Characterization of a Yohimbine-Induced Rat Anxiety Model

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Background

Anxiety disorders constitute the most prevalent form of mental disorders, with an estimated lifetime prevalence of 14%. They manifest with a variety of peripheral and central symptoms. Despite the subjective and complicated nature of the symptoms experienced by patients suffering from anxiety disorders, rats have proven to be an invaluable tool to mirror several symptoms and have been employed in drug development. In this study we are inducing an anxiety-like state in rats by application of the anxiogenic drug Yohimbine.

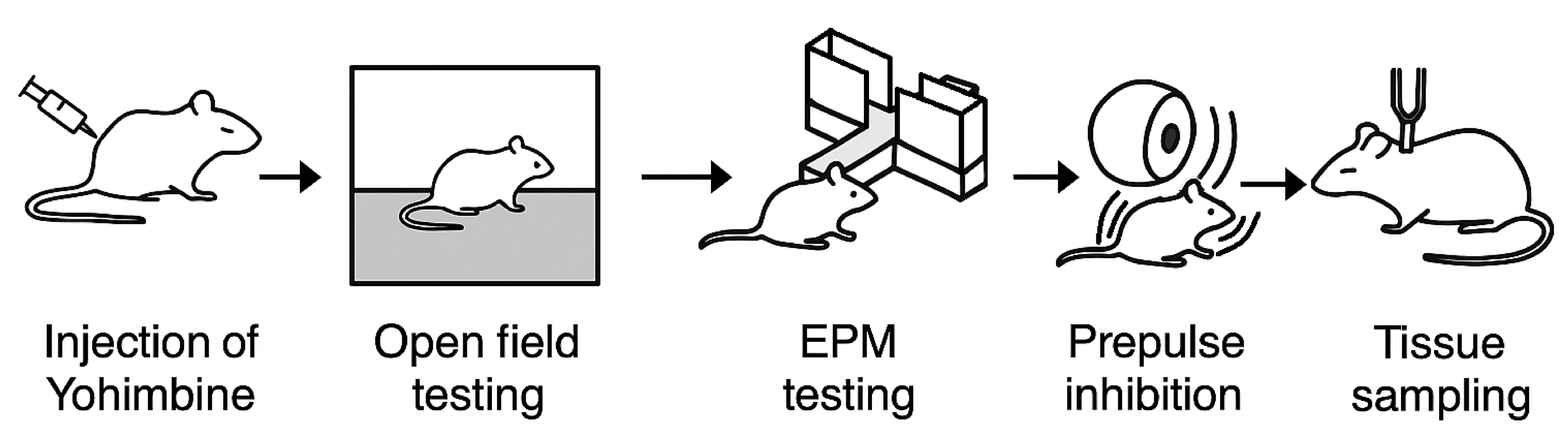
Methods

After application of the anxiogenic compound Yohimbine, male Lister-hooded rats (8 weeks) were tested in a behavior battery containing open field (OF), elevated plus maze (EPM), and prepulse inhibition (PPI) test before being sacrificed directly afterwards. Blood, urine, cerebrospinal fluid (CSF), and brain were collected. Biochemical analysis was done for corticosterone and serotonin, with other anxiety-related markers such as adrenocorticotropic hormone (ACTH) in progress.

Results

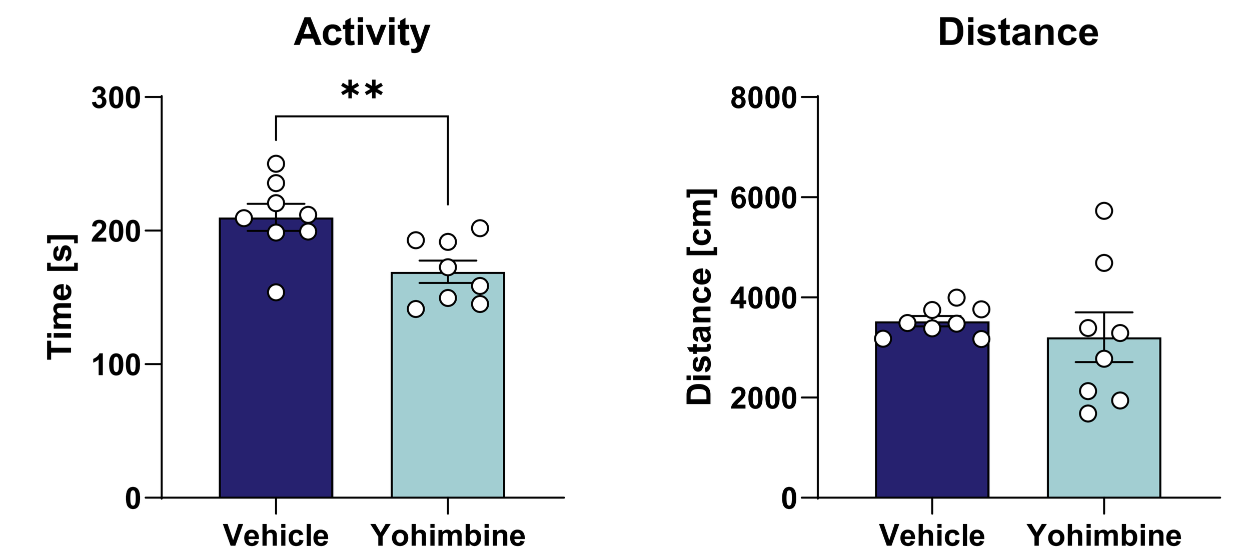
Behavior

Initial data shows strong anxiogenic effect of the inducing agent Yohimbine in the anxiety focused behavior battery. In OF, animals show reduced explorative behavior by decreased overall activity. During EPM testing, Yohimbine injected animals spend significantly more time in the closed arm over the open arm and show less open arm entries overall. PPI testing highlighted the significantly increased startling and a trend to reduced inhibition by the prepulse. Relatively small inhibition in control groups can be explained by the intended high stress testing paradigm.



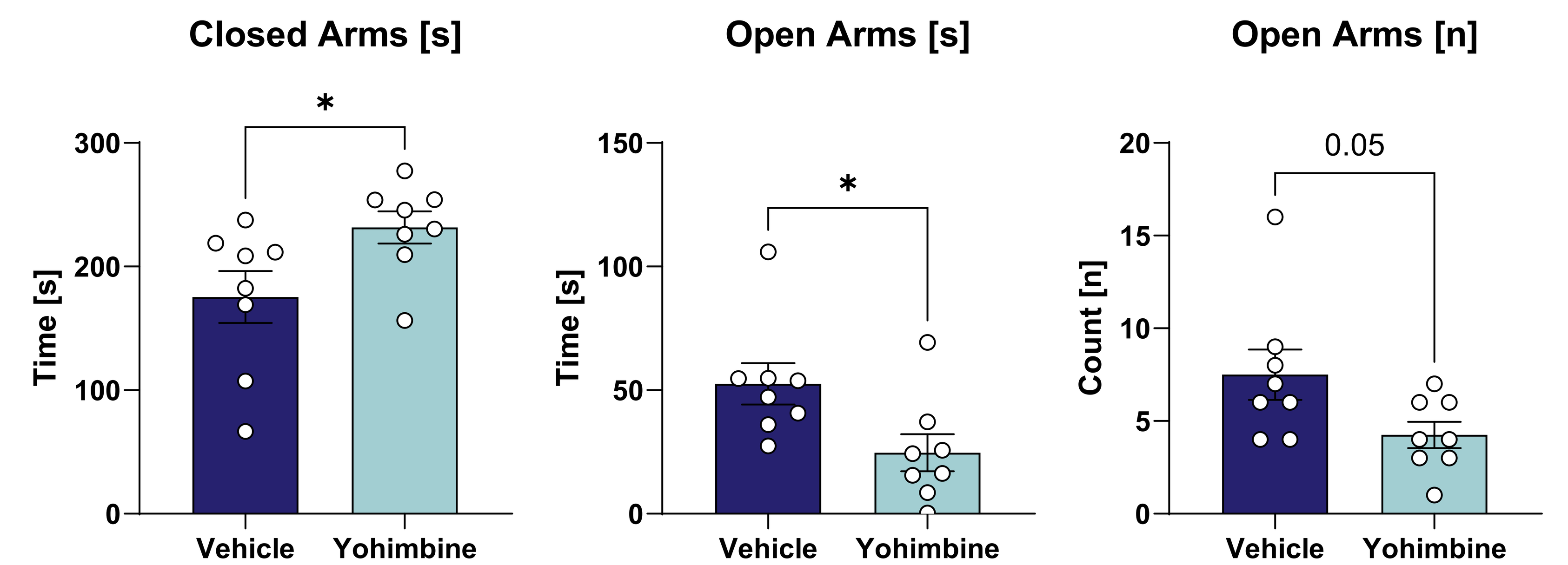
▲**Figure 1: Overview of experimental design.** Animals were treated with Yohimbine and entered a behavior battery consisting of OF, EPM, and PPI testing before being sacrificed for collection of blood, urine, CSF, and brain.

Open Field



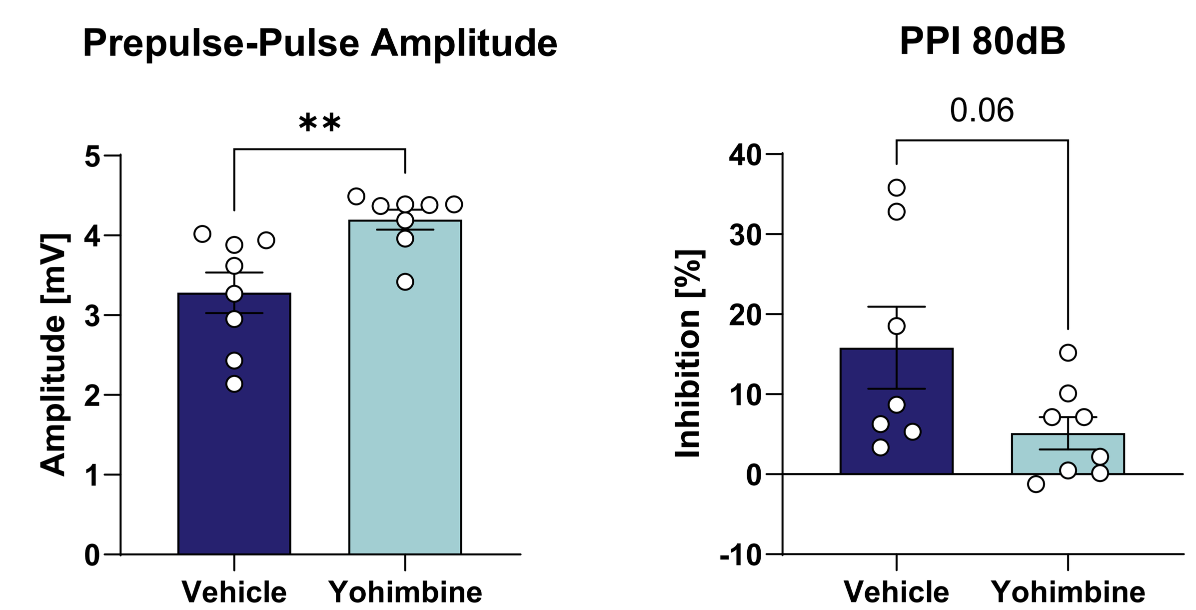
▲**Figure 2: Yohimbine application reduces explorative behavior of rats in OF.** Animals were injected with Yohimbine or vehicle and placed into an open box arena shortly after to record explorative behavior. Mean ± SEM; n = 8 per group. Unpaired t-test. **p <0.01.

Elevated Plus Maze



▲**Figure 3: Induced rats show significant avoidance of the open arm in EPM.** Treated animals were transferred from OF testing directly onto EPM. Animals were released on the open arm, facing the center zone. Mean ± SEM; n = 8 per group. Unpaired t-test. *p <0.05.

Prepulse Inhibition

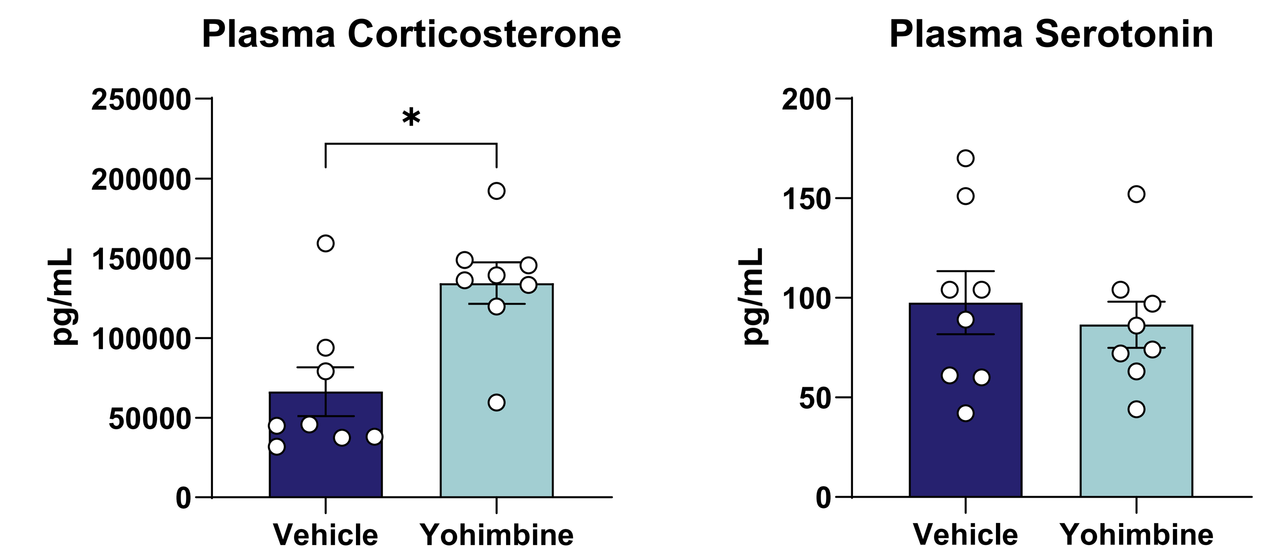


▲**Figure 4: PPI reveals increased startling in Yohimbine treated rats.** Treated animals were transferred from EPM testing directly into PPI boxes. Response to startling stimulus with or without prepulse was recorded as startling amplitude. Decrease in amplitude with or without prepulse is used to calculate inhibition. Mean ± SEM; n = 8 per group. Unpaired t-test. **p <0.01.

Biochemistry

Multiple fluids and tissues were sampled directly after the last behavior testing, including CSF, urine, blood and brain parts. Platelet-rich plasma showed a significant increase in release of the stress hormone corticosterone in Yohimbine treated animals. No differences in serotonin levels were observed. Additional anxiety-related markers are currently under investigation.

Platelet-Rich Plasma



▲**Figure 5: Yohimbine treated animals show a significant increase in stress hormone release.** Animals were tissue sampled directly after last behavior, terminal blood was collected, and platelet-rich plasma prepared. Corticosterone and serotonin levels were determined using ELISA. Mean ± SEM; n = 8 per group. Unpaired t-test. *p <0.05.

Summary

Taken together, these results highlight the robust anxiety inducing effects of Yohimbine treatment in multiple behavioral and biochemical readouts. Additional biochemical testing is ongoing, and repeatability and reference items are currently evaluated with additional cohorts. As anxiety-related disorders are becoming more prevalent, this paradigm proves to be a promising model for further vital treatment development.