

Potent screening tool finds new roles for some drugs in rest, waking

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File photograph by Justin Ide.

(PhysOrg.com) -- A robust new technique for screening drugs' effects on zebrafish behavior is pointing Harvard University scientists toward unexpected compounds and pathways that may govern sleep and wakefulness in humans.

Among their more intriguing findings, described this week in the journal *Science*: Various anti-inflammatory agents in the immune system, long known to induce [sleep](#) during infection, may also shape normal sleep/wake cycles.

The new research identifies several compounds with surprising effects on sleep and wakefulness in [zebrafish](#). But it also suggests that despite the evolutionary gap between them, zebrafish and mammals may be

strikingly similar in the [neurochemistry](#) underlying their rest/wake cycles, meaning these same compounds may prove effective in people.

"Many current drug discovery efforts rely on screening conducted outside the body," says Alexander F. Schier, professor of molecular and cellular biology at Harvard. "Although such screens can be successful, they cannot recreate the complex neuroscience of entire organisms. These limitations are particularly acute for behavior-altering drugs because [brain activity](#) cannot be modeled in a Petri dish or test tube."

Together with postdoctoral fellows Jason Rihel and David Prober, Schier and other collaborators used their automated [screening technique](#) to monitor zebrafish sleep and wakefulness for two days following administration of some 5,600 compounds, creating more than 60,000 distinct behavioral profiles. By applying clustering algorithms to organize these molecules, the researchers identified 463 drug candidates that significantly altered rest and wakefulness, many of which had not previously been known to have such effects.

"For instance, we found that a diverse set of anti-inflammatory compounds increased wakefulness during the day, with much less effect at night," Schier says. "Although these compounds have long been known to promote sleep during infection, this is an indication that the molecules that regulate the immune system may also play a role in setting normal daytime activity levels."

Anti-inflammatory agents found to affect sleep/wake cycles included cytokines, non-steroidal anti-inflammatory drugs (NSAIDs), and the immunosuppressant cyclosporine. Schier and colleagues also found calcium channel inhibitors that increased rest with minimal effects on waking behavior and a class of potassium channel blockers found in a wide variety of drugs -- including antimalarials, antipsychotics, and antihistamines -- that selectively increased wakefulness at night without

affecting total rest.

"Behavioral profiling reveals nuanced relationships between drugs and their targets," Schier says. "It can characterize large classes of compounds and reveal differences in effectiveness, potential side effects, and combinatorial properties that might not otherwise be detected."

Schier and his colleagues plan to expand their zebrafish screening to include many more uncharacterized compounds and to assay behaviors that, in humans, are associated with psychiatric disorders.

More information: www.sciencemag.org/current.dtl

Provided by Harvard University

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