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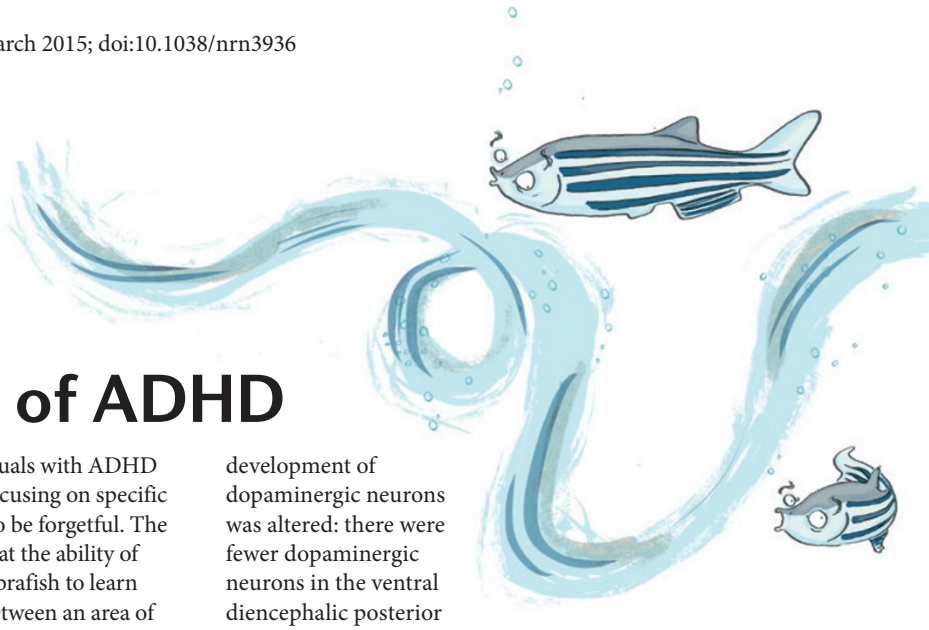


PSYCHIATRIC DISORDERS

A zebrafish model of ADHD

Attention-deficit hyperactivity disorder (ADHD) is linked to abnormalities in circadian rhythms, yet little is known about how circadian dysfunction affects disease pathogenesis. Wang and colleagues now show that zebrafish carrying a loss-of-function mutation in a key circadian gene, *period 1b* (*per1b*), exhibit symptoms that mimic those of ADHD and show how this model can provide insight into ADHD-like changes in behaviour.

To imitate the circadian dysfunction observed in ADHD patients, the authors used retroviral insertion to generate *per1b*-mutant zebrafish. The mutant fish exhibited altered circadian rhythmicity when housed in constant darkness, confirming the importance of Per1b for normal circadian function.

A key symptom of ADHD is hyperactivity. The authors showed that *per1b*-mutant zebrafish were three times more active than their wild-type counterparts. The mutant zebrafish also showed increases in exploratory behaviour and in their tendency to attack a mirror image of themselves; characteristics that are representative of hyperactivity. These phenotypes were ameliorated by treatment with two common ADHD drugs.

Many individuals with ADHD have difficulty focusing on specific tasks and seem to be forgetful. The authors found that the ability of *per1b*-mutant zebrafish to learn an association between an area of their tank and an electric shock was impaired in comparison to that of wild-type fish, as was their memory of the task the following day.

Another defining feature of ADHD is impulsivity. The authors trained the animals in a task in which a light was associated with food delivery. In a testing phase, *per1b*-mutant animals were less able to wait close to the light during a 4-minute delay between light presentation and food delivery, an indication of increased impulsivity. The mutant fish were also more sensitive than wild-type animals to rapid changes in light and dark, mimicking the increased sensitivity of patients with ADHD to environmental changes.

The authors next examined the dopaminergic system, which is hypothesized to be dysfunctional in patients with ADHD, in the mutant fish. They revealed changes in expression of two key genes involved in dopamine metabolism, *monoamine oxidase* (*mao*) and *dopamine-β hydroxylase* (*dbh*), as well as changes in expression of several dopamine transporters and receptors. The authors also found that the development of dopaminergic neurons was altered: there were fewer dopaminergic neurons in the ventral diencephalic posterior tuberculum (an area that is a key regulator of behaviour) in the mutant fish, and those present were noticeably disorganized. Furthermore, the levels of expression of several genes involved in dopamine-neuron development were altered.

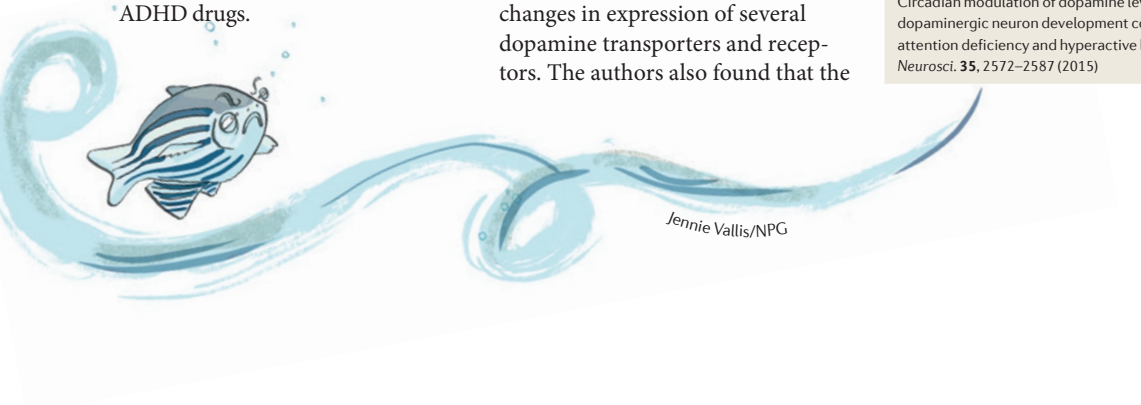
To assess the importance of the circadian pathway in ADHD-like behavioural changes in other species, *Per1*-knockout mice were also investigated. Like the mutant zebrafish, these animals exhibited hyperactivity and impulsivity, and impaired learning and memory, as well as changes in genes encoding proteins involved in dopamine metabolism.

This study presents a model of circadian disruption that is associated with hyperactivity and attention deficiency in a system that may be suitable both for high-throughput drug discovery approaches and for mechanistic studies.

Katherine Whalley

ORIGINAL RESEARCH PAPER Huang, J. *et al.* Circadian modulation of dopamine levels and dopaminergic neuron development contributes to attention deficiency and hyperactive behavior. *J. Neurosci.* **35**, 2572–2587 (2015)

> “*per1b*-mutant zebrafish were three times more active than their wild-type counterparts”



Jennie Vallis/NPG