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By: Vlad Tarko, Senior Editor, Sci-Tech News



[The Biochemical Cause of Depression Has Been Found](#)

By Paul Greengard's team

Antidepressant drugs work in different ways and doctors have little idea why exactly do they work. Paul Greengard, who has already earned a Nobel prize, has found that depression is caused by the deficiency of a certain specific chemical. Paul Greengard is a Rockefeller University neuroscientist and has received the 2000 Nobel Prize in Physiology or Medicine for discoveries about the workings of the neuronal signaling systems. The neurons interact via certain chemical molecules called neurotransmitters. Various disorders can be linked either to problems regarding the underproduction or overproduction of certain neurotransmitters or to the inappropriate number of neurotransmitter receptors in the cells. Antidepressants generally work by regulating the number of a certain neurotransmitter called serotonin. However, it is thought that depression is caused by faulty serotonin receptors. Paul Greengard and his colleagues have found the chemical which is the natural responsible for the regulation of the serotonin system: a certain protein, referred to as p11. The scientists have found p11 by studying how a particular serotonin receptor works - they have searched for the particular protein which interacts with the serotonin receptor and makes it more active. The researchers then suspected that p11 levels might be directly involved in the development of depression, anxiety and similar psychiatric illnesses. To test this idea, the researchers examined p11 levels in the brains of depressed humans and "helpless" mice, considered a model of depression since they exhibit behaviors similar to those of depressed humans. They compared these two groups to non-depressed humans and control mice. Levels of p11 were found to be substantially lower in depressed humans and helpless mice, which suggests that altered p11 levels may be involved in the development of depression-like symptoms. The researchers also examined the p11 levels after treatments designed to boost weak serotonin systems in brain cells by administering to mice two types of antidepressants - a tricyclic, a monoamine oxidase (MAO) inhibitor, and electroconvulsive therapy (ECT). "These three different ways of treating depression all caused an increase in the amount of p11 in the brains of these mice," said Greengard. "They all work in totally different ways, but in all cases they caused the same biochemical change. So, it's pretty convincing that p11 is associated with the main therapeutic action of antidepressant drugs." Since humans and mice with symptoms of depression were found to have substantially lower levels of p11 in brain cells compared to non-depressed animals, Greengard and colleagues hypothesized that if p11 levels were increased, mice would exhibit antidepressant-like behaviors, and if p11 were reduced, mice would exhibit depression-like symptoms. The fact that apparently it all comes down to a certain protein, suggests that the cause of depression could be genetic. The genetic code is nothing but a code for the production of various proteins. Thus, the scientists searched for the gene responsible for the production of p11. As hypothesized, mice with over-expressed p11 genes, compared to control mice, had increased mobility in a test that is used to measure antidepressant-like activity. They also had more serotonin receptors at the cell surface and thus the neuronal system had an increased serotonin transmission capacity. The opposite occurred when researchers molecularly knocked out the p11 gene in mice. Compared to control mice, knockout mice had fewer receptors at the cell surface, reduced serotonin signaling, decreased responsiveness to sweet reward, and were less mobile, behaviors which are considered depression-like. Moreover, the serotonin receptors of p11 knockout mice were less responsive to serotonin and antidepressant drugs compared to those of control mice, which further implicates p11 in the main action of antidepressant medications. "Manipulations that are antidepressant in their activity increased the level of the protein and

those which are depressant reduce it," said Greengard. "It seems as though antidepressant medications need to increase p11 levels in order to achieve their effect." Future studies should elucidate exactly how antidepressants increase levels of this molecule, he added.
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