Why don't antidepressants work in some patients?

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Mouse study shows it may be down to your environment.

SSRI antidepressants (Selective Serotonin Reuptake Inhibitors, the best known being Prozactm) are amongst the most commonly taken medicines. However, there seems to be no way of knowing in advance whether or not SSRIs will work effectively. Now a group of European researchers has developed a new theory of SSRI action, and tested it in stressed mice. The results, which are presented at the ECNP conference in Vienna, show why the circumstances we find ourselves in may influence whether an antidepressant works or not.

According to researcher, Silvia Poggini (Istituto Superiore di Sanità, Rome), "There is no doubt that antidepressants work for many people, but for between 30 and 50% of depressed people, antidepressants don't work. No-one knows why. This work may explain part of the reason."

The researchers have proposed that simply increasing the levels of serotonin, by taking an SSRI, does not cause a recovery from depression, but puts the brain into a condition where change can take place -- it increases the plasticity of the brain, making it more open to being changed. "In a certain way it seems that the SSRIs open the brain to being moved from a fixed state of unhappiness, to a condition where other circumstances can determine whether or not you recover" said Ms Poggini. According to the researchers, it is the environmental conditions you find yourselves in at the time of the treatment which determines whether you are likely to get better or worse.

To test this, they took a sample of mice which they subjected to stress for two weeks. They started treating the mice with the SSRI fluoxetine, and split the group. They continued to stress half (n=12) of the group of mice but the other half of the mice were subjected to a more comfortable environment. They then tested all the mice to measure the levels of the stress-related cytokines in the brain. Cytokines are protein-related molecules which aid cell to cell communication in the immune system.

They found that mice kept in a more comfortable environment showed an increase in the expression of pro-

inflammatory cytokines and decreased anti-inflammatory-related genes, as well as showing fewer signs of depression, whereas those under continuous stress showed the opposite effect (i.e. a decrease in pro-inflammatory cytokines, and an increase in anti-inflammatory gene expression, with more signs of depression). The fluoxetine-treated mice exposed to the comfortable environment showed a 98% increase in the pro-inflammatory cytokines IL-1? while mice kept in a stressed environment and treated with fluoxetine showed a 30% decrease in the pro-inflammatory cytokines TNF-?.

This indicates that the environment determines the response to antidepressants. According to Silvia Poggini, "This work indicates that simply taking an SSRI is probably not enough. To use an analogy, the SSRIs put you in the boat, but a rough sea can determine whether you will enjoy the trip. For an SSRI to work well, you may need to be in a favourable environment. This may mean that we have to consider how we can adapt our circumstances, and that antidepressant treatment would only be one tool to use against depression."

She cautioned "Our studies have a number of limitations. First of all, we are not explaining the complete range of actions of SSRIs. It's also an animal model, so clinical and epidemiological studies are needed to further test the validity of the hypothesis. Our results are preliminary and we strongly recommend that patients stick to the treatment prescribed by their doctors."

Commenting, Dr Laurence Lanfumey (Centre de Psychiatrie et Neuroscience Inserm, Paris), Member of the ECNP Executive Committee, said, "This original study is a nice model for combined behavioral and pharmacological treatments in depression- like disorders. The idea that environment could impact the output of a pharmacological treatment has been suggested for years, but this work brings direct biological evidences of such an interaction. Although the present work also raised several questions, this kind of experiment is important to do to bridge the gap between behavior and SSRIs efficacy."