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Research article

Docosahexaenoic acid reduces cellular inflammatory response following permanent focal cerebral ischemia in rats

Cheng-Yi Chang [a 1], Yu-Hsiang Kuan [b 1], Jian-Ri Li [c], Wen-Ying Chen [d], Yen-Chuan Ou [c], Hung-Chuan Pan [e], Su-Lan Liao [f], Shue-Ling Raung [f], Chen-Jung Chang [g], Chun-Jung Chen [f h i j k]

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Abstract

Cellular inflammatory response plays an important role in ischemic brain injury and anti-inflammatory treatments in stroke are beneficial. Dietary supplementation with docosahexaenoic acid (DHA) shows anti-inflammatory and neuroprotective effects against ischemic stroke. However, its effectiveness and its precise modes of neuroprotective action remain incompletely understood. This study provides evidence of an alternative target for DHA and sheds light on the mechanism of its physiological benefits. We report a global inhibitory effect of 3 consecutive days of DHA preadministration on circulating and intracerebral cellular inflammatory responses in a rat model of permanent cerebral ischemia. DHA exhibited a neuroprotective effect against ischemic deficits by reduction of behavioral disturbance, brain infarction, edema and blood–brain barrier disruption. The results of enzymatic assay, Western blot, real-time reverse transcriptase polymerase chain

reaction and flow cytometric analysis revealed that DHA reduced central macrophages/microglia activation, leukocyte infiltration and pro-inflammatory cytokine expression and peripheral leukocyte activation after cerebral ischemia. In parallel with these immunosuppressive phenomena, DHA attenuated post-stroke oxidative stress, c-Jun N-terminal kinase (JNK) phosphorylation, c-Jun phosphorylation and activating protein-1 (AP-1) activation but further elevated ischemia-induced NF-E2-related factor-2 (Nrf2) and heme oxygenase-1 (HO-1) expression. DHA treatment also had an immunosuppressive effect in lipopolysaccharide/interferon-γ-stimulated glial cultures by attenuating JNK phosphorylation, c-Jun phosphorylation and AP-1 activation and augmenting Nrf2 and HO-1 expression. In summary, we have shown that DHA exhibited neuroprotective and anti-inflammatory effects against ischemic brain injury and these effects were accompanied by decreased oxidative stress and JNK/AP-1 signaling as well as enhanced Nrf2/HO-1 expression.

Introduction

Ischemic stroke often causes irreversible brain damage. To date, several mechanisms of ischemic brain injury have been proposed, such as excitotoxicity, edema, apoptosis, oxidative stress and inflammation [1], [2], [3], [4]. Ischemic stroke triggers a complex cellular response which includes both the activation of local glial cells and the recruitment of inflammatory cells from the systemic circulation. There is compelling evidence to suggest that the activation of resident glial cells, the infiltration of leukocytes and the consequences of pro-inflammatory and neurotoxic mediator production are detrimental in stroke-associated secondary brain damage and contribute to infarct evolution [5], [6]. The inhibition of post-stroke-associated pro-inflammatory mediator production has been shown to attenuate ischemic brain injury [7], [8], [9]. Supporting evidence further shows that deficiency or neutralization of lymphocytes or leukocytes leads to diminished infiltration of leukocytes, decreased pro-inflammatory mediator production and reduced brain infarction [10], [11], [12], [13]. These studies suggest that in addition to its role in host defense mechanisms, cellular and humoral inflammation may contribute significantly to the pathogenesis and outcome of ischemic stroke. Therefore, inflammatory mechanisms which are activated after brain ischemia might play an important role in the pathogenesis of brain injury secondary to ischemia. Such mechanisms are the target of ongoing efforts in translational cardiovascular research.

Fatty acids from fish oil are emerging as powerful yet safe disease-modifying nutrients. There is considerable research indicating that dietary supplementation of fish oil or ω-3 polyunsaturated fatty acids (PUFAs) has a beneficial effect on the ischemic brain. The

existing evidence indicates that the ischemic neuroprotective effect of PUFAs in chronic dietary supplementation or single injection prior to injury involves stabilization of membrane integrity, improvement of local cerebral blood flow, blockade of glutamatergic transmission, reduction of eicosanoid production, enhancement of anti-oxidative capacity and/or induction of chaperon proteins [14], [15], [16], [17]. There is considerable evidence highlighting the importance of anti-inflammatory effect in ischemic brain protection caused by ω-3 PUFAs. Accumulating studies suggest that potential mechanisms underlying the anti-inflammatory actions of ω-3 PUFA include competitive inhibition of conversion of arachidonate to pro-inflammatory lipid intermediates, serving as endogenous ligands for peroxisome proliferators activated receptor-γ (PPAR-γ), generation of anti-inflammatory lipid mediators such as resolvins and protectins, interruption of NF-κB signaling, activation of AMP-activated protein kinase (AMPK) and up-regulation of nuclear factor erythroid 2-related factor 2 (Nrf2) [9], [18], [19], [20]. Although experimental evidence has shown that ω-3 PUFAs have clinical applications, the anti-inflammatory mechanisms by which they protect the brain have yet to be fully elucidated.

In view of the aforementioned properties of ω-3 PUFAs, their anti-inflammatory effect has been postulated to be a crucial mechanism in their neuroprotective effect against stroke. Because fish oil is a major source of docosahexaenoic acid (DHA, 22:6), it can be hypothesized that DHA is a potential nutraceutical candidate for treatment of ischemic stroke. Previously, we found that pre-treatment with DHA attenuated postischemic brain injury involving the inactivation of damaging mechanisms and activation of survival mechanisms [21]. To extend the scope of relevant studies, we therefore wanted to examine whether DHA pre-treatment would alleviate post-stroke inflammation by reducing cellular inflammatory response after experimental permanent focal cerebral ischemia, and if it did, to determine the regulatory characteristics of the beneficial cellular inflammatory response.

Section snippets

Animals and cerebral ischemia

The Animal Experimental Committee of Taichung Veterans General Hospital approved the protocol of the animal study. Male Sprague–Dawley rats (300–350 g) were randomly allocated to two experimental groups. The final number of rats included for analysis was shown as indicated. The sham-operated group was divided into vehicle treatment (8 animals) and DHA treatment (8 animals) subgroups. The ischemia group was divided into vehicle treatment (62 animals) and DHA treatment (62 animals) subgroups. …

DHA reduces permanent cerebral ischemia-induced brain damage

There is considerable research indicating that single or repeated administration of fish oil or ω-3 PUFA has a beneficial effect on the ischemic brain in rodents [14], [15], [16], [17]. Previously, we found that single or repeated administration of DHA at a concentration of 500 nmol/kg prior to ischemia had a beneficial effect against focal cerebral ischemia/reperfusion injury involving strengthening of survival mechanisms and attenuation of damaging mechanisms [21]. To substantiate these …

Discussion

There are multiple interrelated mechanisms that cause progressive brain damage after the onset of ischemic stroke. Among the proposed mechanisms, inflammatory response not only has a fundamental role in the pathophysiology of cerebral ischemia, but also is considered to be a risk or trigger factor for stroke [5], [34], [35]. A growing body of evidence shows that inhibition of the inflammatory response may provide effective, preventive or therapeutic interventions to reduce cerebral ischemic …

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1 Cheng-Yi Chang and Yu-Hsiang Kuan contributed equally.

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