Why don't the drugs work? Controlling inflammation can make antidepressants more effective

September 10 2019

Research shows that controlling inflammation may be key to helping the brain develop the flexibility to respond to antidepressant drugs, potentially opening the way for treatment for many millions of people who do not respond to the drugs. This is experimental work on mice, and has not yet been confirmed in humans. It is presented together for the first time at the ECNP Congress in Copenhagen, after a series of publications in peer-reviewed journals.

Group leader, Professor Igor Branchi (Istituto Superiore di Sanità, Rome), said:

"If confirmed in humans, these results may have fairly far-reaching implications. The work shows that neuroplasticity and inflammation are interdependent, and that to provide the right conditions for the antidepressant to work, inflammation need to be tightly controlled".

Depression is the leading cause of disability worldwide, and is a major burden on society. It is commonly treated by drugs called Selective Serotonin Reuptake Inhibitors (SSRIs). Unfortunately, SSRIs don't work for around 1/3 of people, meaning that they have very limited options for treatment.

Antidepressants are known to increase the ability of the brain to form new connections, a process called neuroplasticity. They have also been

shown to help control levels of brain inflammation. In a new study, Italian scientists set out to test whether there would be an optimum balance between neuroplasticity and inflammation.

In a first study, the scientists fed mice the SSRI antidepressant fluoxetine (Prozac) to increase the neuroplasticity of their brains and found the mice had a change in the expression of inflammatory markers. When they then housed the mice for three weeks in a stressful environment to cause inflammation, giving the mice fluoxetine caused the inflammation to decrease. By contrast, when exposed to a relaxing environment, known to reduce inflammation, feeding the mice fluoxetine resulted in higher activity in genes associated with inflammation.

"The first step was to link the brain's ability to deal with change, the neuroplasticity, to inflammation", said lead researcher Dr. Silvia Poggini (Istituto Superiore di Sanità, Rome). "Once we had shown that, the next step was to change the levels of the inflammation to see what happened to plasticity".

This led to a second study, where the researchers treated the mice either with lipopolysaccharide, a drug which increases inflammation, or with ibuprofen, which decreases inflammation. By doing this they were able to change the level of inflammation, rather like increasing or decreasing the volume of music. While doing this, they measured plasticity markers in the mice, to see whether changes in inflammation increased or decreased neural plasticity.

Dr. Poggini continued,

"We found that neural plasticity in the brain was high as long as we were able to keep inflammation under control. But both too high and too low inflammation levels meant that the neural plasticity was reduced—in line

with the reduced efficacy of antidepressants in mice with altered levels of inflammation".

When the mice were tested for depression-like responses such as anhedonia and cognitive bias, the mice showed behavioural changes which reflected the expected balance between plasticity and inflammation.

Igor Branchi added:

"If the results can be translated to humans, then controlling inflammation might lead to more effective use of antidepressants. This may be done by drugs, but we may also consider preventing high inflammation arising in the first place, which may lead us to look at other parameters which lead to the stress which causes this problem. More generally, this work shows us that SSRI antidepressants are not one-size-fits-all drugs, and that we should look at other options for improving drug response".

Professor Carmine M. Pariante, Professor of Biological Psychiatry at King's College London, says that 'This paper really provides new insight into the relationship between the brain, inflammation, and antidepressant response. We have known for some time that depressed patients with increased inflammation do not respond to antidepressant treatment, but this study finally proposes the biological mechanisms underpinning these effects. Most importantly, the study also proposes that low inflammation can be equally harmful in depressed patients, also preventing response to antidepressants, a finding that, if replicated in humans, will have important clinical implications".

Professor Pariante was not involved in this work.

More information: Poggini el al: The interaction between inflammation and neural plasticity controls the efficacy of serotoninergic

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Branchi: Interplay between inflammation and neuroplasticity in promoting antidepressant treatment 2019.ecnp.eu/programme/Program … ctdetails/0000374170 Relevant publications:
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Provided by European College of Neuropsychopharmacology