A Transgenic Rat Model for Reducing Adult Neurogenesis

30.05

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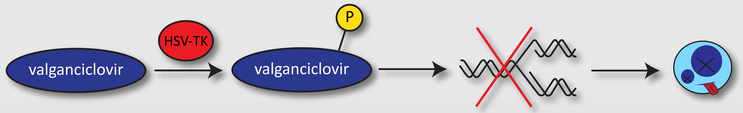
1. Summary

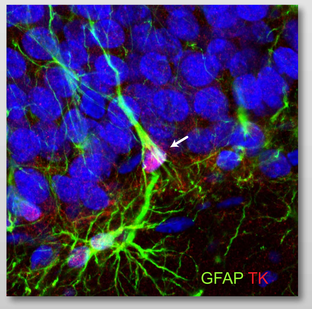
The function of adult neurogenesis remains unclear. While many tools for manipulating neurogenesis have been developed for mice, there are fewer for rats. Radiological and chemical strategies have been used to inhibit adult neurogenesis in rats but these methods may also have undesired side effects. Since rats have a larger brain and can perform complex behaviors, it would be useful to have additional rat models for studying neurogenesis. To address this gap we therefore developed a transgenic GFAP-TK rat in which adult neurogenesis can be specifically inhibited. Preliminary results suggest that, as in mice, reduced adult neurogenesis leads to anhedonia.

2. GFAP-TK rats

Transgenic rats were created in which Herpes Simplex Virus Thymidine Kinase (HSV-TK) was expressed under control of the GFAP promoter.

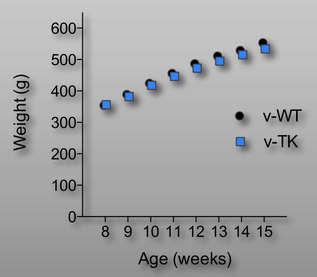


The antiviral drug valganciclovir is phosphorylated by HSV-TK and interferes with DNA replication during cell division. This kills the GFAP+ radial cells that give rise to new neurons but spares post-mitotic astrocytes.

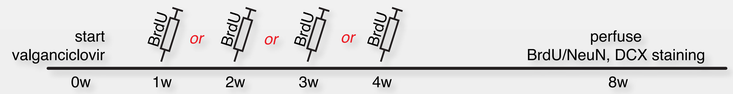


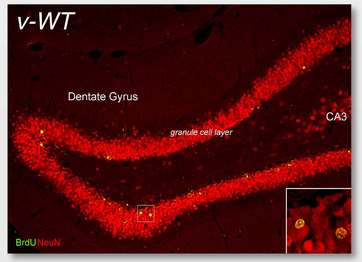
Confocal image of a radial cell in the dentate gyrus of a GFAP-TK rat, immunostained for GFAP and TK (arrow).

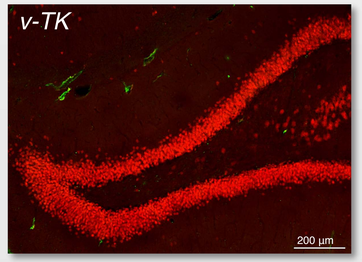
GFAP-TK rats, treated with valganciclovir to inhibit neurogenesis (v-TK rats), gain weight normally (left). v-TK and v-WT rats are cute (above).

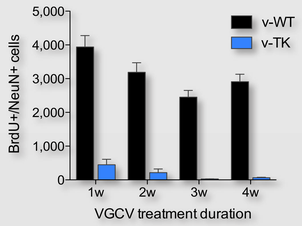


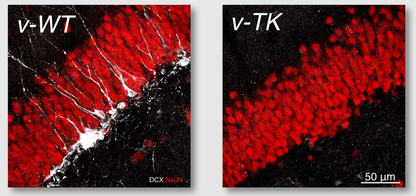
3. Inhibiting dentate gyrus neurogenesis



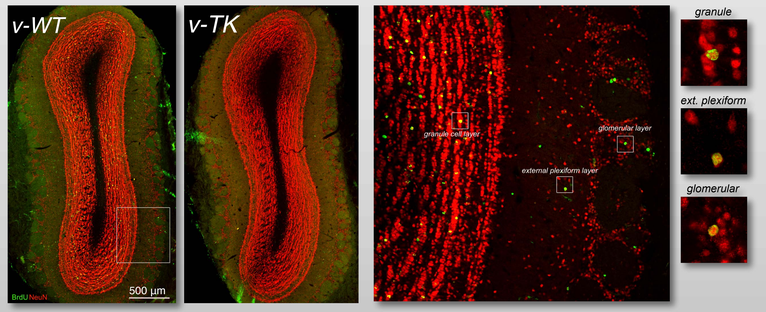




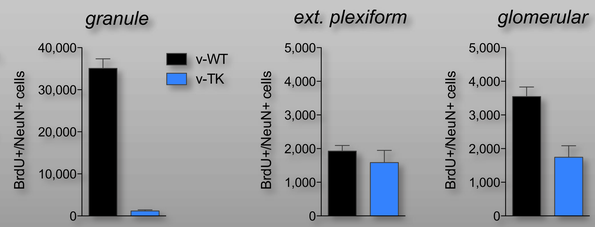




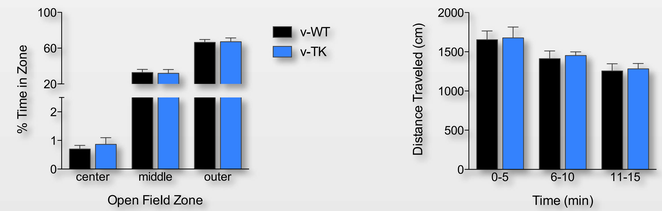
4. Inhibiting olfactory bulb neurogenesis



TK rats treated with valganciclovir for 4w had very few mature, adult-born neurons.

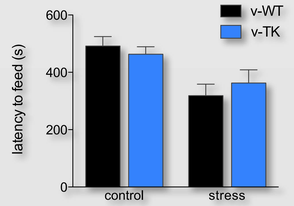


5. Normal open field behavior



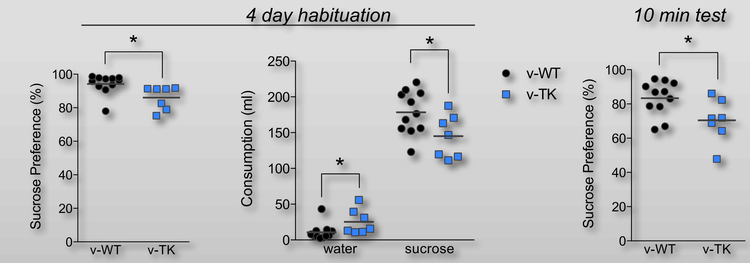
WT and TK rats, treated with valganciclovir for 6w, displayed similar anxiety and locomotor behaviors in the open field. Left: time spent in the center of the open field, the middle, and the outer region near the wall (t-test, genotype effects all P>0.6). Right: Distance traveled during the 15 min exposure (2-way RM ANOVA effect of time P<0.001).

6. Normal novelty-suppressed feeding



There was no significant difference in anxiety behaviors between WT and TK rats in the novelty-suppressed feeding test. Rats were treated with valganciclovir for 6-8w before testing. Restraint stress signifcantly reduced the latency to begin feeding in the novel environment (2-way ANOVA, P<0.001).

7. Anhedonia in the sucrose preference test



After treatment with valganciclovir for 6w, TK rats displayed an anhedonic phenotype in the sucrose preference test. Left: Sucrose preference during a 4 day habituation period where water and sucrose were both freely available (t-test P<0.05). Center: v-TK rats consumed more water and less sucrose that v-WT rats during habituation (2-way RM ANOVA, interaction P<0.01, post hocs P<0.05). Right: v-TK rats also showed reduced sucrose preference following deprivation, during a 10 min test P<0.05).

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