Sleep-wake rhythm: Fish change our understanding of sleep regulation

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Clown loach (Chromobotia macracanthus). Credit: Wikimedia Commons, CC BY-SA 4.0

Contrary to common belief, not all vertebrates regulate their sleep-wake rhythm in the same way. University of Basel researchers have discovered

that some fish—unlike humans—do not need orexin to stay awake. This molecule was thought to be necessary for normal wake and sleep rhythms in vertebrates. Humans without orexin suffer from narcolepsy.

Until recently, it was assumed that vertebrates share similar mechanisms controlling sleep behavior. That's why researchers have been using fish in the past 20 years as a model organism to study sleep and its regulation.

Now a team led by Professor Alex Schier at the Biozentrum, University of Basel, has made a surprising discovery in a South Asian fish species: Clown loaches, which can also be found in zoos and aquariums, exhibit normal sleep rhythms, but their sleep is regulated in a different way. They lack the so-called orexin signaling pathway (also known as Hypocretin signaling pathway), previously considered to be essential for controlling sleep and wake in all vertebrates.

The results of the study have been published in *Current Biology*.

Sleep-wake rhythm without orexin

"We were very surprised that clown loaches show normal sleep rhythms and, above all, they can easily be awakened despite a defective orexin pathway," says first author Dr. Vassilis Bitsikas. So, this carp species does not fall into a fainting state, as it is common in narcolepsy and does not require orexin to regulate their sleep-wake cycle.

Initially, the idea was to study the orexin signaling pathway in clown loaches in more detail. As these fish simply stop swimming when they sleep and rest on their sides, it is easy to observe them when they are actually sleeping. "They seemed the ideal model organism for our sleep study. However, further investigations revealed that clown loaches lack a functional orexin signaling pathway," reports Vassilis Bitsikas.

Narcolepsy in mammals

In humans, a functional orexin signaling pathway is essential to maintain sleep-wake rhythms. Deficiencies in this pathway lead to narcolepsy. Patients suffering from this condition experience excessive sleepiness during the day, sudden loss of muscle tone (cataplexy) and uncontrolled sleep attacks, from which they can hardly be woken up.

This neurological disease is caused by loss of nerve cells in the brain producing orexin, a neurotransmitter that keeps us awake. "So far, it was assumed that deficiency in orexin disrupts normal sleep-wake behavior across all vertebrates. Now it turned out that this assumption is obviously wrong," explains Alex Schier.

Fish regulate their sleep differently

The researchers also discovered that not only clown loaches, but also zebrafish can control their sleep-wake rhythm without relying on orexin.

"They still maintain normal sleep and wake behavior despite a defective orexin signaling pathway. So, they don't rely on it to remain awake," reports Vassilis Bitsikas. Accordingly, this fish species might have developed separate or compensatory sleep control mechanisms by comparison to mammals. "It would be interesting to find out when and why different control systems have evolved in vertebrates," says Alex Schier.

Fish have often been used as model organisms for studying the evolution of sleep. "The new findings have reshaped our understanding of sleep and wake regulation. Fish may hold some secrets that could help us uncover why certain animals are more vulnerable to narcolepsy than others," emphasizes Vassilis Bitsikas.

More information: A vertebrate family without a functional Hypocretin/Orexin arousal system, *Current Biology* (2024). DOI: 10.1016/j.cub.2024.02.022. www.cell.com/current-biology/f … 0960-9822(24)00164-7

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