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Research Article

EFFECTS OF FATTY ACID SPECIES ON NEURONAL INFLAMMATION

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A B S T R A C T

Reducing neuroinflammation is essential for the treatment of various neurologic and autoimmune diseases. The use of dietary components to reduce neuroinflammation is a research topic. Different types of dietary fatty acids affect neuroinflammation. Neuroinflammation in the brain occurs through mediators released from microglia. Among the inflammatory mediators reported to be removed from microglia, proinflammatory cytokines; interleukin (IL)-1β, IL-6, IL-2 and tumor necrosis factor-α and anti-inflammatory cytokines IL-10 and IL-4. Fatty acids divide into three groups according to their carbon chain length. The effect of each fatty acid type on neuroinflammation differs. The neuroprotective effect of SFAs triggers neuroinflammation. Polyunsaturated fatty acids (PUFA) in human neurodegenerative disorders are known. But, each type of PUFA can have different effects.

INTRODUCTION

Microglia are the most abundant mononuclear phagocytes in the central nervous system (CNS), which play an essential role in maintaining normal brain function [1]. Inflammation in the brain occurs through mediators released from microglia. According to current data, microglia play a dual role in immune-mediated brain diseases; In addition to contributing to myelin destruction and lesion formation, they are also accepted to provide myelin regeneration as they suppress inflammation and support tissue repair [2, 3]. Both inflammatory and anti-inflammatory cytokines are released from microglia.

It is known that dietary factors play a key role in metabolism and have an effect on the release of neuroprotective cytokines [4]. The European Society for Clinical Nutrition and Metabolism (ESPEN) has drawn attention to the relationship between Multiple Sclerosis, one of the immune-based and neurodegenerative diseases, and polyunsaturated fatty acid (PUFA) consumption in the guideline for the management of clinical nutrition in neurological diseases. ESPEN suggests with B evidence level that lower amounts of saturated fatty acids (SFA) and higher amounts of PUFA should be consumed to prevent this disease. ESPEN also published in the same guide that omega-3 fatty acids have no effect on the frequency and severity of attacks in Multiple Sclerosis but that omega-6 fatty acids may have possible beneficial effects [5].

In inflammatory diseases of the central nervous system, it is essential to know the pro-inflammatory or anti-inflammatory effects of the foods taken in the diet, which is a continuous and inevitable action regarding the course of the disease. In recent years, studies conducted to determine the effect of fatty acids on neurological disorders have reported that each fatty acid group may have different therapeutic effects in various neurological diseases [6]. It is also known that omega-3 fatty acids and omega-6 fatty acids have both protective and detrimental effects [7].

Microglia and Neuroinflammation

Microglia are the first line of defense at the central nervous system level [8]. Microglia release many soluble factors such as chemoattractants, pro-inflammatory and anti-inflammatory cytokines, and neurotrophic factors when activated [9,10,11]. Inflammatory cytokines released from microglia are interleukin (IL)-6, tumor necrosis factor-α (TNF-α), IL-1β and IL-17[12,13]. It has been observed that TNF-α and IL-1β, inflammatory cytokines released from microglia, increase glutamate-mediated excitatory neurotransmitters[14]. Chronic activation of microglia can lead to neurodegenerative diseases.

Neuroinflammation and Fatty Acid Metabolism

With advances in medicine and technological approaches, signaling molecules called bioactive lipids were discovered. Bioactive lipids are determinants of cellular events such as cell growth, proliferation and cell apoptosis. In addition, it acts as a regulator of cyclooxygenase (COX) pathways to regulate inflammation and microglia-mediated immune processes. Bioactive lipids regulate many metabolic events using complex pathways. Bioactive lipids regulate proinflammatory eicosanoid production, neuron apoptosis, monitoring of

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microglial cell activity and central nervous system homeostasis [15].

Approximately 60% of the mammalian brain consists of phospholipids [16]. In particular, docosahexaenoic acid (DHA) and arachidonic acid (AA), provide 25% of the fatty acids in the brain. DHA constitutes 90% of the total amount of omega-3 in the brain. Dietary consumption of α-linolenic acid (ALA) becomes vital for synthesizing these long-chain fatty acids in the body [17].

Grades of long-chain PUFAs in the brain are associated with the amount of PUFA in the diet and long-chain PUFA. Eicosapentaenoic acid (EPA), DHA, and AA have been recognized as docosanoids and many lipid eicosanoids that are actively involved in regulatory responses in inflammation. Bioactive lipids include eicosanoids, prostaglandins, prostacyclins, thromboxanes, leukotrienes, etc. All of these compounds have been reported to be crucial for regulating inflammation, as they have both inflammatory and anti-inflammatory effects and modulate immune responses [18].

Eicosanoids, a class of bioactive lipid mediators, are biologically active, oxygenated AA metabolites. AA is a PUFA with 20 carbon atoms and four double bonds (C20: 4). It consists of linoleic acid (C18 : 2) which adds two carbons to its chain and further desaturation (double bond accumulation). These metabolic processes occur via COXs, lipoxygenases (LOXs) and cytochrome P450 enzyme systems. The fatty acids that are the substrates of these enzyme systems are arachidonic acid (20:4, omega-6), linoleic acid (18:2, omega-6), gamma-linolenic acid (18:3, omega-6), ALA (18:3, omega-3), eicosatetraenoic acid (20:5, omega-3) and docosahexaenoic acid (20:5, omega-3) [19,20].

In mammals, linoleic acid is obtained strictly from food sources. Of the approximately 10 g of linoleic acid ingested daily, only about 1 mg is accepted as the end product of AA metabolism. Following its formation, AA esterifies to cell membrane phospholipids [20].

PUFAs, which affect neuroinflammation, can also show their effectiveness through the endocannabinoid system. DHA, omega-3 fatty acid and AA, omega-6 fatty acid plays a significant role in the production of endocannabinoids (eCB), which have to regulate effects on the central nervous system and associate with anabolic and catabolic enzymes. The endocannabinoid system includes its receptors (KB1 and KB2). The function of eCB is to remain body energy homeostasis through nutrient availability discovery in discriminating areas of the central nervous system [17]. It has been shown in a mouse study that dietary DHA and AA affect KB1 receptor synthesis [21]. AA determines the production of eCB enzymes, which plays a role in the organizing of secretion of neuroinflammatory cytokines by microglia and astrocytes. The high amount of PUFA in the Western diet can cause overstimulation of the endocannabinoid system and cause neuroinflammation[22].

Classification of Fatty Acids

Fatty acids divide into three groups according to their carbon chain length. Those with 2-4 carbons are short-chain fatty acids, those with 6-10 carbons are medium-chain, and those with 12-28 long-chain fatty acids. Since fatty acids in nature synthesize from double carbon atoms in lipogenesis, they usually contain an even number of carbons. The most common fatty acids have 14-22 carbon atoms [23].

When fatty acids classify according to the number of double bonds in their carbon chains, they divide into three. Those with no double bonds in the carbon chain classify as SFA, those with one single, double bond as monounsaturated fatty acids (MUFA), and those with two or more double bonds classify as polyunsaturated fatty acids (PUFA). PUFA divide into two groups, omega-3, and omega-6, according to the carbon order in which the double bond locate. Omega-9 fatty acids are a subgroup of MUFA [23].

Saturated fatty acids and their effect on neuroinflammation

All carbons in the hydrocarbon chain of saturated fatty acids saturate with hydrogen. Since no non-bonding carbon atom exists in the carbon chain, they cannot form double bonds. Most of the animal fats and some oils of vegetable origin fall into this group [23].

Studies using a microglial cell line show that SFA can stimulate microglial activity. It trigger to the production of proinflammatory mediators that may subscribe to neuronal death [24].

Unsaturated fatty acids and their effect on neuroinflammation

Unsaturated fatty acids have unsaturated carbons in the hydrocarbon chain. Carbon atoms not bond in the carbon chain can form double bonds. Most of the oils of vegetable origin fall into this group. Unsaturated fatty acids divide into two groups PUFA and MUFA [23].

Monounsaturated fatty acids and neuroinflammation

Fatty acids have a single, double bond in the hydrocarbon chain. Examples include oleic acid (18:1, omega-9), vaccenic acid (18:1), and palmitoleic acid (16:1). The best dietary sources of monounsaturated fatty acids (MUFA) are sunflower, olive, peanut, avocados, canola, and nuts. MUFA is also part of fat, most of which is animal fat, such as fat from beef, pork, chicken, etc.[25].

In the Dietary Guidelines for Americans 2015-2020, the replacement of SFAs with MUFA and PUFA is recommended to reduce the risk of chronic disease [25].

The beneficial effects of omega-9 fatty acids on health are known [26]. Pure olive oil, which is rich in omega-9 fatty acids, reduces the risk of death, cardiovascular disease and related death risk, and the risk of damage from cancer, Parkinson's, and Alzheimer's diseases [27-28]. In this study, the effectiveness of the tocopherol family and oleic acid against oxidative damage in mitochondrial and peroxisomal dysfunction of BV-2 microglial cells induced by 7-ketocholesterol, a lipid peroxidation product, was investigated. As a result of the study, it is reported that a protective effect against neurodegeneration can achieve with dietary intervention (tocopherols, fatty acids, polyphenols, *etc.*) [29]. Similarly, the effectiveness of omega-3 and omega-9 fatty acids investigate the antioxidant capacity against the oxidant effect of 7-ketocholesterol. In this study, inhibition of cell growth of microglia cells, mitochondrial dysfunctions, overproduction of reactive oxygen species and lipid peroxidation, increased plasma membrane permeability were investigated. As a result of the study, it was concluded that dietary antioxidants

(docosahexaenoic acid and oleic acid) could inhibit neurodegeneration by suppressing inflammation [30].

The neurotherapeutic effects of omega-9 monounsaturated fatty acid oleic acid (OA), one of the major element of the Mediterranean diet, are known [31]. ESPEN has drawn attention to the relationship between Multiple Sclerosis, one of the neurodegenerative diseases, and PUFA consumption in its guideline for the management of clinical nutrition in neurological diseases. They suggested with B evidence level that lower amounts of SFA and higher amounts of PUFA should be consumed to prevent this disease. In this guide of ESPEN, there is no notification about MUFA. While there are studies on the antioxidant effects of MUFA, its effects on neurodegeneration are still open to research [5].

Anti-inflammatory effect of oleic acid is currently the subject of literature. In a study investigating the efficacy of oleic acid and anthocyanin in cardiometabolic diseases in 2021, it was reported that the co-administration of these two bioactive nutrients was effective in reducing protein gene expressions in inflammation-related pathways [32].

It has been proven that dietary palmitic acid, omega-6 fatty acid, can affect neuronal and microglial homeostasis, and excessive consumption can increase neuroinflammation. It is reported that oleic acid added to cultures with mixed microglia and neurons reduces the inflammatory effect of palmitic acid [33].

Polyunsaturated fatty acids and neuroinflammation

Polyunsaturated fatty acids are divided into two main classes, omega-3 fatty acids and omega-6 fatty acids. Omega-3 fatty acids the third carbon from the methyl end of the carbon chain, respectively, has a double bond. Food in rich omega-3 are flaxseed, sea products and fish. ALA, EPA and DHA are essential omega-3 fatty acids Because of that ALA includes 18 carbons, EPA 20 carbons and DHA 22 carbons. EPA and DHA are considered “long-chain” omega-3s [34].

Omega-6 fatty acids, the sixth carbon from the methyl end of the carbon chain, respectively, have a double bond. Foods rich in omega-6 fatty acids can be listed as walnuts, sunflower oil, grape seed oil, corn oil, and soybean oil [23].

Omega-3 and omega-6 fatty acids have different roles in neural development[17]. Omega-3 fatty acids reduce gene expressions of proinflammatory cytokines, microglia cell death and neuronal inflammation by participating in eicosanoid synthesis. It has been reported that it may have a curative effect on recurrent chronic neurological diseases caused by neuroinflammation[35,36].

The balance of omega-6 and omega-3 fatty acids is necessary for homeostasis and normal development throughout the life cycle [37]. The change in the diet's omega-6/omega-3 fatty acids ratio causes different metabolic effects. Studies to understand the balance between fatty acids and the metabolic effects of this balance are still the subject of research today. Other diet types contain different fatty acid ratios. The ratio between fatty acids omega-6/omega-3=15-20/1 indicates a 'Western-style diet' [22, 37, 38]. The high omega-6/omega-3 ratio causes cardiovascular disease, obesity, diabetes, cancer and inflammatory autoimmune disease risk [39,40]. While the ratio of omega-6/omega-3=13/1 is associated with the presence of chronic disease, it has been reported that reducing the ratio between fatty acids to 7/1 protects against cancer and cardiovascular diseases [41]. Additionally, this ratio is one of the healthy eating goals [22]. It has been reported that the ratio of omega-6/omega-3=4/1 reduces cardiovascular deaths by 70% [39]. The omega-6/omega-3=2/1 ratio has been observed to suppress inflammation in inflammatory diseases. In other studies, the rate of suppressing inflammation was reported to be in the range of 1-3/1 [39, 42]. There are different nutritional models used in neurodegenerative diseases for the management of neuroinflammation.[43]

In studies examining the relationship between omega-6/omega-3 ratio and inflammation, the low omega-6/omega-3 ratio has significant clinical and laboratory effects. The low omega-6/omega-3 ratio suppresses systemic inflammation, prevents endothelial activation in cardiovascular diseases, and improves serum biochemical test abnormalities in acute and chronic diseases, sepsis, chronic renal failure and acute pancreatitis. It is predicted that by maintaining the appropriate balance between fatty acids, inflammation in metabolism can be reduced and even nutritional therapy, including dietary fatty acid regulation can replace oral aspirin therapy in the following years [44].

CONCLUSION

Fatty acids are classified according to the carbon chain length and the number of double bonds and the position of the double bond in the carbon chain. The effect of each fatty acid type on neuroinflammation differs. SFAs trigger neuroinflammation, while PUFAs can have different effects within themselves. While omega-3 PUFAs suppress neuroinflammation, omega-6 PUFAs generally trigger neuroinflammation. Although MUFAs do not have an apparent impact on neuroinflammation, they are effective in reducing the neuroinflammation caused by PUFAs.

Considering the effects of fatty acids on neuroinflammation, the nutritional model can be created for inflammatory diseases.

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