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# Modifying an obesity drug could reduce side effects like anxiety and depression

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A new version of an obesity drug that caused serious psychiatric side effects could help people lose pounds without experiencing the anxiety, depression and suicidal thoughts previously associated with it. The research, published in *Bioorganic and Medicinal Chemistry*, shows that the new version of the drug can still work without reaching the brain in rats, avoiding the side effects.

The researchers behind the study, from RTI International in the US, say this means the new version of the drug could be used in the future for treating obesity. And their approach could also support the development of drugs to tackle liver disease, metabolic conditions and high blood cholesterol.

In our bodies we have cannabinoid receptors that control appetite, mood, memory and pain. The obesity drug Rimonabant stops these receptors from working. But the drug was found to have serious psychiatric side effects in a small number of the people who took it. Because of this, the drug was never approved in the US and manufacturer Sanofi-Aventis pulled from the European market voluntarily.

In the new study, the researchers altered the drug so it no longer gets into the brain, which stops it from having psychiatric side effects.

Study author Dr. Rangan Maitra, from RTI International in the US, explained: "There is a real need for new medicines to treat metabolic conditions like obesity. We are working with chemists to alter the drug

Rimonabant and create compounds that cannot get into the brain. We hope this will help create drugs that can treat people with these conditions, without them having to suffer the side effects."

Dr. Maitra and colleagues modified the original Rimonabant compound by changing its weight, polarity and other properties to try to stop it from getting into the brain.

Tests in rats found that one of the versions, called 8c, blocks the target receptor and is much less likely than the original drug to get into the brain and affect the central nervous system.

The researchers found that 8c mostly stays in the blood and works on cannabinoid receptors found in parts of the body other than the brain. In comparison, more than half of the original drug Rimonabant entered the brain.

It's early days for the research, and the new version of the drug will need to go through testing before it can be used to treat people, but the researchers say it's a step in the right direction. Their study also outlines how scientists can test drugs designed to target cannabinoid receptors to make sure they are working outside the brain.

"Drug development is a long and arduous process," said Dr. George Amato, co-author of the study. "You have to develop hundreds, if not thousands, of compounds before you get the right one. The challenge is that some medicines that are absorbed in the gut also get into the brain. We set out to find compounds that absorb across the gut barrier but not the brain barrier. We've identified some, and they'll now serve as lead structures for further refinement."

**More information:** Alan Fulp et al, Pyrazole antagonists of the CB1 receptor with reduced brain penetration, *Bioorganic & Medicinal*

*Chemistry* (2016). DOI: 10.1016/j.bmc.2016.01.033