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Invited Commentary

Dietary interventions with *n*-3 fatty acids or probiotics targeting post-myocardial infarction depression

In this issue of the *British Journal of Nutrition,* Gilbert *et al.*[1] describe attenuation of post-myocardial infarction (MI) depression by dietary supplementation with *n*-3 fatty acids or probiotics in a rat model. This paper indicates the importance of dietary intervention to avoid post-MI depression. Previously, it was shown that a high-PUFA diet enriched with *n*-3 fatty acids or a low-PUFA diet enriched with probiotics (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175), when fed before the ischaemic period, reduced apoptosis in the limbic system of the brain and reduced circulating pro-inflammatory cytokines[2,3]. This recent study further demonstrates that a diet containing either high *n*-3 PUFA or probiotics, when given after the onset of ischaemia/reperfusion, is also able to inhibit apoptosis in the limbic system, reduce circulating levels of pro-inflammatory cytokines and attenuate post-MI depression. These studies indicate that *n*-3 fatty acids or probiotics may be very useful dietary components in attenuating post-MI depression.

Depression is a common symptom of MI[4]. Approximately 10–50 % of all MI patients show symptoms of depression with variable severity[5]; however, approximately one in six patients with MI experience major depression[6–8]. The common symptoms are depressed mood, diminished interest or pleasure and low self-esteem. Some patients exhibit these symptoms at initial hospitalisation, whereas in others depression may occur during recovery from MI or 1–4 months post-MI[5]. Patients with depression are likely to be non-compliant with medical treatment regimens[9,10] and have a greater dropout rate from cardiac rehabilitation programmes[11]. Post-MI depression is often associated with cardiac readmission and a poor quality of life during the first year, with a significantly increased risk of subsequent death[12]. Post-MI depression is an independent risk factor for increased mortality. Patients with post-MI depressive disorder carry a 2·0- to 2·5-fold increase in the relative risk of new cardiovascular events and cardiac mortality[12]. Furthermore, they incur high costs for health care services due to hospital readmission. Although controversial, patients with major depression have been shown to have decreased brain serotonin (5-hydroxytryptamine) activity[13]. Serotonin metabolism in the central nervous system is influenced by pro-inflammatory cytokines[14]; IL-1, interferon (IFN)-α, IFN-γ and TNF-α all up-regulate the serotonin transporter, thus causing a depletion of extracellular serotonin, whereas IL-4 (an anti-inflammatory cytokine) reduces serotonin uptake[14–16]. It is interesting that Gilbert *et al.*[1] demonstrated lower concentrations of plasma monocyte chemoattractant protein-1, a pro-inflammatory cytokine, on the high-*n*-3 PUFA diet and an increase in IL-4, an anti-inflammatory cytokine, on the probiotic diet. Although this study did not monitor serotonergic activity, inhibition of apoptosis in the dentate gyrus and the medial amygdala suggests that cytokines play an important role in the attenuation of post-MI depression. Inhibition of pro-inflammatory cytokines is not only beneficial for attenuating depressive symptoms, but may also help to reduce the inflammation caused by MI.

A growing number of studies support a role for *n*-3 fatty acids in depression and neuropsychiatric dysfunction. Depressed patients have significantly depleted total *n*-3 PUFA and DHA in serum and erythrocyte membranes[17,18]. In cross-sectional investigations, infrequent or reduced fish consumption was independently associated with depressive symptoms and a higher rate of depression, whereas higher fish consumption was well correlated with a lower prevalence of major depression[19,20]. Other studies have shown that increased seafood consumption is also predictive of reduced postpartum depression and bipolar disorders[21]. The *n*-3 fatty acids, EPA and DHA, can mediate anti-depressive effects through multiple mechanisms. *n*-3 Fatty acids are incorporated into all cell membranes, especially those of the brain and myocardium. These fatty acids are known to assist in nerve cell signalling and neurodevelopment. *n*-3 PUFA regulate serotonergic and dopaminergic neurotransmitters and thereby have a direct effect on depressive symptoms[22,23]. Furthermore, these fatty acids also provide beneficial effects to MI patients by modulating the activities of cardiac ion-channel proteins[24]. In addition to this, *n*-3 fatty acids are well known for their anti-inflammatory properties. The anti-inflammatory effects of *n*-3 fatty acids are mediated through their effects on arachidonic acid (AA) metabolism. AA serves as a precursor to inflammatory mediators such as thromboxanes, PG and leukotrienes. *n*-3 Fatty acids not only compete with AA for incorporation into cell membranes, but also compete (especially EPA) with AA for rate-limiting enzymes for the synthesis of the above-mentioned inflammatory mediators. Moreover, the anti-apoptotic properties of *n*-3 fatty acids may also improve depression via a neuroprotective mechanism. For example, DHA facilitates the activation and translocation of Akt, an anti-apoptotic protein[25], and induces the expression of the Bcl-2 anti-apoptotic protein in neuronal cells[26]. DHA also reduces the activation of caspase-3, a pro-apoptotic protein[27]. Furthermore, as mentioned by

Gilbert *et al.*[1], DHA generates neuroprotectin D, a powerful anti-inflammatory mediator that activates pro-survival signals down-regulating apoptosis. The results reported by Gilbert *et al.*[1] showed a similar reduction in apoptosis and inhibition of caspase activity by a high-*n*-3 PUFA diet. Although the authors have not examined the potential mechanism of DHA in attenuating post-MI depression in their model, it is likely that *n*-3 fatty acids may be acting through multiple mechanisms. The outcome of this study by Gilbert *et al.*[1] is not surprising because the effects of *n*-3 fatty acids on inflammation and depression are well-documented; however, the effect of probiotics on attenuating post-MI depression is an interesting finding in this paper.

Probiotics are live organisms that colonise the gut following their oral consumption and consequently have a beneficial effect, either directly or indirectly via their metabolic products, on the overall health of the host. Probiotics transiently colonise the gut, where they increase their concentration and create a balance in the gut microbiota to the benefit of the host. As reviewed by Sherman *et al.*[28], the common beneficial effects of probiotics include antimicrobial activity towards enteric pathogens, maintenance of immune homeostasis in the gut, stimulation of anti-inflammatory cytokine secretion and reduced secretion of pro-inflammatory cytokines and influence on the activity of genes to help fight disease. Recent studies have also found a probiotic link between the brain and the gut. The enteric nervous system, which is the intrinsic nervous system of the gastrointestinal tract, plays an important role at the brain–gut axis. The vagus nerve is the primary route that the gut bacteria use to transmit information to the brain. A probiotic (*B. longum* NCC3001) has been shown to help normalise anxiety-like behaviour in mice with infectious colitis[29]. Another probiotic (*L. rhamnosus*) affects γ-aminobutyric acid in certain brain regions, reducing anxiety- and depression-related behaviours[30]. Gilbert *et al.*[1] provide further evidence of probiotic effects on the brain–gut axis. Their data clearly indicate that probiotics attenuated post-MI depression in rats by inhibiting apoptotic processes in the dentate gyrus and the medial amygdala of the limbic system. The effect of the probiotic was associated with an increased plasma concentration of the anti-inflammatory cytokine, IL-4. It is interesting to note that combining high *n*-3 PUFA and probiotics showed no further improvement in attenuation of the post-MI depression. The authors suggest involvement of common pathways or a plateau effect. It is possible that, perhaps, by combining an *n*-3 fatty acid with probiotics, an additive or synergetic effect can be achieved with lower concentrations of these agents.

The study performed by Gilbert *et al.*[1] has enormous translational potential. It remains to be seen if similar effects can be reproduced in patients with post-MI depression. Both *n*-3 fatty acids and probiotics are inexpensive natural substances that are largely devoid of any side effects, and they can be easily incorporated into the diets of patients who have had an MI. In addition, either *n*-3 fatty acids or probiotics, or their combination, can be used as an adjunctive treatment to other antidepressants, not only to treat post-MI depression, but to treat other conditions with depressive symptoms as well.

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