

Anti-inflammatory effects of omega-3 fatty acids could help reduce depression

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The omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in oily fish. Researchers from the National Institute of Health Research (NIHR) Maudsley Biomedical Research Centre assessed the effects of high doses of EPA and DHA in lab-grown neurones and then in patients to help clarify how they reduce inflammation and depression. This novel approach allowed the scientists to identify an important molecular mechanism which can help inform the development of potential new treatments involving omega-3 fatty acids for patients with depression.

Lead author Dr. Alessandra Borsini, NIHR Maudsley BRC Senior Postdoctoral Neuroscientist at King's College London, said: "Using a combination of laboratory and patient research our study has provided exciting new insight into how [omega-3 fatty acids](#) bring about anti-inflammatory effects that improve depression. For some time we have known that omega-3 PUFA can induce anti-depressant and anti-inflammatory effects but, without further understanding of how this happens in the [human brain](#), it has been difficult to develop treatments. Our study has helped shine a light on

the molecular mechanisms involved in this relationship which can inform the development of potential new treatments for depression using omega-3 PUFA."

Previous research has shown that people with [major depressive disorder](#) have higher levels of inflammation in their bodies than those without the disorder. There are currently no proven anti-inflammatory treatment strategies for depression and, although two important omega-3 PUFAs, EPA and DHA, have been shown to provide anti-inflammatory and antidepressant effects, the precise mechanism by which they do this is unknown.

Depression in a dish The study set out to test the theory that when omega-3 fatty acids are utilised and processed in the body, some of their metabolites (known as lipid mediators) are able to protect the brain from the harmful effects of inflammation. Researchers used a validated in vitro human cell model known as 'depression in a dish' that was developed at the NIHR Maudsley Biomedical Research Centre and which uses cells from the hippocampus, a part of the brain fundamental in many cognitive, memory and learning areas thought to be important in depression. Hippocampal cells play an important role in the production of new neurones—neurogenesis.

The study showed that treating human hippocampal cells with EPA or DHA before being exposed to chemical messengers involved in inflammation called cytokines, prevented increased cell death and decreased neurogenesis. Both these impacts had been previously observed in cells exposed to cytokines alone. Further investigation confirmed these effects were mediated by the formation of several key lipid mediators produced by EPA and DHA, namely hydroxyeicosapentaenoic acid (HEPE), hydroxydocosahexaenoic acid (HDHA),

epoxyeicosatetraenoic acid (EpETE) and epoxydocosapentaenoic acid (EpDPA), and these were detected for the first time in human hippocampal neurones. Further investigation showed that treatment with an enzyme inhibitor increased the availability of two of these metabolites (EpETE and EpDPA) suggesting a possible way by which future treatments could be optimised.

Professor Anna Nicolaou, professor of Biological Chemistry at the Faculty of Medical and Human Sciences, The University of Manchester, who led the team that measured the lipid mediators using mass spectrometry said: "The lipid mediators that our research identified are broken down in the body relatively quickly, which means they may only be available for a relatively short time. By testing the effect of inhibitors of the enzymes involved in the metabolism of omega-3 PUFA we showed that we can greatly improve how long they can have an effect in the body and ultimately, increase their efficacy. This is very important for the development of new treatments and means that patients could be given higher doses of EPA and DHA together with these enzyme inhibitors to increase the amount of these important compounds in their blood over time."

Omega-3 metabolites in patients

The study assessed twenty-two patients with major depression who were given either 3 grams of EPA or 1.4 grams of DHA daily for twelve weeks. The lipid metabolites of EPA and DHA were measured in their blood before and after the omega-3 PUFA treatment, along with a score of their depressive symptoms. In both groups of patients, EPA or DHA treatment was associated with an increase in their respective metabolites and a significant improvement in depressive symptoms—an average reduction in symptom scores of 64% and 71% in the EPA and DHA groups respectively. In addition, higher levels of the same metabolites identified in the in vitro experiments were correlated with lower levels of depressive symptoms.

The levels of EPA and DHA used in this study are concentrations that most likely cannot be achieved with dietary consumption of oily fish, a rich source

of omega-3 PUFAs, but require therapeutic supplements.

Future Research

The results of the study indicate that the bioactive lipid mediators produced by the breakdown of EPA and DHA in the body could be targeted as a mechanism to reduce depression and inflammation but there is a need to ensure that their effects are prolonged in order for this approach to be successful. Previous research indicates a key enzyme in the omega-3 fatty [acid](#) metabolism could be a valid option for drug repurposing and could be used for other inflammation-associated brain disorders, including depression, where at least a sub-group of patients often have chronic levels of inflammation.

Senior author of the paper, Professor Carmine Pariante, NIHR Maudsley BRC Affective Disorders Interface with Medicine Theme Lead said: "There is ever growing interest in the links between the immune system, inflammation and depression but in order to develop new treatments in this area we need to better understand the mechanisms behind these relationships. Our study has provided important insight into how known anti-inflammatory compounds—the omega-3 PUFA—help reduce depression. By identifying and measuring the exact lipid mediators that are involved, identifying the enzyme that prolongs their effects and finding the same lipid mediators in depressed patients treated with omega-3 PUFA and demonstrating improvements in symptoms, we have provided vital information to help shape clinical trials for future therapeutic approaches with omega-3 fatty acids.

"It is important to highlight that our research has not shown that by simply increasing omega-3 fatty acids in our diets or through taking nutritional supplements we can reduce inflammation or depression. The mechanisms behind the associations between depression and omega-3 PUFA are complicated and require further research and clinical trials to fully understand how they work and inform future therapeutic approaches."

The study was a collaboration between researchers from King's College London, The University of

Manchester and China Medical University.

The paper "Omega-3 [polyunsaturated fatty acids](#) protect against inflammation through production of LOX and CYP450 [lipid mediators](#): relevance for major [depression](#) and for human hippocampal neurogenesis" was published today in *Molecular Psychiatry*.

More information: "Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis" *Molecular Psychiatry* (2021).

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