Effect of Liver Zhx2 Overexpression on Oxycodone Addiction Model Behaviors

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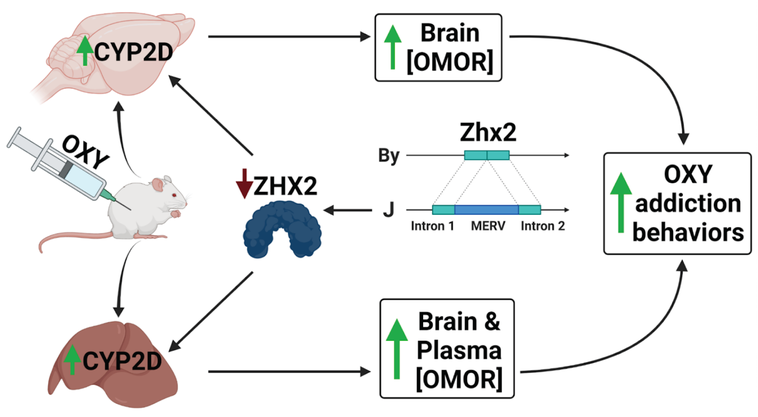
Introduction

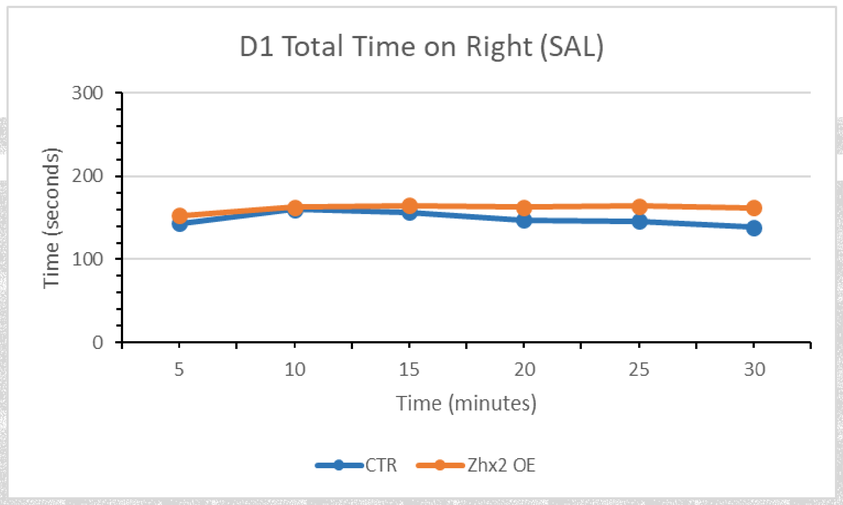
Genetic influence plays a pivotal on opioid addiction model behaviors, as noted by numerous research and medical journals. Therefore, the next logical step to take would be to identify specific genetic factors that influence opioid use, in an effort to produce new treatments for opioid misuse.

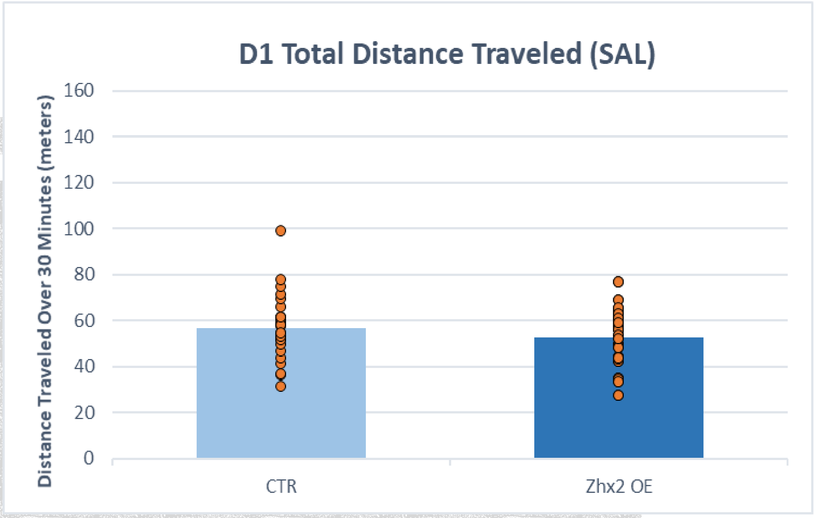
The Bryant Lab had previously observed differences in oxycodone state-dependent learning and locomotion between females of two closely related mouse substrains: BALB/cJ and BALB/cByJ, along with robust differences in brain concentration of the oxycodone metabolite oxymorphone. Genetic mapping implicated the Zhx2 gene, located in the 15th chromosome, which is less expressed in cJ mice than cByJ, and potentially affects differences in oxycodone to oxymorphone metabolism, thus impacting addiction model behaviors.

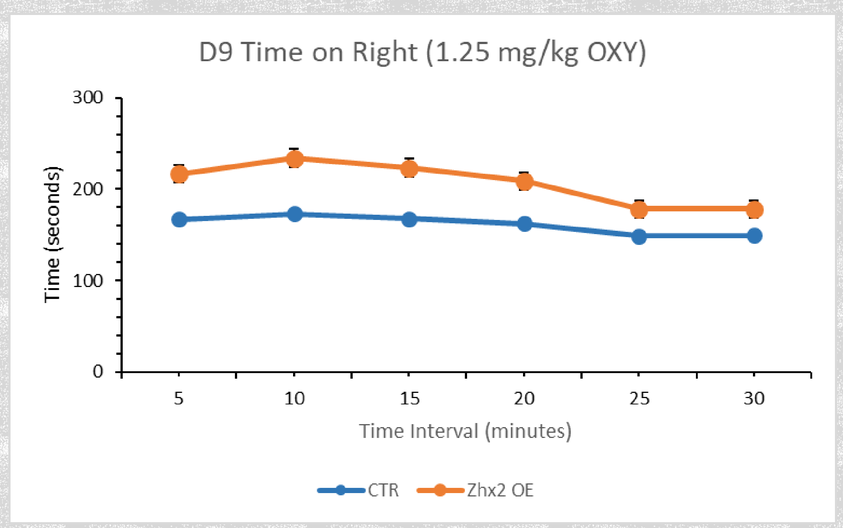
Our primary objective was to assess whether Zhx2 overexpression in the liver could impact oxycodone addiction model behaviors based on the liver's primary role in drug metabolism.

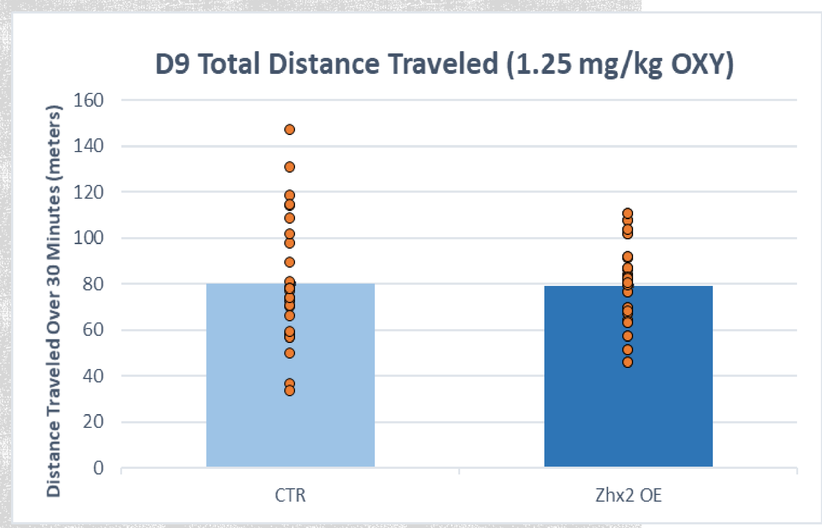


Results









On day 9, mice from both cohorts 1 and 2 with the liver Zhx2 overexpression spent more time on the oxycodone paired (right) side of the chamber on average than those without this feature, with highly variable results within each group. Mice with Zhx2 overexpression also traveled slightly less on average on day 9, although this was not a statistically significant difference.

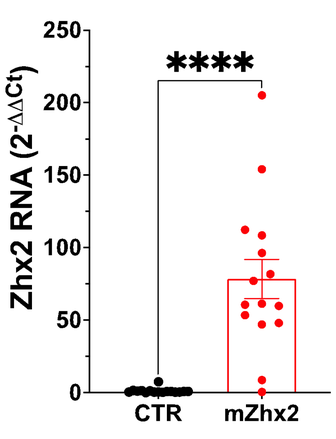
Conclusions

The collective data from both cohorts suggests that Zhx2 gene expression in the liver has some degree of influence on oxycodone state-dependent learning, given the differences in time spent on the oxycodone paired side of the chamber, and locomotion based on the distance traveled around the chamber, though to a lesser extent.

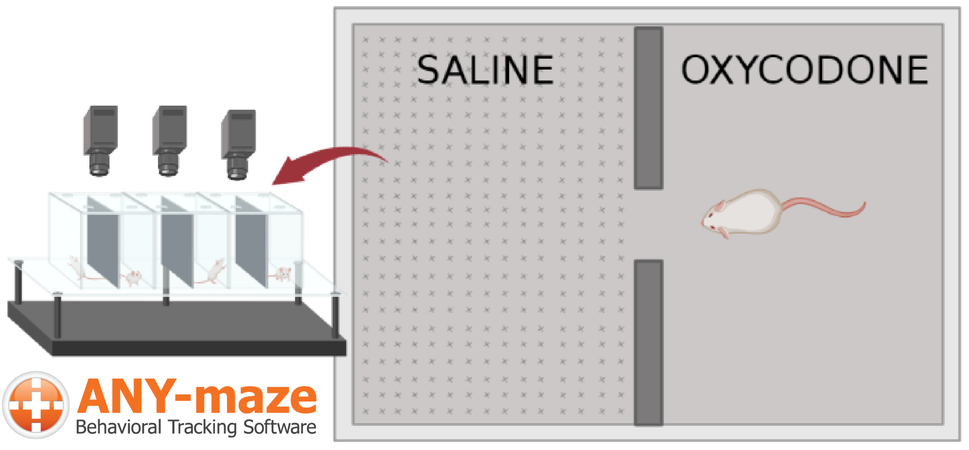
The cohorts had an age difference of 10 days, although both had reached similar maturity levels and were of the same sex. Follow-up experiments in the lab will assess whether brain Zhx2 overexpression has a stronger influence on oxycodone addiction model behaviors compared to that of liver Zhx2.

Methods

In two separate cohorts, the first being 79 and the second 89 days old respectively, only female BALB/cJ mice were tested through our conditioned place preference (CPP) paradigm, with one group of mice within each cohort being treated with adeno-associated virus to overexpress Zhx2 specifically in the liver (Zhx2 OE) while the other one receives a similar version of the virus has no effect on gene expression (CTR). In the CPP paradigm, mice had access to both chamber sides on day 1, whereas on days 2-5, mice were confined to one of two sides of the chamber and were injected with 1.25mg/kg oxycodone (right side) or saline (left side) every other day to let them associate treatment with the experimental context, with the amount of solution depending on their weight as recorded each day. On day 8 the mice have full access to both sides of the chamber while under the saline control treatment. The same procedure occurs on day 9, the final test day, with the exception being that the mice receive the 1.25 mg/kg oxycodone treatment instead.



After being injected with the respective treatment, the mice were recorded using video cameras on top of each individual testing chamber. The video feed was then analyzed using the Anymaze Behavior Tracking Software, which measured the amount of time the mice spent on each side of the chamber, as well as the distance each mice traveled around the chamber (locomotion).*



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References

*Created with BioRender.com