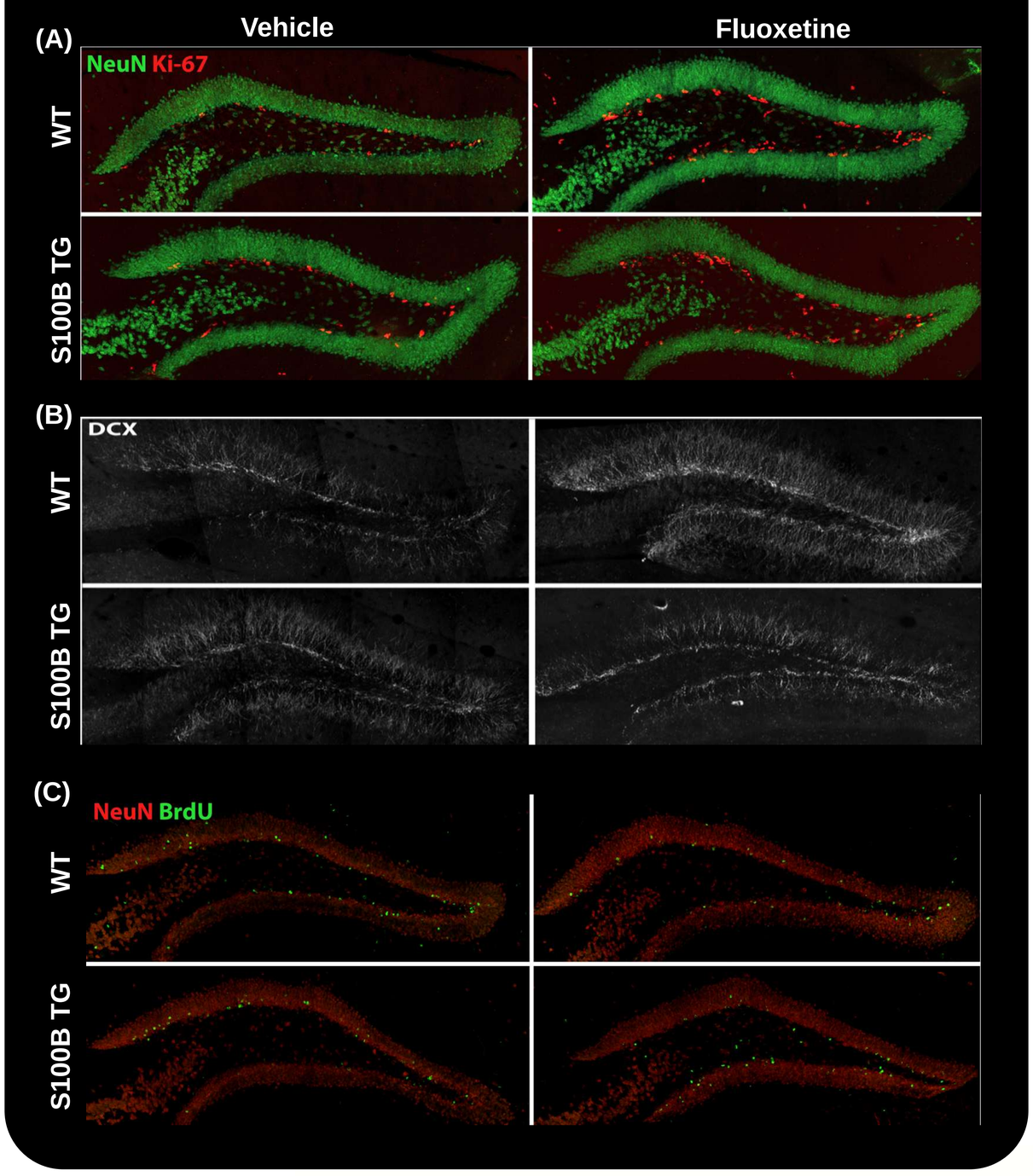
* - p<0.05, Newman-Keuls post-hoc analysis



✓ **An increase in cell proliferation, but not cell survival, in TG mice indicates that higher S100B levels may increase cell proliferation.**

✓ **The higher cell proliferation in TG mice did not occlude the effects of fluoxetine, suggesting that fluoxetine activates additional pathways.**

Figure 3: Markers for (A) cell proliferation, (B) ongoing neurogenesis and (C) cell survival – in immuno-labeled dentate gyrus from WT and TG mice chronically treated with vehicle or fluoxetine



Methods

- 8 to 9 animals were randomly assigned to each group
- Fluoxetine treatment: 10mg/kg, 21 days, i.p.
- bromodeoxyuridine (BrdU) was given, i.p., twice daily (75 mg/kg) for 3 consecutive days before the above-mentioned treatment with fluoxetine began.
- On the final day of injections, brains were fixed via transcardial perfusion, for immunohistochemical analysis

References:

[1] Kindlund-Högberg A.M., Zhang X., Svenningsson P (2009) Int J Neuropsychopharmacol 12(2), 201-15

[2] Kleindienst A, et al. (2005) J Neurotrauma 22(6), 646-55

[3] Baudry, A , et al. (2010) Science 329 (5998), 1537-41

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Disclosure: The authors declare no potential conlfict of interest