Current Topics

Lipid Mediators and Pain Signaling

Unsaturated Fatty Acids and Pain

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Fatty acids, which are the essential nutrients for humans, are an important source of energy and an essential component of cell membranes. They also function as signal transduction molecules in a range of biological phenomena. Recently, an increasing number of physiologic and pharmacologic reports on fatty acids have improved our understanding of the association of fatty acids with certain diseases. It has also become apparent that functional properties of fatty acids are modulated by factors such as the amount of individual fatty acid intake and their distribution among organs. Recently, the functional relationship between polyunsaturated fatty acids and pain has been the focus of many studies. Both basic and clinical studies have shown that a dietary intake of *n*-3 series polyunsaturated fatty acids results in a reduction in the pain associated with rheumatoid arthritis, dysmenorrhea, inflammatory bowl disease, and neuropathy. In addition, levels of *n*-6 series polyunsaturated fatty acids are high in patients with chronic pain. These results indicate that polyunsaturated fatty acids play a vital role in pain regulation. In this review, we summarize a number of basic and clinical studies on polyunsaturated fatty acids and their association with pain.

Key words polyunsaturated fatty acid; pain; antinociception

1. INTRODUCTION

Fatty acids are an essential nutrient for humans and are involved in a variety of biological functions. For example, lipids are an important energy source, and phospholipids and cholesterols derived from fatty acids are structural components of cell membranes.[1] In addition, fatty acid metabolites, such as prostaglandins, thromboxanes, and leukotrienes, play crucial roles as bioactive lipophilic signaling molecules.[2]

Fatty acids are classified as saturated fatty acids that have no double bonds or unsaturated fatty acids that have double or triple bonds. Based on the number of double bonds present, unsaturated fatty acids are further divided into monounsaturated fatty acids with only one double bond and polyunsaturated fatty acids (PUFAs) with two or more double bonds (Fig. 1). PUFAs are further grouped into the following: *n*-3 series (the first double bond is between C3 and C4 from the methyl end of the carbon chain) of fatty acids represented by α-linolenic acid (C18:3), eicosapentaenoic acid (EPA, C20:5), and docosahexaenoic acid (DHA, C22:6); and *n*-6 series (the first double bond is between C6 and C7 from the methyl end of the carbon chain) of fatty acids represented by linoleic acid (C18:2), γ-linolenic acid (C18:3), dihomo-γ-linolenic acid (C20:3), and arachidonic acid (C20:4)[3] (Fig. 2).

Saturated and monounsaturated fatty acids are used as energy substrates, while PUFAs are precursors for phospholipids and prostaglandins. Dietary deficiency in linoleic acid and α-linolenic acid causes a series of health problems including skin disorders, infertility, and lowered immunity.[4] Known physiological functions of *n*-3 PUFAs are antioxidation,[5] antiinflammation,[6] and cardiovascular and neuronal protection.[7] Moreover, clinical studies found therapeutic effects of *n*-3 PUFAs against the risk of cardiovascular events, attention deficit hyperactivity disorder,[8] Alzheimer's disease,[9] depression,[10,11] and various other degenerative

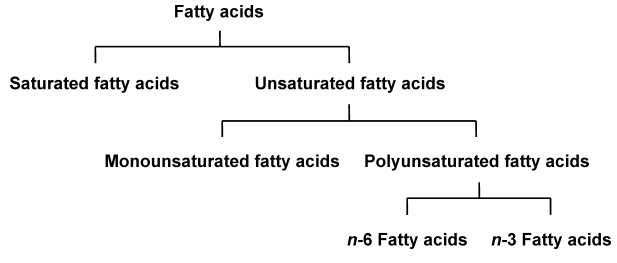

Fig. 1. Classification of Fatty Acids

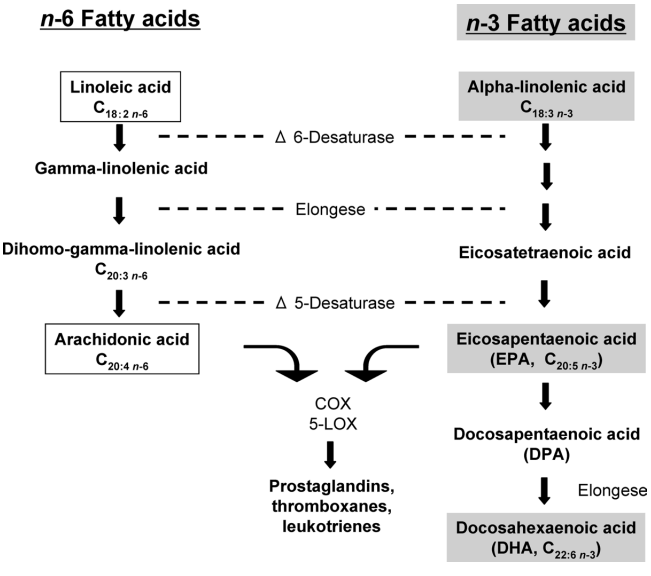

Fig. 2. Biosynthesis of Principal Polyunsaturated Fatty Acids

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neurological disorders.[12] Thus, it has become apparent that *n*-3 PUFAs are involved in a variety of physiological functions.

A number of physiological and pharmacological studies indicated that the physiological functions of *n*-3 PUFAs are influenced by the amount of intake and subsequent cellular distribution of individual fatty acids. As one of their diverse functions, fatty acids, especially unsaturated fatty acids, we are shown to regulate pain. Conventionally, nonopioid analgesics such as nonsteroidal antiinflammatory drugs, opioid analgesics such as morphine, and supplementary analgesics have been used to relieve pain. However, some patients develop drug resistance, and therefore novel analgesics and/or supplemental analgesics are needed. In this review, we focus on the association between unsaturated fatty acids and pain.

2. DIETARY FATS AND PAIN

Dietary fats are digested and absorbed in the small intestine and enter the circulation as fatty acids through lacteals. The fatty acids are then stored in adipose tissue as triglycerides, used by the liver and skeletal muscles as needed, and oxidatively decomposed. Basic studies in animals showed that fatty acids modulate acute and chronic nociceptive responses.[13,14] In mice with partial sciatic nerve injury, dietary fatty acids (such as those from corn oil and soy oil) also suppressed mechanical allodynia and thermal hyperalgesia.[15,16] Such mechanisms are thought to involve interactions between dietary lipids and proteins. When the dietary composition of linoleic acid, an *n*-6 PUFA, and α-linolenic acid, an *n*-3 PUFA, was altered, a group with a diet containing a large amount of α-linolenic acid exhibited reduced thermal hyperalgesia compared with a group that received a large amount of linoleic acid.[17] This suggests a close association of *n*-3 PUFAs with pain control.

3. *n*-3 PUFAs AND PAIN

n-3 PUFAs are abundant in fish oil. They function as an essential fatty acid in various physiologic reactions and play vital roles in homeostasis. Recently, a possible involvement of *n*-3 PUFAs in pain control has gathered considerable attention because numerous studies have reported a regulatory role of *n*-3 PUFAs against inflammatory pain associated with rheumatoid arthritis,[18—20] dysmenorrhea,[21] and inflammatory bowel disease.[22] *n*-3 PUFAs suppress the production of inflammatory cytokines and eicosanoids,[23,24] and such antiinflammatory action by PUFAs is believed to result in pain suppression. In addition, *n*-3 PUFA intake blocks the activity of mitogen-activated protein kinase,[25] which is involved in the modulation of central sensitization induced by inflammatory and neuropathic pain, suggesting another potential pathway to inhibit pain transmission.[26,27] Interestingly, intake of α-linolenic acid, one of the *n*-3 PUFAs, has been reported to suppress the production of lysophosphatidic acid, a factor strongly related to the development of neuropathic pain.[28]

Docosahexaenoic acid (DHA), one of the *n*-3 PUFAs, has a 22-carbon chain with six double bonds. In humans, DHA is neither synthesized nor interconverted from other *n*-3 or *n*-6 fatty acids, and therefore the amount of DHA in the human body reflects the amount acquired from dietary sources such as fish oil. A large proportion of DHA exists as membrane phospholipids, especially phosphatidylethanolamine and phosphatidylserine, in the cortical synaptic membranes, retina, and neurons of the central nervous system.[29] DHA is also found in the heart as well as in sperm and breast milk.[30]

We have proposed the possible involvement of DHA in pain control because of its dose-dependent antinociceptive effects observed in various pain tests[31] and its calming effect on neuropathic pain (Fig. 3). The physiological and pharmacological functions of DHA which support our proposal include 1) an antiinflammatory effect *via* the suppression of the arachidonic acid cascade,[32] 2) inhibition of voltage-gated sodium channels,[33,34] 3) agonistic action toward transient receptor potential vanilloid 1 (TRPV1) that is closely associated with the onset of inflammation,[35] and 4) inhibition of calcium channels.[33,36] Furthermore, we have elucidated that one of the actions contributing to the antinociceptive mechanisms of DHA is not performed directly on the opioid receptor, but indirectly through the release of an endogenous opioid peptide β-endorphin[37] (Figs. 4, 5).

Recently, the G-protein-coupled receptor (GPCR) deorphanizing strategy has successfully identified multiple receptors for free fatty acids (FFAs).[38] Interestingly, among these receptors, the G-protein receptor (GPR) 40[39] and GPR120 are activated by long-chain FFAs such as EPA and DHA.[40] GPR40, which is preferentially expressed in pancreatic β-cells, mediates insulin secretion,[41] and GPR120, which is

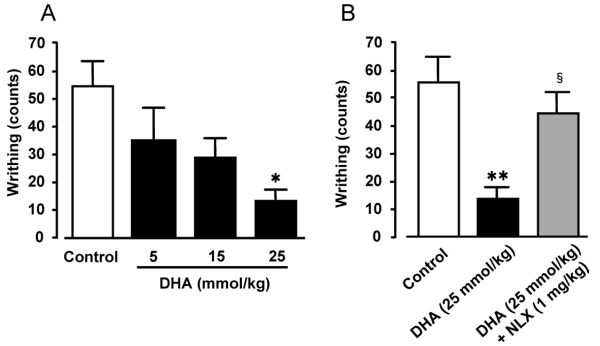

Fig. 3. Antinociceptive Effect of DHA on Acetic Acid Writhing Behavior in Mice (A) and Effect of Naloxone on DHA-Induced Antinociceptive Activity in Mice (B)

Data are shown as mean±S.E.M. (n=8). $^{**}p<0.01$, $^{*}p<0.05$ compared with the control group (one-way ANOVA and Dunnett's test). $^{\S}p<0.05$ compared with the 25 mmol/kg DHA-treated group (one-way ANOVA and Scheffe's test). From Nakamoto *et al.*[31]

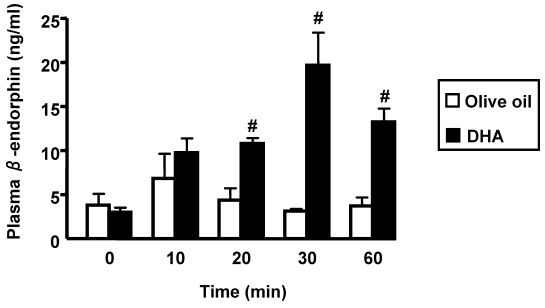

Fig. 4. Time–Course of the Plasma Levels of β-Endorphin after DHA Administration

$^{\#}p<0.05$ compared with the olive oil-treated group (one-way ANOVA and Scheffe's test). Modified from Nakamoto *et al.*[37]

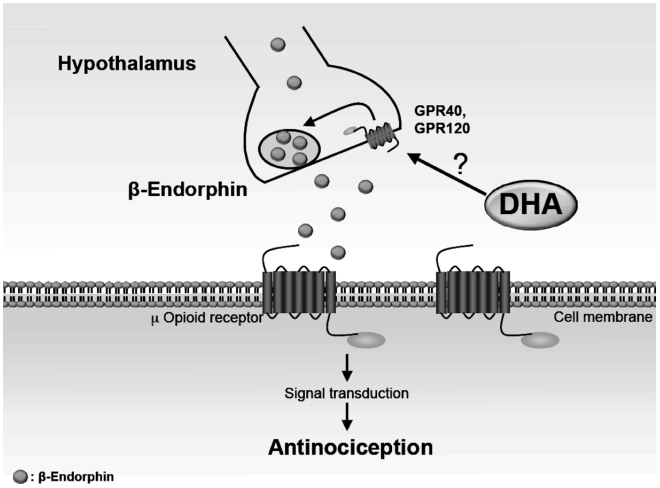

Fig. 5. Hypothetical Scheme of β-Endorphin Release in DHA-Induced Antinociception

The scheme outlines the potential mechanism of β-endorphin release in DHA-induced antinociception in this system.

abundantly expressed in the intestine, promotes insulin secretion[42] and the secretion of glucagon-like peptide-1[43] and cholecystokinin.[44] Accordingly, these receptors may contribute to regulating the secretion of opioid peptides such as β-endorphin. In a more recent study, we have demonstrated that the intracerebroventricular injection of GW9508, a GPR40- and GPR120-selective agonist, has significant antinociceptive effects in the formalin test in mice (unpublished data). However, the precise molecular function of GPR40 and GPR120 in the mouse brain is still unclear. Further studies on the relationship between pain and GPR40 or/and GPR120 should be of considerable interest.

With regard to clinical studies of *n*-3 PUFAs, a meta-analysis of 17 randomized control trials by Goldberg and Katz demonstrated the association of *n*-3 PUFAs with inflammatory pain due to rheumatoid arthritis, dysmenorrhea, and inflammatory bowl disease.[45]

4. METABOLITES DERIVED FROM *n*-3 PUFAs AND THEIR ASSOCIATION WITH PAIN

The beneficial effects of *n*-3 PUFAs on various inflammatory diseases have been explained by the antagonistic action of *n*-3 PUFAs toward the arachidonic acid cascade.[46,47] However, recent studies have demonstrated that, when metabolized by cyclooxygenase and lipoxygenase, DHA and EPA are converted into powerful antiinflammatory molecules, the resolvins and protectins.[48] Schwab *et al.* reported that resolvin E1 and protectin D1, *n*-3 PUFA-derived mediators, activated a recovery process of inflammation.[49] In addition, Xu *et al.* have recently reported that resolvin E1 and resolvin D1 suppressed inflammatory pain.[50] The mechanism of action in this case is believed to be due to resolvin reacting with chem R23, a receptor for resolvin, and suppressing the expression of extracellular signal-regulated kinase and neuronal excitation *via* *N*-methyl-D-aspartate.[50] Epoxy docosapentaenoic acid (EpDPE) and epoxy eicosatetraenoic acid (EpETE) derived from DHA and EPA, respectively, by cytochrome P450 also appear to reduce inflammatory pain.[51] Interestingly, a clinical study showed that the long-term intake of *n*-3 PUFAs

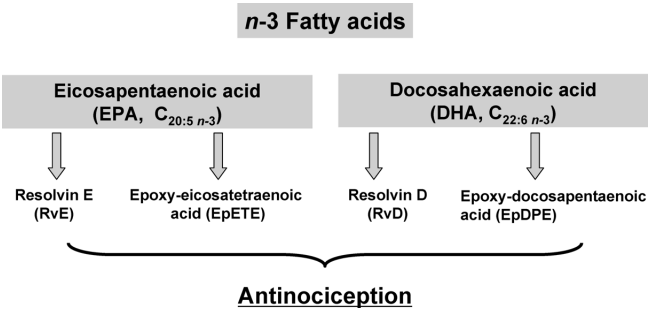

Fig. 6. Metabolites Derived from *n*-3 Polyunsaturated Fatty Acids and Their Association with Pain

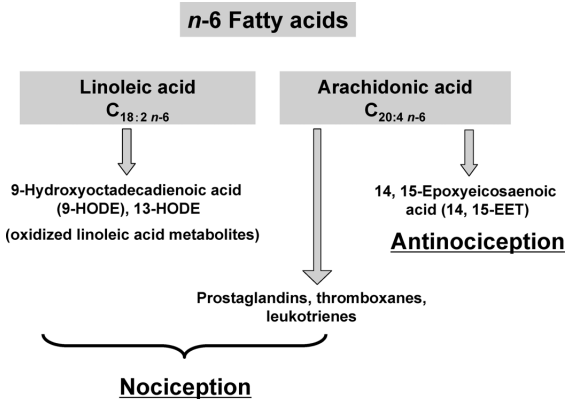

Fig. 7. Metabolites Derived from *n*-6 Polyunsaturated Fatty Acids and Their Association with Pain

inhibits neuropathic pain.[52] These findings indicate that the intake of *n*-3 PUFAs is highly effective in reducing inflammatory and neuropathic pain and that the metabolites of fatty acids are involved in such activity (Fig. 6).

5. *n*-6 PUFAs AND PAIN

n-6 PUFAs are generally considered bad for the health because prostaglandins, inflammatory eicosanoids, and inflammatory cytokines, such as interleukin-1 and -6, are derived from *n*-6 PUFAs. For example, analysis of serum *n*-3 and *n*-6 PUFA composition in patients with the complex regional pain syndrome (a neuropathic pain syndrome associated with autonomic nervous and immune abnormalities) revealed that these patients had significantly increased levels of dihomo-γ-linolenic acid (C20:3) and docosatetraenoic acid (C22:4).[53] Patwardhan *et al.*[54] also reported that the 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE, oxidized linoleic acid metabolites, induced pain. Furthermore, these metabolites, formed upon the exposure of cell membranes to noxious heat, are suggested to activate TRPV1 and contribute to the thermal responsiveness of this channel.[55] For this reason, *n*-6 PUFAs have been considered novel factors involved in the molecular mechanism that induces pain.

On the other hand, some studies reported that *n*-6 PUFAs are associated with the suppression of pain. Arachidonic acid, one of the major *n*-6 PUFAs, has been studied intensively because it is an important structural component of cell membranes and a precursor molecule for prostaglandins and leukotrienes that are associated with blood pressure, inflam-

mation, and platelet aggregation. Epoxyeicosatrienoic acid (EET), a metabolite of arachidonic acid formed by CYP2J and CYP2C, members of the cytochrome family, has been known for its antihypertensive effects and inhibition of platelet aggregation. Recently, though, it has become apparent that the metabolites 14- and 15-EET also play a role in pain inhibition.[56] Furthermore, an inhibitor of soluble epoxy hydrolase which hydrolyzes epoxyeicosatrienoic acid was reported to show an antinociceptive effect.[57] These studies thus demonstrated that *n*-6 PUFAs, such as arachidonic acid, both inhibit and induce pain transmission (Fig. 7).

6. CONCLUSION

The important functional role of fatty acids in both the onset and suppression of pain has become increasingly apparent in recent years. In particular, the physiological and pharmacological mechanisms of *n*-3 PUFAs have been studied intensively from a broad perspective, and the safety of PUFAs has also been established. Therefore, the application of *n*-3 PUFA in many clinical areas is expected to increase in the future. By vigorously conducting research on fatty acids as novel molecules that regulate pain, we believe that it is possible to reveal the mechanisms involved in the onset of intractable pain and develop new drugs that can relieve such pain.

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