Risk factor for psychiatric disorders has different effects depending on sex, finds research

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The protein FKBP51 is considered a risk factor for psychiatric disorders. However, for the first time, new research results have shown

positive effects. Instead of making people anxious or impairing their ability to think, the protein can have the opposite effect and thus promote resilience. The effect it has depends on the type of cells in which it becomes active.

Furthermore, sex plays a decisive role. Female model animals reacted either fearfully or courageously to the protein, while males were cognitively weakened or strengthened. The results do not make the development of a blocking drug any easier. But they show all the more how important basic research and sex-specific studies are.

The fact that FKBP51 is a risk factor for the occurrence of stress-related psychiatric disorders has been repeatedly shown, among others through extensive research conducted by the Max Planck Institute of Psychiatry in recent years. Research in this area is becoming more and more detailed, and now scientists are presenting a study that suggests that the effects of FKBP51 are more complex than previously thought.

The team, led by research group leader Mathias Schmidt, studied the function of the protein in two different cell populations. In glutamatergic cells, which have an excitatory effect on nerve cells, and in GABAergic cells, which have an inhibitory effect. In addition, the neuroscientists also differentiated according to the sex of the test animals. This is because disorders such as depression occur about twice as often in women as they do in men. But studies that investigate sex-specific differences are rare. Mice were used as the model organism for this basic research.

The results are astonishing—the effects are opposite. In females, the "risk gene" FKBP51 manipulates anxiety; in males, it affects cognitive performance. Looking at the different cell types, the effects are opposite there, too. When FKBP51 is blocked in GABAergic cells, female mice reacted less anxiously, while males performed better cognitively. In

glutamatergic cells, just the opposite happened, females were more anxious and males more cognitively impaired.

The "risk gene" FKBP51 can thus also have positive effects, as demonstrated for the first time in this study. Depending on the site of action and sex, it can cause phenotypes of stress-related psychiatric disorders, but it can also have a resilience-promoting effect. "That doesn't completely surprise me," Schmidt admits, "FKBP51 is found in so many places in the body—if it were so harmful, it would have been downregulated during evolution."

In addition to the behavioral level, the researchers also looked at the structural level. Using imaging techniques, they were able to show that a brain region that controls anxious behavior was altered in the female mice. In the males, the hippocampus, which controls cognitive abilities, was altered. These results fit neatly with the sex-specific behavioral changes and were further strengthened by findings at the level of gene expression in these regions.

FKBP51 is thus more complicated than anticipated. Pharmacologists are already working on agents to block the risk factor. In light of this new study, this is likely to become even more difficult, a typical process in drug development. "Our results show how important it is to investigate fundamental effects, especially in a sex-specific way," Schmidt says.

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