

Introduction

- Earlier work has shown that systemic administration of beta-adrenergic antagonist (beta-blocker) propranolol greatly reduces nonphotically induced phase shifts of circadian rhythms indicating that noradrenergic transmission is crucial to non-photic phase shifts.

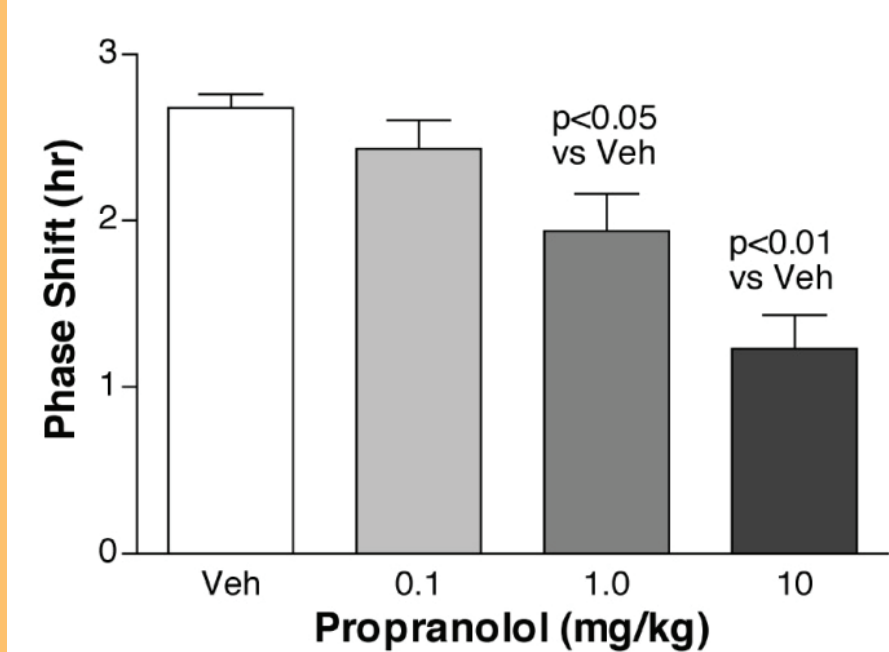
- Earlier work in this lab supports the idea that Central activation is needed for nonphotic clock resetting through a beta-ergic mechanism. Administration of a beta-antagonist; propranolol, showed an inhibition of phase shift.

- Peripheral administration of Propranolol, a beta-adrenergic blocker that crosses the blood brain barrier, significantly reduces behaviorally induced (non-photic) clock resetting.

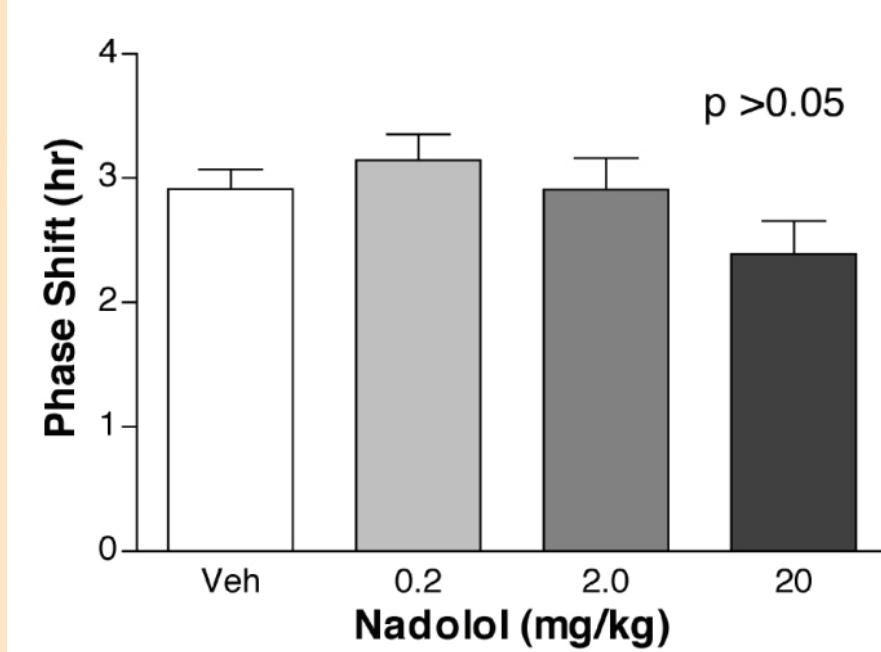
- Peripheral administration of Nadolol, a beta-adrenergic blocker that does not cross the blood brain barrier, had no effect on behaviorally induced (non-photic) clock resetting.

To verify that this effect is centrally mediated and to determine the type(s) of receptors responsible for the effect, we have begun to administer drugs that stimulate or block adrenergic receptors via cannulae implanted lateral ventricles of hamsters. This mode of administration eliminates the possibility of drug effects through interactions with peripheral receptors and allows us to use drugs that cannot cross the blood-brain barrier or that are subject to rapid degradation in the peripheral circulation. We predict that noradrenergic antagonists will attenuate nonphotically induced phase shifts. Whereas noradrenergic agonists will induce nonphotic-like phase shifts in the absence of nonphotic stimulation.

Administration of Propranolol Attenuates Nonphotic Phase Shifts with Increasing Concentrations



Peripheral Administration of Nadolol Shows no Significant Effect on Nonphotic Phase Shift.



Discussion

The results of this experiment support the hypothesis that noradrenergic agonists, such as isoproterenol, induce phase shifts in male Syrian hamsters and most likely do so through a beta-receptor mechanism. The results of this experiment are preliminary. However, the data thus far are consistent with the hypothesis beta-ergic receptors mediate nonphotic phase shifts in hamsters. Previous work has shown that the nor-adrenergic antagonist Propranolol (which crosses the blood brain barrier), blocks nonphotic phase shifts in hamsters.

Future Work

- *Further administration of Isoproterenol to solidify current findings.

- *Confirmation of propranolol's blocking effect via central administration.

- *Other Beta-antagonists and agonists may be used in the future to see if similar results are observed, thus supporting the original hypothesis that circadian rhythms operate through a beta-receptor mechanism.

- *Attempt to narrow down the specific adrenoceptor subtype(s) that mediate nonphotic clock resetting by use of subtype-specific agonists and antagonists.

Central Administration of Noradrenergic Drugs and Circadian Phase Shifts

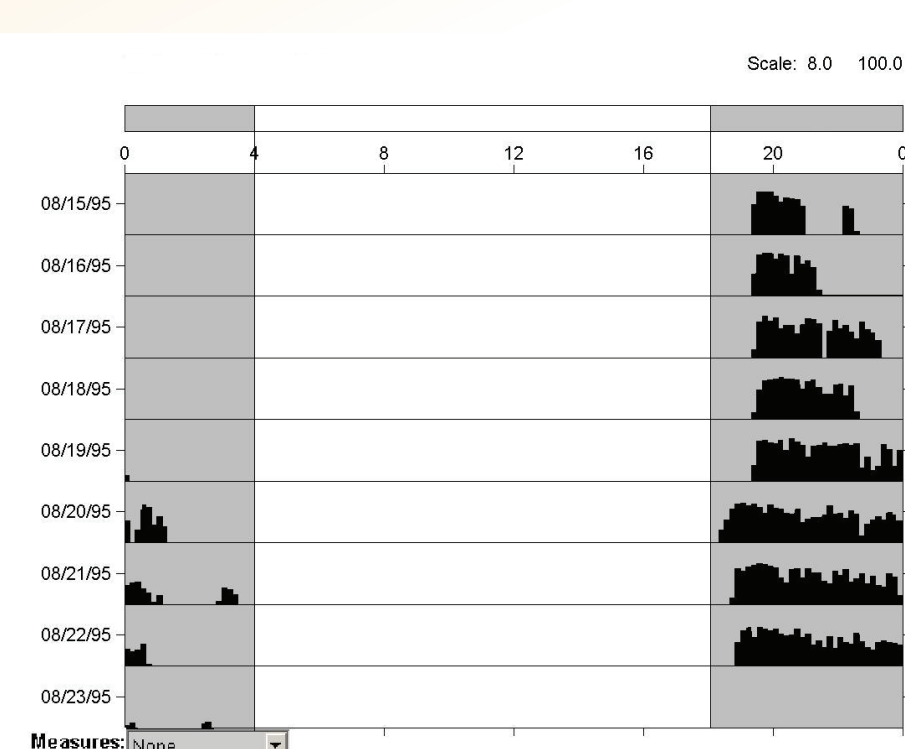
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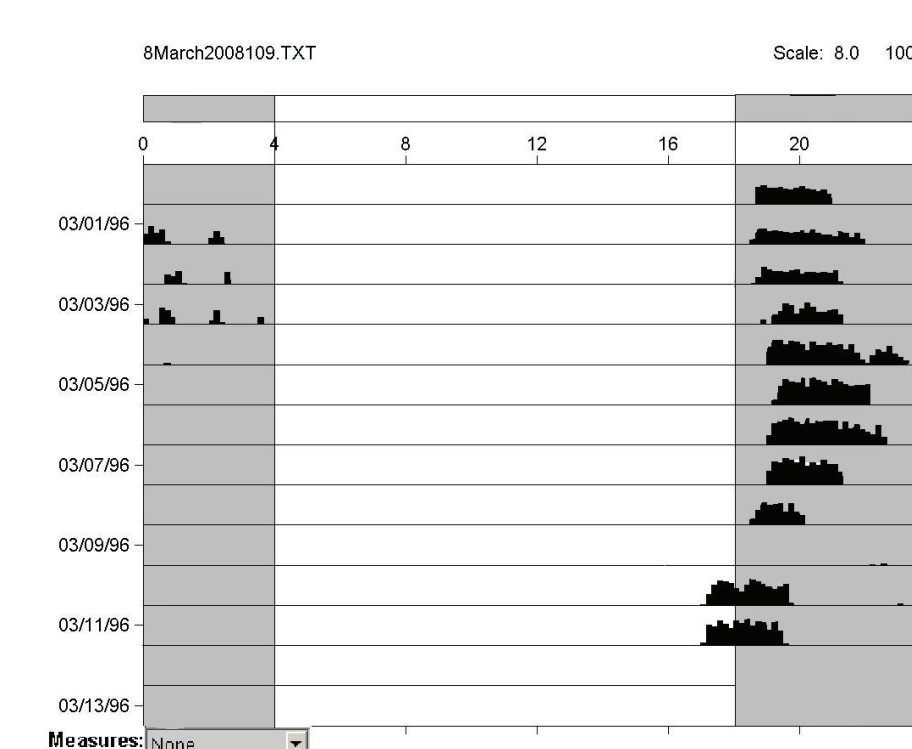
Materials and Methods

Male Syrian Hamsters between eight to ten weeks of age were used for surgical implantation in this experiment. The animals were housed in standard polyethylene bucket cages for the duration of the experiment. Surgical implantation of the 8.0 millimeter (mm.) stainless steel cannulae was done at approximately 10 weeks of age. We predict that noradrenergic antagonists will attenuate nonphotically induced phase shifts. Whereas noradrenergic agonists will induce nonphotic-like phase shifts in the absence of nonphotic stimulation.

ICV Injections of Saline Solution Induce a 1.3 Hour Phase Shift



ICV Injections of Isoproterenol Induces a 2.82 Hours Phase Shift



Surgical Procedure

- Animals were implanted with a 22 gauge stainless steel cannulae into their lateral ventricle.

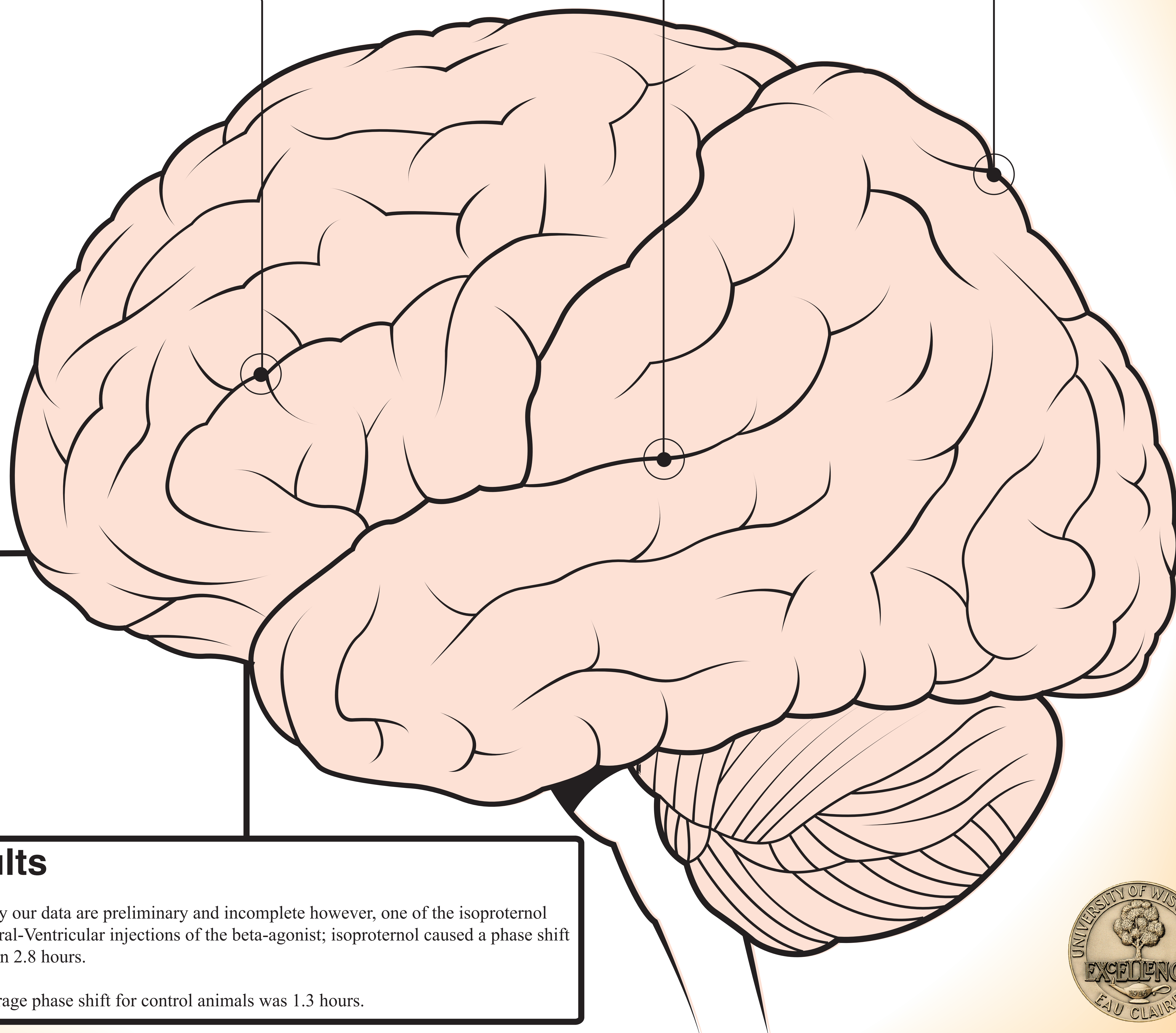
Experimental Procedure

- Animals were transferred to a polyethylene bucket cage with an attached exercise wheel. The Light-Dark cycle was 14 hours light: 10 hours darkness.

- Revolutions of the exercise wheel were recorded on a computer. After 12 days of recording, injections into the lateral ventricle were given.

- A five (5) microliter (μ l.) injection of isoproterenol was given to half of the males (n=2).

- A control using saline injections was given to the remaining hamsters (n=3).



Results

- Currently our data are preliminary and incomplete however, one of the isoproterenol Intra Cerebral-Ventricular injections of the beta-agonist; isoproterenol caused a phase shift of more than 2.8 hours.

- The average phase shift for control animals was 1.3 hours.

Acknowledgements

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