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Diabetic neuropathic pain improvement by inhibition of constitutive 5HT₆ receptor activity in rats - TH17

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Background

Chronic neuropathic pain affects 20% of patients with type 1 and 2 diabetes mellitus. In these patients, neuropathic pain is often associated with **cognitive deficits** and decreased quality of life. The **serotonin type 6 (5-HT₆)** receptor has recently emerged as a modulator of chronic pain and cognitive functions. The 5-HT₆ receptor interacts with intracellular proteins including **mTOR** (mechanistic Target Of Rapamycin), also involved in neuropathic pain and in the regulation of cognitive functions. The present study addresses the involvement of 5-HT₆ receptor constitutive activity and mTOR signaling in neuropathic pain in the experimental model of streptozocin (STZ)-induced diabetic (D) rats.

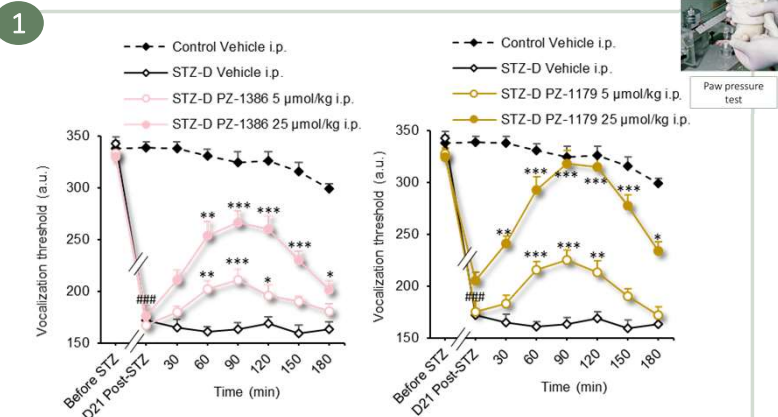
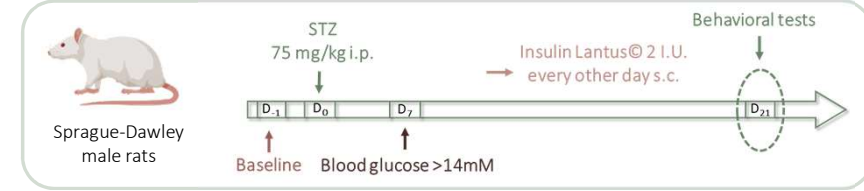


Figure 1. Intraperitoneal administration of 5-HT₆ receptor inverse agonists PZ-1386 and PZ-1179 improves mechanical hyperalgesia to paw pressure in STZ-D rats (n = 11-15/group). ###P<0.001 vs. values measured before STZ; a.u., arbitrary units; *P<0.05, **P<0.01, ***P<0.001 vs. values measured before the drug/vehicle (water) injection (D21 Post-STZ), 2-way ANOVA.

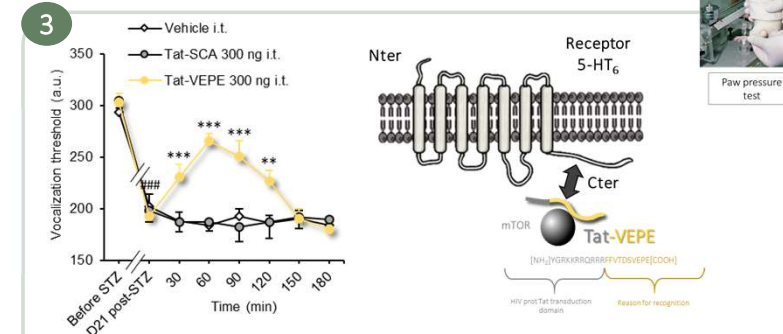
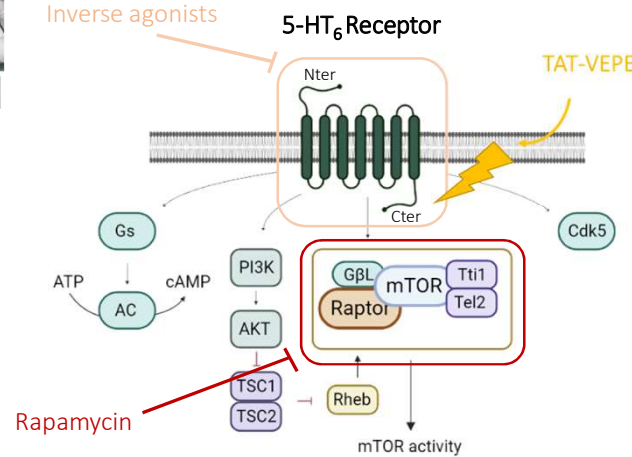


Figure 3. Intrathecal administration of Tat-VEPE attenuates mechanical hyperalgesia (paw pressure test) in STZ-D rats (n = 6-7 /group). ###P<0.001 vs. values measured before STZ. a.u., arbitrary units; **P<0.01, ***P<0.001 vs. values measured before the drug/vehicle injection (D21 Post-STZ), 2-way ANOVA.

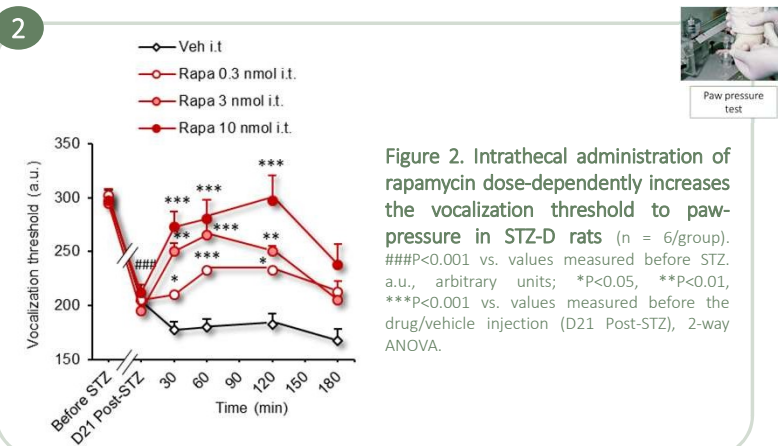


Figure 2. Intrathecal administration of rapamycin dose-dependently increases the vocalization threshold to paw-pressure in STZ-D rats (n = 6/group). ###P<0.001 vs. values measured before STZ. a.u., arbitrary units; *P<0.05, **P<0.01, ***P<0.001 vs. values measured before the drug/vehicle injection (D21 Post-STZ), 2-way ANOVA.

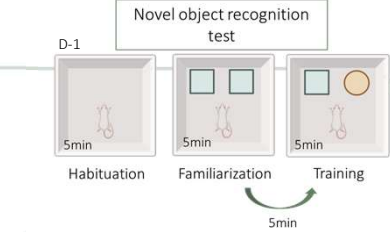
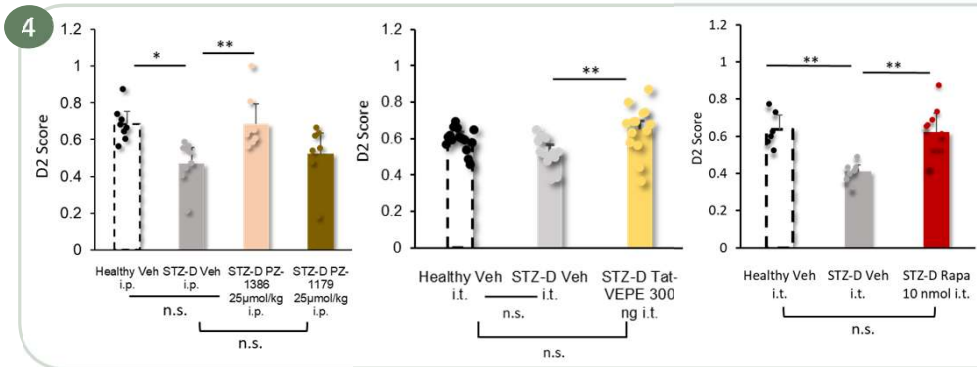


Figure 4. Injection of PZ-1386, Tat-VEPE or rapamycin but not PZ-1179 improves cognitive deficits (novel object recognition test) in STZ-diabetic (STZ-D) rats (n = 7-16/group). D2 score = exploration time of novel object/exploration time of both objects; *P<0.05, **P<0.01, vs. STZ-D Vehicle group, 1-way ANOVA.

Conclusion

These results suggest that the constitutive activity of the 5-HT₆ receptor has a harmful influence in **diabetic neuropathic pain**. Thus, **targeting 5-HT₆ receptor/mTOR complex activity** or 5-HT₆ receptors with inverse agonists represents new strategies to treat **painful diabetic neuropathy** and associated **cognitive co-morbidities**.