

Depressed fish could help in the search for new drug treatments

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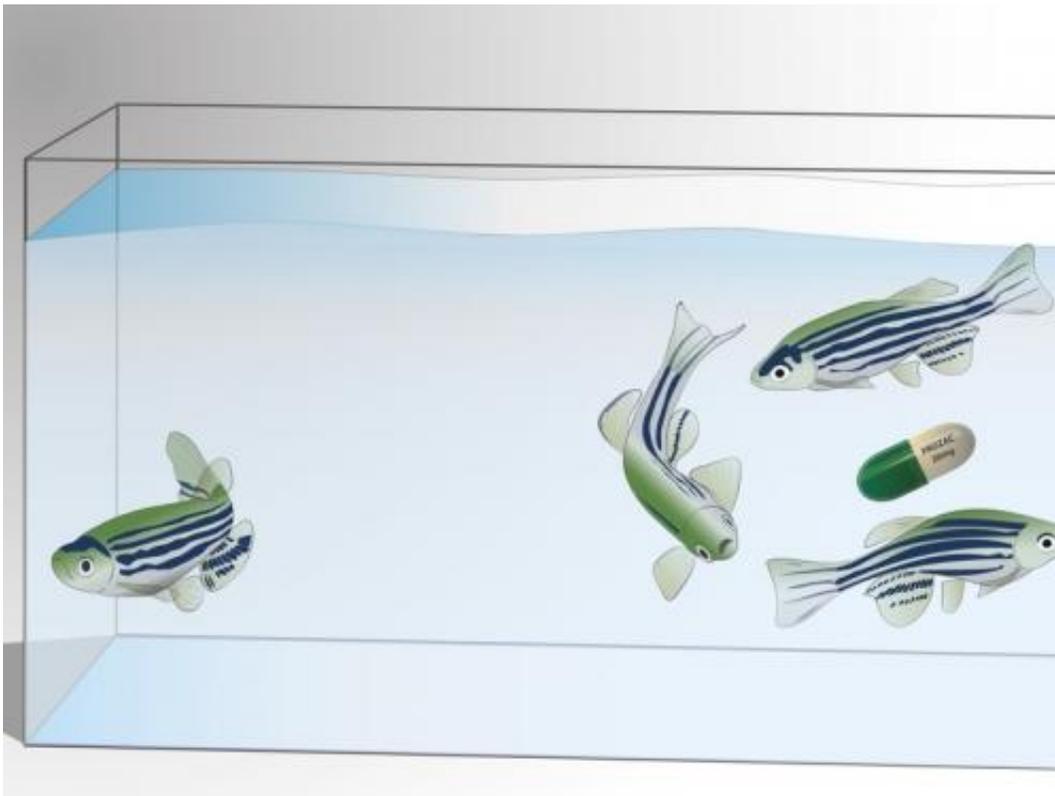
The zebrafish (*Danio rerio*) is a popular model organism for many questions in the field of genetics and developmental biology. Credit: MPI f. Neurobiology

Chronic stress can lead to depression and anxiety in humans. Scientists working with Herwig Baier, Director at the Max Planck Institute of Neurobiology in Martinsried, recently discovered a very similar correlation in fish.

Normally, the [stress](#) hormone cortisol helps [fish](#), as in humans, to regulate stress. Fish that lack the receptor for cortisol as a result of a genetic mutation exhibited a consistently high level of stress. They were

unable to become accustomed to a new and unfamiliar situation. The fishes' behaviour returned to normal when an antidepressant was added to the water. These findings demonstrate a direct correlation between [chronic stress](#) and behavioural changes which resemble depression. The findings could also open the door to an effective search for new drugs to treat psychiatric disorders.

In stressful situations, the body releases hormones in order to ready itself for a fight or flight reaction. But it is equally important for the [hormone level](#) to return to normal after a certain time. If that does not happen, chronic stress can result, a condition which is linked with depression and anxiety, among other things. Whether stress is a trigger or merely a side effect of such affective disorders remains unknown.



Zebrafish with a mutation in the glucocorticoid receptor exhibit passive behaviour in a stressful situation. The behaviour returns to normal with a

commercial antidepressant in the water. The findings demonstrate a significant correlation between stress regulation and mood disorders, one which evidently plays a central role in humans, too. Credit: Max Planck Institute of Neurobiology / Schorner

The indication of a [causal relationship](#) between stress and depression comes from totally unexpected quarters. Herwig Baier's team of scientists from the Max Planck Institute of Neurobiology in Martinsried and the University of California in San Francisco observed that zebrafish suffering from chronic stress as a result of a genetic mutation showed signs of depression in behavioural tests. The zebrafish is a popular model organism for biological and medical issues. So far, however, it has not been an obvious research object for the study of psychiatric disorders. That could be about to change.

"These mutant fish behaved very strangely when we moved them to a new aquarium," reports Herwig Baier. All animals experience stress upon moving to an unfamiliar environment. Being separated from members of their own species places the fish under added pressure. Zebrafish initially act withdrawn in this situation and swim around very hesitantly in the first few minutes. But ultimately, curiosity prevails and they begin to investigate their new tank. However, the fish with the mutation had a particularly strong reaction to the isolation: they sank to the bottom of the tank and stayed completely still. They took an exceptionally long time to get used to the new environment.

An analysis of these "lethargic" fish showed that they had an extremely elevated concentration of the stress hormones cortisol, CRH and ACTH. "We therefore postulated that these fish were suffering from chronic stress and were exhibiting certain aspects of depressive or perhaps over-anxious behaviour," says Baier. Pursuant to this assumption, the

scientists added the antidepressant fluoxetine (commonly marketed under the trade name Prozac, among others) to the water. The fish's behaviour actually returned to normal shortly afterwards.

What was it that made these fish so different? The scientists uncovered a mutation in the glucocorticoid receptor, which is present in almost all of the body's cells and which binds the hormone cortisol. Normally, when cortisol is bound to this receptor it restricts the release of the stress hormones CRH and ACTH. It is this regulating mechanism that enables humans and many animal species to cope with stress. In the type of fish the scientists examined, however, the glucocorticoid receptor was unable to function and so the level of stress hormones remained high.

"Although there are a whole range of drugs available for depression, no one yet knows what the relationship is between their effect and the [stress hormones](#)," explains Herwig Baier. "Our findings provide the first evidence of a possible connection." Understanding the molecular and neurobiological relationships between stress regulation and affective disorders is important in the search for new treatments and drugs. The scientists' discovery is therefore also of interest to the pharmaceutical industry, given that the zebrafish could turn out to be a good [model organism](#) for a large-scale search and testing of new drugs.

Provided by Max Planck Society

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