

Yohimbine-Induced Circadian Clock Resetting in Mice

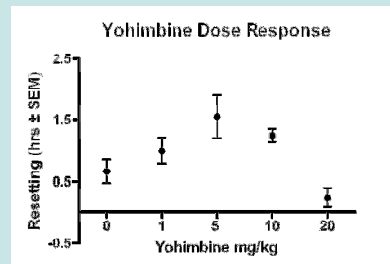
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Introduction

Mice are nocturnal animals that exhibit predictable activity patterns controlled by their internal (circadian) clock. We have demonstrated that a mouse's circadian clock can be reset to an earlier time through the administration of yohimbine, a selective adrenergic agonist. We determined that a 5 mg/kg yohimbine dose induced maximal clock resetting of about 1.5 hours. Next, we showed that yohimbine's clock resetting effect is dependent on the time of day at which it is administered. While a 5 mg/kg yohimbine dose induced resetting of 1.5 hours when given 6 hours prior to the normal lights-off time (ZT6), that same dose induced no clock resetting when given at the lights-off time (ZT12).

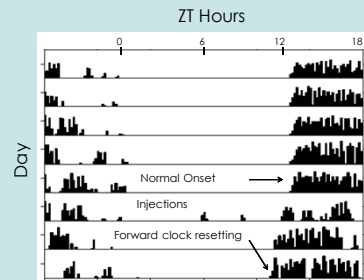
Experiment 1: Yohimbine Induces Circadian Clock Resetting

Mice of the C57BL/6 strain were entrained in 12 hrs. light: 12 hrs. dark for 14-20 days. A between subjects design was used in which animals were given a subcutaneous injection of either, 1, 5, 10 or 20 mg/kg yohimbine, or a saline control (0.9% NaCl) at ZT6. Lights were turned off immediately following the injection. Animals were kept in darkness for 3+ days.



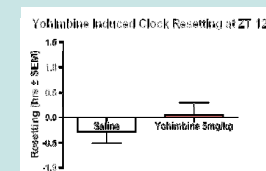
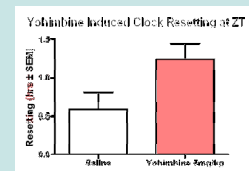
Results

We found that a 5 mg/kg yohimbine dose induced maximal clock resetting with a average phase shift of 1.5 hours. Resetting varied significantly with dose (ANOVA, $p=0.0022$) and was significantly greater for animals treated with a 5 mg/kg dose as compared to the control (t-test, $p < 0.05$).



Experiment 2: Yohimbine's Clock Resetting Effect is Phase Specific

Mice were entrained in 12 hrs. light: 12 hrs. dark for 14-20 days. Subcutaneous injections of either yohimbine (5 mg/kg) or a saline control (0.9%) were administered at either ZT6 or ZT12. Lights were turned off immediately following the injection and animals were kept in darkness for 3+ days.



Results

Yohimbine administered at ZT12 did not induce significant forward clock resetting (t-test, $p=0.35$). At ZT6, however, yohimbine treated animals showed significantly more resetting as compared to controls (t-test, $p=0.05$).

Conclusion and Further Research

We have shown that a 5 mg/kg dose of yohimbine induces a maximal clock resetting of 1.5 hours when administered at ZT6. This is consistent with earlier work suggesting that adrenergic activation is critical for circadian clock resetting induced by stimuli during the light phase or subjective day. Previous work has suggested that this type of drug-induced clock resetting can be also mediated by dopaminergic systems in the brain. For that reason, we plan to test whether yohimbine-induced clock resetting can be blocked by the adrenergic antagonist propranolol and the dopaminergic antagonist clozapine.

Acknowledgement

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