Role of circadian rhythms and sleep in neurotoxicant effects

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Abstract

20-25% of the workforce perform shift work, associated with increased disease risk, including neuropsychiatric diseases. The mechanism of these associations is poorly understood. Shift workers are active and feed at night when internal circadian clocks promote sleep and fasting. Such circadian misalignment may increase vulnerability to chemicals, as xenobiotic uptake and detoxifying metabolism show circadian variability. Given the prevalence of shift work and the burden of neuropsychiatric diseases, we must understand how the effects of neurotoxicants are modulated by shift work. High throughput screening (HTS) is required to test many chemicals.

The objective of this proposal is to perform experiments that will set the stage for determining how sleep deprivation and circadian misalignment affect chemical toxicity, using behavioral HTS in the freshwater planarian *Dugesia japonica*. We will achieve this objective by characterizing *D. japonica* sleep/wake behavior and circadian rhythms, and studying the effects of time-of-day and sleep deprivation on the toxicity of diazinon, a neurotoxicant.

As invertebrates with a circadian rhythm, tractable neuronal circuits, conserved neurotransmitter systems, and behaviors amenable to HTS, planarians are well-suited for this project. We will test the hypothesis that planarians' sensitivity to neurotoxicants is modulated by time of day and by sleep deprivation through 2 aims. In aim 1, we will characterize the circadian behavior and metabolism of *D. japonica* and test effects of time of day on diazinon neurotoxicity. In aim 2, we will determine whether *D. japonica* sleeps and test effects of sleep deprivation on diazinon neurotoxicity. This project will establish *D. japonica* as a model system to study the role of time-of-day and sleep deprivation on neurotoxicant effects. The data generated in this project will provide a foundation and preliminary data for a NIEHS grant proposal, to study the effect of sleep, circadian time, and simulated shift work on neurotoxicant effects.