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Beyond cardiovascular medicine: potential future uses of icosapent ethyl

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The REDUCE-IT trial demonstrated that icosapent ethyl, an ethyl ester of eicosapentaenoic acid (EPA), reduced cardiovascular events in an at-risk population by a substantial degree. While the cardiovascular protective properties of this compound are now proven, several other potential uses are being actively explored in clinical studies. These areas of investigation include cancer, inflammatory bowel disease, infections, Alzheimer's disease, dementia, and depression. The next decade promises to deepen our understanding of the beneficial effects that EPA may offer beyond cardiovascular risk reduction.

Introduction

The data supporting use of the prescription medication icosapent ethyl in patients similar to those enrolled in the Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE-IT) are robust.[1–8] Several registry analyses have found that these results may be

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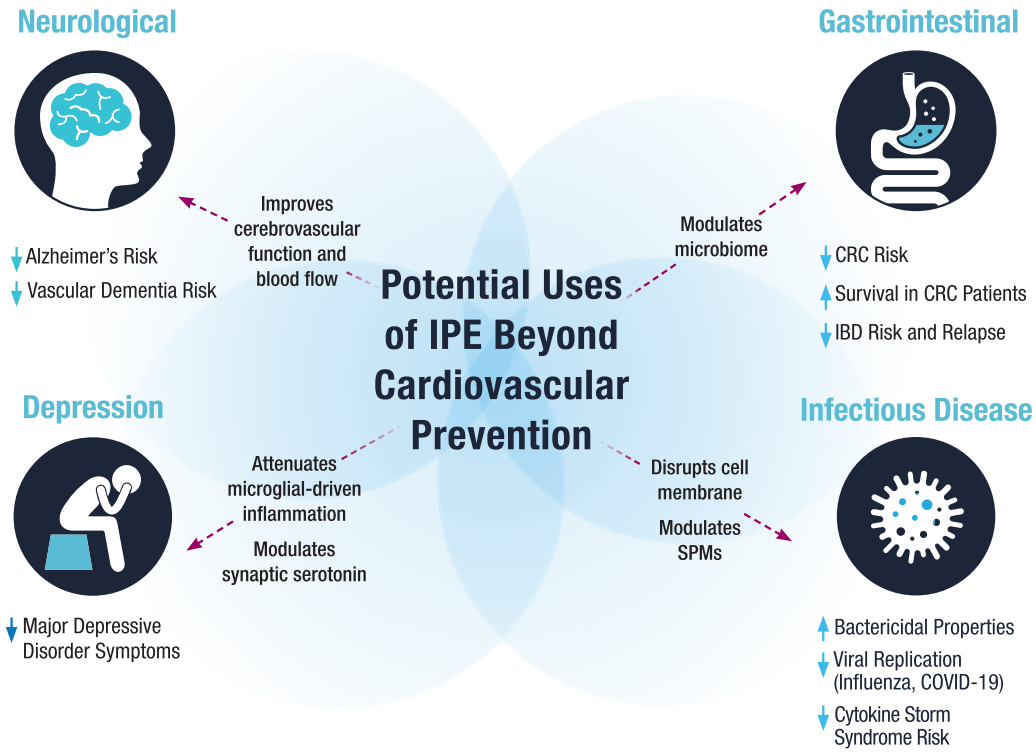

Figure Ongoing Research on Icosapent Ethyl Outside of Cardiovascular Prevention. CRC, colorectal cancer; IBD, inflammatory bowel disease; IPE, icosapent ethyl; SPMs, specialized pro-resolving mediators.

applicable to a large proportion of patients with established atherosclerosis involving any arterial bed or with diabetes mellitus.[9-11] Analyses from REDUCE-IT support that the primary mode of cardiovascular benefit is mediated through high blood eicosapentaenoic acid (EPA) levels, with basic science experiments ongoing to delineate the exact downstream molecular mechanisms.[12] REDUCE-IT included ~10% of patients with normal triglycerides.[1,13,14] This subgroup had a similar relative risk reduction as patients with higher triglyceride levels. Some physicians will feel comfortable extrapolating from the current data to these patient subsets even absent further large-scale clinical trial testing—especially in higher risk patients.

Remaining questions in the cardiovascular space include whether higher loading doses might provide incremental value in acute settings, such as at the time of myocardial infarction, ischaemic stroke, or revascularization. Patients with a history of such events have already been shown to have significant benefit from treatment with icosapent ethyl in REDUCE-IT, but might they derive even greater benefit if the drug had been administered at the time of the event? The observation from a prespecified analysis of REDUCE-IT showed that higher levels of on-treatment EPA were highly correlated with lower rates of new heart failure, providing potential support for higher maintenance doses of icosapent ethyl.[12] Furthermore, studies are warranted to see if icosapent ethyl could be used specifically to reduce first or recurrent heart failure.[15] Thus, there is a pressing need for further research of EPA in cardiovascular medicine. Perhaps even more intriguing is the potential utility of EPA in other disease states.

Although the exact mechanisms of action of EPA in reducing cardiovascular events are not fully known, they are likely multifactorial. The lipid effects of EPA may include increased plasma lipoprotein lipase activity and decreased lipogenesis in the liver.[16] The non-lipid effects may include anti-inflammatory properties, anti-oxidant effects, arterial plaque modification and regression, anti-thrombotic and anti-platelet effects, cell membrane stabilization, and enhanced endothelial function.[17,18] The central theme figure captures the potential mechanisms of action for the ensuing discussions in this article (Figure). These mechanisms need to be investigated further in ongoing and future clinical trials.

Potential gastrointestinal applications of eicosapentaenoic acid

Laboratory data support a potential benefit of EPA for the reduction of colorectal cancer (CRC) risk.[19] In a small randomized placebo-controlled trial (RCT) of 55 patients with familial adenomatous polyposis, an inherited CRC predisposition syndrome, it was demonstrated that supplementation with EPA 2 g daily for 6 months reduced the number and size of adenomatous rectal polyps (the benign precursor of the majority of 'sporadic' CRCs) by 20–30%.[20] These findings led to a phase III RCT, the seAFOod Polyp

Prevention Trial, which tested the effect of the same dose of EPA in individuals with 'sporadic' colorectal adenomatous polyps detected at colonoscopy in the English Bowel Cancer Screening Programme (BCSP).[21] Although the intervention did not reduce the primary endpoint of the number of individuals with one or more adenomatous polyps, a statistically significant reduction was observed in the secondary outcome of the number of adenomatous polyps, particularly those in the left colon, an endpoint that is more relevant to contemporary trials conducted in quality-assured colonoscopy programmes, such as the English BCSP. To examine the potential of EPA for primary prevention of CRC, a prespecified ancillary study of colonoscopy outcomes was carried out in the large phase III Vitamin D and Omega-3 Trial (VITAL) of 25 871 US adults free of cancer and cardiovascular disease at enrolment.[22] After treatment with omega-3 fatty acids at a dose of 1 g daily [including 460 mg EPA and 380 mg docosahexaenoic acid (DHA)] for a median of 5.3 years, there was no difference in the risk of either adenomatous or serrated polyps (the other major precursor of CRC). Interestingly, a lower risk of adenomatous polyps was reported in the omega-3 fatty acid group compared with those assigned to placebo among individuals with low plasma levels of omega-3 fatty acids at baseline. A beneficial association of omega-3 fatty acid supplementation was also observed in African-Americans, but not in other racial/ethnic groups. These hypothesis-generating findings of a potential preventive effect of a low dose of omega-3 fatty acids in individuals with low omega-3 fatty acid status or African-American persons need to be validated in future large RCTs.

In addition to potential reduction in CRC risk, recent data support benefit of high marine omega-3 fatty acid intake for survival of patients with established CRC. In a Phase II RCT of EPA 2 g daily in 88 patients undergoing liver resection for CRC liver metastasis, EPA treatment increased overall and disease-free survival and reduced the vascularity score of metastatic tumours compared with placebo.[23] Similar beneficial associations between high EPA intake after CRC diagnosis and improved survival have been reported in observational studies.[24,25] Based on these data, a larger-scale, placebo-controlled phase III RCT [EPA for Metastasis Trial 2 (EMT2), NCT03428477] of treatment with EPA (4 g icosapent ethyl daily) was launched in the UK for patients undergoing liver resection for CRC liver metastasis. The findings of EMT2 are expected to become available in 2023 and will shed light on the potential of integrating adjuvant EPA therapy into management of CRC patients.

In contrast to oral supplementation, two intravenous infusions of mixed omega-3 fatty acids at a dose of 0.2 g/kg/day before and after surgery did not change serum levels of inflammatory markers and, unexpectedly, resulted in more infectious post-operative complications in a recent RCT involving patients undergoing elective surgical resection for primary CRC.[26]

The anti-inflammatory properties of EPA have been investigated in the context of inflammatory bowel disease (IBD). An initial report that EPA reduced relapse risk in Crohn's disease[27] has not been replicated by other RCTs and systematic reviews that suggest no overall benefit from omega-3 fatty acids for the clinical course of Crohn's disease or ulcerative colitis (UC).[28] However, observational studies continue to link omega-3 fatty acid intake and blood levels with reduced IBD risk,[29] and a recent RCT concluded that EPA therapy reduced faecal calprotectin levels in UC patients.[30] Further studies of the precision use of EPA for IBD prevention and treatment in defined circumstances (e.g. maintenance of remission in UC) are warranted.

One mechanism that might explain possible anti-cancer and anti-inflammatory effects of EPA in the gastrointestinal tract is modulation of the gut microbiome.[31] There is evidence that EPA and other omega-3 fatty acids are associated with an increased number of immunomodulatory bacteria, such as *Lactobacillus* and *Bifidobacterium*, and short-chain fatty acid-producing bacteria.[32] In support of the relevance of these microbiome associations with CRC and IBD, many of the EPA-enriched bacteria are found to be depleted in CRC and IBD (e.g. short-chain fatty acid-producing bacteria),[33] whereas the bacteria reduced by EPA may promote CRC (e.g. *Fusobacterium nucleatum*).[34–39] Eicosapentaenoic acid may also modify gut environmental conditions and change the composition of microbes.[40–44] Ongoing clinical trials are investigating the effect of EPA on modulation of the intricate relationship between the gut microbiome and tumour immunity (e.g. NCT03661047, NCT03428477, and NCT04216251).

Eicosapentaenoic acid and infectious disease

Infectious diseases (lower respiratory tract infection, diarrheal diseases, tuberculosis, malaria, and human immunodeficiency virus, among others) are the leading causes of mortality in low-income countries.[45] Bacterial strains resistant to antibiotics continue to arise secondary to spontaneous mutations and antibiotic over-utilization.[46] The ongoing global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) brought renewed concern and focus to humanity's vulnerability to the rapid, widespread transmission of a dangerous virus against which we have neither vaccine nor treatment.[47] Sepsis continues to pose formidable challenges both in terms of understanding its underlying pathophysiology and instituting effective treatment.[48] Identifying novel approaches to the treatment of infectious diseases remains a major focus of scientific and clinical inquiry worldwide.

Polyunsaturated fatty acids (PUFAs) may exert beneficial effects in the setting of infection.[49] The antibacterial effects of fatty acids were first recognized in the 1880s by Koch.[50] It was reported that the skin microbiome is kept in check by PUFAs produced in dermal layers.[51] The PUFAs exert a complex range of effects that impact bacterial viability and control the intensity of the inflammatory response induced by cellular constituents of the immune system. The omega-3 fatty acid EPA has drawn particular attention in these respects.

Membrane effects of eicosapentaenoic acid

Eicosapentaenoic acid is esterified to phospholipids (principally phosphatidylcholine and phosphatidylethanolamine at the sn-2 site) in the lipid rafts of cell and bacterial

membranes.[52] A broad range of gram-positive (e.g. *Bacillus subtilis*, *Listeria monocytogenes*, *Staphylococcus aureus*) and gram-negative (e.g. *Escherichia coli*, *Helicobacter pylori*, *Pseudomonas aeruginosa*) bacteria, mycobacteria, and cyanobacteria were reported to be susceptible to the growth-inhibiting and cidal effects of EPA when studied *in vitro*.[53,54] Eicosapentaenoic acid induces pathogen injury by altering the fluidity of bacterial membranes and disrupting the cell wall and cell membrane.[55] This results in transmembrane ion and metabolite leaks, alterations in the interactions among membrane proteins, impaired enzyme activity, loss in nutrient uptake capacity, cell lysis, and inability to engage in electron transport and oxidative phosphorylation, among other effects.[56–59] There are no human clinical trials which have evaluated the efficacy of EPA in the setting of active infection independent of antibiotic therapy.[60] Polyunsaturated fatty acids may also inhibit the replication of enveloped viruses.[61] Eicosapentaenoic acid has been reported to inhibit the replication of the hepatitis C virus, an example of an enveloped virus.[62] Because COVID-19 and other SARS-associated coronaviruses are enveloped, it has been suggested that omega-3 fatty acids be tested to resolve infection more quickly and prevent cytokine storm syndrome.[63,64] A number of trials are actively enrolling subjects with COVID-19, or at high risk of infection, to determine the effect of EPA, if any, in preventing infection with SARS-CoV-2 or mitigating inflammatory disease sequelae.[65–68]

Specialized pro-resolving molecules

Cytokine storm syndrome (CSS) is systemic inflammatory response that can be precipitated, for example, by viral infection [COVID-19, Middle East respiratory syndrome coronavirus (MERS), influenza] and gram-negative sepsis.[69] Cytokine storm syndrome is a manifestation of a hyperactivated immune system. In the setting of infection, it is crucial that the immune and inflammatory responses be activated in a way that efficiently clears infection without incurring tissue destruction and death of the host.

Therapeutic efforts to attenuate inflammation and reduce risk for CSS events are extraordinarily challenging. Inflammation is a critical component of host defence. Finding a balance between controlling inflammation without compromising the capacity to fight infection is no simple physiological matter. Molecular signalling pathways that could resolve the inflammatory response in CSS are inappropriately inhibited. Under normal conditions, once infection and injured tissue are cleared, intrinsic safety mechanisms to resolve inflammation are activated. This is mediated by specialized pro-resolving mediators (SPMs) of inflammation.

Specialized pro-resolving mediators (also called immunoresolvents) are formed from arachidonic acid as well as EPA, docosapentaenoic acid, and DHA. These PUFAs are liberated from cell membrane phospholipids and are precursors to the maresins, protectins, resolvins, and lipoxins, all of which are SPMs and participate in the resolution of inflammation. The SPMs bind to highly specific surface receptors on target cells.[70]

A variety of models suggest that EPA beneficially impacts inflammatory tone through SPMs and other mechanisms. The E series resolvins are downstream metabolites of EPA. RvE1 inhibits cytokine production, reduces leucocyte infiltration, promotes both neutrophil apoptosis and macrophage phagocytic activity to clear cellular and inflammatory debris (i.e. efferocytosis) and is a more potent anti-inflammatory agent than aspirin or dexamethasone.[71,72] RvE2 also inhibits neutrophil infiltration and induces potent anti-inflammatory activity.[73] Both RvE1 and RvE2 stimulate IL-10 production.[74] In an experimental murine model of aspiration pneumonia, the infusion of RvE1 reduced intrapulmonary levels of numerous interleukins and cytokines, increased bacterial clearance, reduced neutrophil infiltration, and increased survival.[75] The therapeutic utility of RvE1 is being evaluated in a variety of scenarios, including infection and inflammatory diseases.

Eicosapentaenoic acid and its downstream metabolites, the E series resolvins, may offer novel approaches to the treatment and/or prevention of infection and cytokine storm that need to be further investigated in large, well-controlled clinical trials.

Potential uses of eicosapentaenoic acid in Alzheimer's disease, dementia, and depression

Alzheimer's disease and dementia

Dementia due to Alzheimer's disease (AD) is a devastating illness leading to progressive neurodegenerative changes and cognitive decline. In 2019, there were roughly 50 million people living with dementia worldwide.[76] The number of people living with dementia due to AD is expected to triple by 2050.[76] Alzheimer's disease is characterized by a chronic, progressive neurodegeneration resulting from the accumulation of fibrillary proteins in the form of beta-amyloid (Aβ) plaques and hyperphosphorylated tau tangles.[77] Overaccumulation of these substances leads to dysfunction of synapses and neuronal loss.[78] Importantly, these neurodegenerative changes begin decades before clinically apparent disease.[79,80] The National Institute on Aging (NIA)-Alzheimer's Association developed research criteria for defining the asymptomatic or preclinical stages of AD as well as progression to mild cognitive impairment (MCI) and AD[81] based on *in vivo* measures of beta-amyloid and hyerphosphorylated tau and neurodegeneration, along with metrics of cognitive ability. Despite their centrality to clinical AD, the cause of dysregulation of beta-amyloid and tau proteins, and subsequent onset of dementia, is poorly understood. Likewise, not everyone who has AD pathology develops symptoms of dementia. A number of other factors from genetics to lifestyle to environmental exposures are likely to influence the onset and course of AD.[82–85]

Indeed, AD often coexists with vascular dementia, which is the second most common cause of dementia after AD.[86,87] Even in the absence of diagnosable vascular dementia, cerebrovascular pathology can be a major risk factor for clinically diagnosed AD and cognitive decline.[88] One post-mortem pathology study found that cerebrovascular disease was evident in 80% of people diagnosed with AD.[89] Vascular risk factors, such as reduced regional cerebral blood flow in areas of the brain related to memory and

learning[90] and arterial stiffness,[91] are related to deficits in cognitive ability. Other cardiovascular risk factors, such as smoking, hypertension, diabetes, hypercholesterolaemia, and elevated body mass index, have been associated with markers of dementia risk, such as lower grey matter volume and reduced white matter integrity.[92] Cerebrovascular dysfunction may be part of the pathophysiology of AD or these risk factors may lower the threshold at which AD pathology burden leads to observable symptoms of dementia.[93,94] More than likely, vascular dysfunction acts synergistically with neurodegenerative changes and leads to cognitive impairment.[93]

Like beta-amyloid and hyperphosphorylated tau accumulation, cerebral dysfunction occurs early in the development of AD pathology and decades before symptoms begin. Yet, the effects of treating such early vascular dysfunction in the brain are poorly understood. There is some evidence that therapeutics which lower risk for vascular dysfunction, such as antihypertensives, also lower the risk for MCI and AD.[95,96] Other cardiovascular risk factors, such as high cholesterol levels, have been associated with MCI and AD risk.[97,98] However, the relationship between circulating cholesterol and cholesterol in the brain is complex, and randomized clinical trials of statins have generally failed to show any therapeutic benefit on cognitive dysfunction.[99] Another potential target for therapeutics are triglycerides and triglyceride-rich lipoproteins. The brain is a cholesterol-rich organ and enzymes involved in lipid transport or metabolism have been linked to risk for AD.[100] The e4 variant of the Apolipoprotein E gene, for example, has long been known to increase risk for AD.[101] Apolipoprotein E plays a role in the catabolism of triglyceride-rich lipoproteins. Another enzyme, lipoprotein lipase, which is critical to the metabolism of triglyceride-rich lipoproteins, is related to both AD pathology and to cardiovascular risk factors and hypertriglyceridaemia.[102,103]

Eicosapentaenoic acid may improve arterial function and cerebral blood flow, attenuating adverse brain changes related to β-amyloid protein, and improving cognition in animals—changes that need to be investigated for protection against AD.[104–107] This agent is readily available for use and has a good safety profile, making it a favourable agent to consider for AD prevention. Currently, Carlsson *et al*. are conducting a small randomized clinical trial to determine if EPA beneficially affects cerebrovascular function or cognitive performance in cognitively healthy adults at increased risk for AD called Brain Amyloid and Vascular Effects of Eicosapentaenoic Acid (BRAVE-EPA) (NCT02719327).[108]

Depression and n-3 polyunsaturated fatty acids: spotlight on eicosapentaenoic acid

Cardiovascular disease and depression represent the two most common causes of disability in high-income countries, and it has been argued that a recurrent depressed mood may be the 'most important driver of overall quality of life'.[109] Nutritional factors, such as dietary consumption of omega-3 and omega-6 PUFAs, for which a marked reduction in the ratio of omega-3/omega-6 PUFAs has been observed in recent decades,[110] may constitute a relevant molecular basis of depressive disorders.

Biological mechanisms implicated in depression

A number of biological mechanisms may be operative in depression; these include effects on the autonomic nervous system, platelet receptors and function, coagulation factors, proinflammatory cytokine production, endothelial function, and neurohormonal factors; a role for genetic factors, potentially involving variants in key genes of neurotransmitter transport, such as that for serotonin, cannot be excluded. Consequently, drugs which increase monoamine availability, and notably serotonin, represent key therapeutics in major depression. However, many patients respond partially or become refractory to treatment by monoamines as shown in the VAST-D randomized clinical trial, and therefore novel therapeutic approaches are warranted.[111]

Clinical relevance of omega-3 polyunsaturated fatty acids to treatment of depression

Over the period of the past 5 years, evidence has suggested a potential role for EPA in treatment of depression. The meta-analyses of Sarris *et al*.[112] and of Hallahan *et al*.[113] were instrumental in providing experimental evidence for the potential benefits of omega-3 PUFAs when administered as dietary supplements to patients with depression. These analyses revealed that the symptoms of depression were attenuated by consumption of omega-3 PUFA dietary supplements. The analysis of Sarris *et al*.[112] showed moderate benefit of EPA-predominant PUFA preparations as an adjunct to conventional anti-depressant therapy in patients with diagnosed depression. However, the study of Hallahan *et al*.,[113] which included 35 randomized, placebo-controlled intervention trials, indicated that DHA-predominant omega-3 PUFAs did not improve depression symptoms relative to placebo, whereas EPA-predominant preparations (>50% EPA) did. Overall, these findings are consistent with those reported in an RCT, which showed that EPA (as an adjuvant to maintenance medication) exerted greater efficacy compared with DHA or placebo in attenuation of mild-to-moderate depression.[114]

Transport and metabolism of eicosapentaenoic acid

Although EPA is synthesized primarily in the liver by enzymatic elongation and desaturation of precursors, such as α-linolenic acid (ALA), it is the exogenous dietary route which most effectively results in increase in circulating EPA concentrations.[115] Circulating EPA occurs primarily in esterified form in the phospholipids, cholesteryl esters, and triglycerides of plasma lipoproteins, (up to ≈ 40 nmol/mL plasma), with minor amounts bound to plasma proteins (<1 nmol/mL).[116,117] It is the latter form which is readily available for uptake by cells and tissues, and indeed in which EPA may be transported into the brain.[115] Absolute tissue levels of EPA in brain are several-fold lower than those of both ALA and DHA (<25 nmol/g as compared to ≈10 000 nmol/g for the latter). The explanation appears to reside in the short half-life and rapid metabolism of EPA in brain tissue, part of which occurs by β-oxidation.[115]

Brain metabolism of eicosapentaenoic acid: role of microglial cells

By which mechanisms might EPA lead to attenuation of the symptoms of depression? A critical element appears to involve brain microglial cells, which preferentially esterify EPA, leading to intracellular EPA concentrations which are two-fold or more higher than those of DHA; this ratio can be compared with an inverse ratio corresponding to an ~100-fold excess of DHA to EPA in whole brain.[115] Microglial cells are found throughout the brain and spinal cord, representing 10–15% of all nervous tissue cells. Importantly, they represent the resident macrophages of the central nervous system, and as such, are active immuno-inflammatory cells.

Evidence in human subjects and in animal models indicates that mood disorders may be associated with dysfunction of the innate and adaptive immune systems.[118] Moreover, chronic inflammation appears to be a critical factor in the formation and maintenance of major depression in some patients; indeed, depression manifests more frequently in patients displaying chronic inflammatory disease states, such as type 2 diabetes, obesity, and rheumatoid arthritis.[119] While the mechanisms which underlie these disorders are complex, evidence is forthcoming that proinflammatory cytokines and inflammatory lipid mediators may modify not only the metabolism of neurotransmitters but also neurogenesis and neuroplasticity.[119] Significantly, microglial cells are implicated in the production of proinflammatory cytokines in response to peripheral inflammation.[120] In addition, post-mortem studies in patients with depression have documented microglial activation in several regions of brain tissue, including the frontal cortex.[121] Considered together then, microglial-driven inflammation appears to represent a key feature of chronically stressed brains, and as such, has been suggested to lead to alteration in the plasticity of neuronal synapses.[122]Microglial-driven inflammation in brain tissue may therefore represent a key factor in the aetiology of depression.[123]

It is well established that EPA, like DHA, exhibits a wide range of biological activities, and that several of these are particularly relevant to the pathophysiology of uncontrolled inflammation.[74,124] The biology of these effects is complex and may involve a direct action of the *n*-3 PUFA itself, such as regulation of gene expression, or an effect of one of its multiple metabolites, among which are the resolvins, pro-resolving mediators of inflammation.[74] For EPA specifically, studies in preclinical models have demonstrated both neuroprotective and anti-inflammatory effects.[115] Moreover, EPA and/or its metabolites have been found to potently attenuate inflammation in microglial cells, an effect which may be mediated by the down-regulation of proinflammatory cytokine production.[74]

Beyond modulation of inflammation, EPA inhibits the synthesis of prostaglandin E_2, itself an inhibitor of presynaptic serotonin release.[125] In this context, it is pertinent that low brain serotonin levels are intimately associated with marked behavioural consequences typical of depression.[126]

Therapeutic potential of eicosapentaenoic acid in depression

Emerging evidence supports the hypothesis that dietary EPA supplementation may alleviate symptoms of depression, and that such effects may be mediated through its anti-inflammatory actions on microglial cells on the one hand, and through indirect modulation of synaptic serotonin levels on the other. Based on the available evidence, an International Society for Nutritional Psychiatry Research expert panel suggests that 1–2 g per day of EPA (net EPA from EPA/DHA combinations) may be utilized as adjunctive treatment for the potential treatment of major depressive disorder.[127] Given the importance of depression to public health worldwide, the suggestion that a rigorously designed, adequately powered RCT be undertaken to evaluate the efficacy of EPA in attenuating the symptoms of depression is worthy of consideration.

Conclusion

In conclusion, beyond the established indications for icosapent ethyl, there remain other important populations in which to study this safe and well-tolerated drug. A role in cancer is being actively investigated. A potential role in combating COVID-19, supported by early, limited basic science data, is being investigated in clinical trials. Other ongoing trials will also help to explore possible benefits in gastrointestinal disorders, preclinical or early AD, dementia, and the treatment of major depression as an adjunct to antidepressants. These and other future trials will determine whether there will be a role for EPA-based therapy outside of cardiovascular medicine.

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