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The role of polyunsaturated fatty acids: The possibility of diet intervention in Parkinson's disease

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Abstract: Parkinson's disease (PD) is a prevalent neurodegenerative illness that causes a gradual loss of dopaminergic (DA) neurons in the substantia nigra (SN). The pathophysiology of PD is still unknown, but unusual lipid metabolism has just been discovered as one of the major variables linked with the disease. foundation and practical guidelines for the prevention and treatment of PD. This article discussed the role of polyunsaturated fatty acids (PUFAs) in the pathogenesis of PD, compared the effects of omega-3 (ω-3) and omega-6 (ω-6) in PD, analyzed the treatment mechanism and methods of ω-3 PUFAs in PD, and proposed new ideas for early intervention of PD. This paper first introduced the classification and source of lipid acids, then analyzed the regulatory role of PUFAs in the pathological process of PD, and then elaborated the neuroprotective effects of ω-3 PUFAs on PD, including anti-inflammation, anti-apoptosis, anti-oxidation, promoting neuron growth and differentiation, improving neurotransmitter balance. Finally, this paper proposes some dietary intervention suggestions, such as increasing the intake of ω-3 and reducing the intake of ω-6, in order to maintain the balance of lipid metabolism and delay the progression of PD. This paper aims to provide a new theoretical basis and practical guidance for the prevention and treatment of PD.

1. Introduction

PD is the most common neurodegenerative condition after Alzheimer's disease. The gradual loss of DA neurons in the SN is the main pathogenic hallmark of PD. This disorder is characterized by motor and non-motor symptoms and involves multiple cellular abnormalities, including α-synuclein (α-syn) accumulation, oxidative stress, mitochondrial dysfunction, loss of protein homeostasis, and autophagy impairment. Despite the cardinal motor symptoms of tremor, bra dyskinesia, and rigidity [1], a variety of non-motor symptoms emerge and influence the quality of life in PD patients throughout time. Furthermore, in recent years, lipid metabolism abnormalities have been relevant in PD pathogeny, and lipid metabolism manipulation has become a feasible strategy to treat the disease [2-4].

A study found that consumption of unsaturated fatty acids was inversely related to the risk of PD [5]. Another research has showed that unsaturated fatty acids cause substantial cytotoxicity in the DA nerve system[6]. As can be seen, not all unsaturated fatty acids are useful to PD sufferers. Maintaining the equilibrium of unsaturated fatty acids in the body may thus be a method of treating PD. ω-3

PUFAs have been widely linked to a beneficial impact against a variety of neurodegenerative diseases[7]. ω-3 PUFAs supplementation reduces behavioral and neurochemical deviations caused by 6-OHDA, indicating a potential neuroprotective action[8]. The precise mechanism by which ω-3 PUFAs effect PD is unknown; despite this, there is a dearth of thorough review in this area. This paper reviewed the significance of unsaturated fatty acid dysregulation in the pathological process of PD, distinguished between beneficial and harmful unsaturated fatty acids for PD, discussed the mechanism and methods of using PUFAs (such as ω-3) to treat PD, and provided novel insights for PD early intervention.

2. Category of fatty acids

According to the number of carbon atoms, fatty acids can be classified as short-chain fatty acids (SCFAs; 1–6 carbons), medium-chain fatty acids (MCFAs; 7–12 carbons), or long-chain fatty acids (LCFAs;>12 carbons). They are naturally occurring compounds that take part in cellular metabolism and can be found in both plant and animal tissues [9]. Based on the quantity of unsaturated double bonds, they can also be classified as saturated fatty acids (SFAs; no double bonds), monounsaturated fatty acids (MUFAs; one double bond), and polyunsaturated fatty acids (PUFAs; more than one double bond). SFAs are found in meat, eggs, and dairy products, MUFAs are mostly found in olive oil, rapeseed oil, nuts, and seeds [10]. PUFAs contain ω-3 and ω-6. The abbreviations "ω-3″ and "ω-6″ used for unsaturated fatty acids reflect the location of the first double bond after the methyl carbon atom on the distal end of the fatty acid chain. ω-3 are abundant in salmon, tuna, fish oil (FO) supplements, chia seeds, walnuts, etc., and ω-6 are mostly found in vegetable oils, sunflower seeds, and soybeans, for example [11]. We mostly talk about PUFAs. Table 1 displays the classification and sources of unsaturated fatty acids.

Table 1: Classification of unsaturated fatty acids

Unsaturated fatty acids	Brief name	Abbreviation (C:D *ω*-X)[1]	Dietary source
MUFA			
Palmitoleic acid	PA	16:1 *ω*-7	Fatty fish, olive oil etc.
Oleic acid	OA	18:1 *ω*-9	Olive oil etc.
PUFA			
Linoleic acid	LA	18:2 *ω*-6	Plants oil (Corn oil, cotton seed oil, soybean oil)
α-Linolenic acid	ALA	18:3 *ω*-3	Plants oil (Linseed oil, canola oil, margarine, lard, walnut)
γ-Linolenic acid	GLA	18:3 *ω*-6	Plant seed, algae
Arachidonic acid	ARA	20:4 *ω*-6	Lard, bacon, ham, walnut
Eicosapentaenoic acid	EPA	20:5 *ω-3*	Fatty fish (Herring, salmon, trout, tuna, cod), fish oil supplement
Docosapentaenoic acid	DPA	22:5 *ω-3*	
Docosahexaenoic acid	DHA	22:6 *ω-3*	

[1]C, number of carbon atoms; D, number of double bonds; ω-X, position of the first double bond counting from terminal methyl carbon. Data elaborated from [1,2].

In most cases, fatty acids are present in sufficient amounts in food consumed by humans. It is also possible to α-synthesize saturated fatty acids from glucose and amino acids if necessary. However,

the desaturase enzyme, which adds a double bond before the ninth carbon from the methyl end, is absent in humans [12]. That is why we must obtain essential fatty acids from food sources, as our bodies cannot create them on their own. Generally, from a nutritional standpoint, EPA, DHA, and their precursors, LA and ALA, are considered essential fatty acids since they are mostly obtained from the diet, but other ω-7 and ω-9 unsaturated fatty acids are not [13]. Therefore, to meet our needs, we require exogenous intake of unsaturated fatty acids, especially ω-3 and ω-6.

2.1 ω-3

DHA, EPA, ALA, and DPA constitute the bulk of the ω-3 PUFAs, Most of the total fatty acids in brain cell membranes are composed of DHA [14], it has been found to have some effect on the brain and may influence CNS diseases through a range of neuroprotective effects such as inhibiting the occurrence of neuroinflammation [15-18]. According to studies, neurological disorders are linked to low amounts of DHA in the body [19,20]. Additionally, DHA is one of the most important components for the production of lipid mediators, which carry out a variety of neural functions including brain cell differentiation and proliferation, apoptosis, and anti-neuroinflammation [17], What's more, it can also improve glial cell cytokine expression and control leukocyte trafficking [21]. Similarly, EPA has been discovered to have an influence on neuronal function and to be advantageous to the brain [22, 23]. Additionally, EPA or DHA administration can have neuroprotection even antidepressant effects by encouraging the release of neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) by astrocytes [24], as well as postponing the onset of depression [25,26]. ALA is a precursor that is subsequently metabolically transformed into EPA and DHA in the human body [27], it has a wide range of pharmacological effects such as anti-inflammation, antioxidation, neuroprotection. ALA has been found to treat nerve damage caused by neurotoxins, and is expected to be used in neurodegeneration [28], clinical trials have shown that taking ALA can lead to a decrease in inflammation markers in the body [29]. Whereas DPA is just an intermediate between EPA and DHA [30-32].

2.2 ω-6

LA, GLA, and ARA make up most of the ω-6 PUFAs. ARA is the second most prevalent polyunsaturated fatty acid in the phospholipids of the nerve cell membrane after DHA. According to a meta-analysis, consuming more ARA was linked to a higher risk of PD [33]. The primary function of ARA metabolites is to promote inflammation by inducing the synthesis of inflammatory mediators, while adequate levels of ARA metabolites support healthy cell and tissue metabolism, excessive levels are frequently a sign of chronic illnesses like inflammation, which has a role in the development of neurodegenerative illnesses [34, 35]. The destruction of DA neurons in the SNpc is mostly attributed to the generation of pro-inflammatory cytokines [36]. However, as a parent of ω-6 PUFAs, LA can be extended and desaturated to form other ω-6 PUFAs that have biological activity, such as GLA and ARA. Theoretically, the more LA is taken, the more of it gets converted to ARA, but this is not the case. In tracer experiments, the conversion of LA to ARA is scarce [37]. Consequently, in this review, we primarily research how ARA affects us.

ARA also contributes to oxidative stress in addition to inflammation. Lipid peroxidation plays a role for the pathogenesis of several neurodegenerative illnesses and is crucial for the toxic effects of α-syn, mitochondrial malfunction, and neuronal death in PD. Furthermore, it appears that the pathophysiology of the DA systems' neurodegeneration is directly related to oxidative stress [6]. The isoprostanes and isofurans, derived from ARA, and neuroprostanes (NeuroPs), derived from DHA are useful in vivo biomarkers of lipid peroxidation. Patients with PD reported higher levels of these biomarkers [38, 39]. Free radicals and enzymes can quickly peroxidize PUFAs. Cellular membrane

integrity is damaged as a result, and the main reaction product—lipid hydroperoxide—decomposes into aldehyde and may be hazardous as a byproduct. Lipid hydroperoxides contribute to or accelerate DNA fragmentation brought on by reactive oxygen species (ROS). The α, β-unsaturated aldehydes produced by lipid peroxidation have the power to activate cellular stress-response mechanisms like cell signaling and death [40, 41]. D T Dexter et al proved that basal malondialdehyde (MDA; an intermediate in the lipid peroxidation process) levels were increased in parkinsonian nigra, they demonstrate that, maybe as a result of ongoing exposure to too many free radicals produced by some endogenous or external neurotoxic species, lipid peroxidation at an elevated level continues to occur in the parkinsonian nigra up until the time of death [42]. Since free radicals and reactive species result in excessive lipid peroxidation, it ends up in the death of nigral cells in PD[43, 44]. Multiple studies suggest that the peroxide developed when unsaturated fatty acids are out of balance is closely linked to neurological disorders, and the symptoms of PD are improved by preventing lipid peroxidation [45].

3. The studies of ω-3 in PD

3.1 Preclinical studies

The benefits of ω-3 for Parkinson's disease may be due to anti-inflammatory and antioxidant properties. Nitric oxide (NO) is an inorganic chemical that is produced by induced nitric oxide synthase (iNOS). Because of its unstable nature, it transforms into nitrite, which destroys the SN and has been related to various neurological illnesses such as PD[46]. INOS is neurotoxic and can be expressed following tissue damage, inhibiting iNOS expression may minimize the loss of DA neurons brought on by iNOS [47, 48]. A local injection of 6-OHDA, a neurotoxin, can result in the loss of DA neurons in the SN to produce a PD model. The neuroprotective effects of ω-3 may be caused by a decrease in iNOS. Research found that after rats were given FO, Supplemental FO lessens 6-OHDA's neurotoxic effects in the striatum area. Rats with 6-OHDA lesion showed a substantial increase in the mean density of iNOS-positive cells in the ipsilateral striatum, and FO administration decreased the mean density of iNOS-positive cells in the medial striatum. 6-OHDA enhanced iNOS expression in the dorsal of SN pars compacta, and FO supplementation corrected this effect. Additionally, according to the astrocyte study, FO supplementation reduced the expression of iNOS in the dorsal of SN pars compacta [49].

Tyrosine hydroxylase (TH) is an important enzyme in the generation of dopamine and is involved in the manufacture of neurotransmitter. Researchers delivered DHA to rats with 6-OHDA injury. TH immunohistochemistry found that 6-OHDA significantly decreased the density of TH-immunoreactive fibers (TH-irF), while DHA increased the density of TH-irF, suggesting the neuroprotective effect of DHA. Glial fibrillary acidic protein (GFAP) and ionizing calcium-binding adaptor molecule (iba-1) are a group of substances that regulate neuroinflammation. According to GFAP and iba-1 immunohistochemistry. DHA was able to correct the 6-OHDA-induced deviation of GFAP and iba-1 levels in the striatum and SN. The NF-E2-related factor 2 (Nrf2) protein's activation is a sign of oxidative stress. The Nrf2 rise brought on by 6-OHDA was slightly decreased by DHA [7]. Although there was a trend toward steady improvement in the ω-3 treatment group's exercise performance in the behavioral trial, there was no statistically significant difference. We speculate that this may be related to ingesting insufficient amounts of ω-3.

Apelin is the ligand of the apelin receptor (APJ), a G-protein-coupled receptor. Several physiological processes, such as vasodilation, lipogenesis inhibition, suppression of cell signal transmission, etc. [50], are regulated by apelin. Some apelin subtypes cause the generation of NO, which leads to vasodilatation [51]. What’s more, APJ is abundantly distributed throughout the central nervous system [52], although it is yet unknown how APJ interacts with ω-3. Researchers gave mice

DHA and discovered that the DHA treatment group performed better than the PD model group in terms of motor performance, motor coordination, and balance stability, which improved motor activity disorders. They also discovered that the DHA treatment group's APJ level in the cerebellum was statistically lower than that of the PD model group [53]. What's more, cerebellar lesions may be the cause of Pd-replaced dystonia [54]. Therefore, we assume that the modulation of APJ may be one of the mechanisms that ω-3 affect PD.

The level of SN injury was determined by the rotational behavior generated by apomorphine (APO) [55], the greater number of rotations, the greater serious the SN damage. Some people described that rats were given DHA and EPA, they discovered that the ω-3 treated group had better exercise performance capacity than the PD model group. The number of rotations was significantly less in the ω-3-treated group than in the PD model group. Additionally, a neurochemical analysis of the brain's lipid peroxidation revealed that the ω-3 treatment group's lipid peroxidation was significantly lower than that of the PD model group, and the level of nitrite was also decreased, suggesting that the antioxidant impact was involved in the neuroprotective effect [8].

1-methyl-4-phenyl-1, 2, 3, 6-Tetrahydropyridine (MPTP) is a neurotoxin used to make PD models that can cause DA neuron death. Study reported that supplementing with DHA successfully decreased rats DA neuronal death brought on by MPTP. In DA neurons injured by PD, neurotrophic factors GDNF and NTN have been demonstrated to have neuroprotective effects. In comparison to the MPTP group, the SN immunostaining of GDNF and neurturin (NTN) in the DHA supplement group was stronger [56-58]. This shows that the modulation of neurotrophic factors may be the cause of the neuroprotective action of ω-3.

Although most academics concur that DHA is useful in treating PD, some have different opinions. Based on a recent study by Maria Rachele Ceccarini et al., EPA is more crucial to neuroprotection than DHA. They discovered that EPA significantly lessened 6-OHDA's neurotoxicity compared to DHA. Moreover, flow cytometry examination indicated that EPA might shield cells from 6-OHDA-induced apoptosis, and transmission electron microscopy revealed that EPA might lessen 6-OHDA-induced mitochondrial and morphological damage to cells. Furthermore, GDNF and BDNF are neurotrophic factor involved in the differentiation of neurons[59, 60] and has been discovered to be decreased in PD [61]. They regard that EPA is more effective than DHA in increasing levels of GDNF and BDNF [62].

Additionally to DHA and EPA, ALA has been reported to have potential benefits for PD. Studies found that ALA prevents 6-OHDA-induced degeneration of elegans DA neurons and improves motor performance, restores 6-OHDA-induced hyperactivity of the cholinergic system, and more importantly, prolongs the survival of elegans [63]. The precise mechanism remains to be clarified, although it is hypothesized that ALA's ability to act as an antioxidant is attributed to its neuroprotective properties [64]. Consequently, we can infer that most of ω-3 preclinical study findings are positive, providing experimental support for upcoming clinical trials.

3.2 Clinical studies

A study comparing 336 controls to 89 PD cases demonstrated an inverse relationship between PD with increased dietary fat intake, especially ω-3 PUFAs [65]. The level of PUFAs in the SN of the brain tissue of PD patients was lower while the level of lipid peroxidation was higher (including the higher level of MDA), according to studies on the brain tissue of patients who died of PD and those who died of non-neurological diseases, suggesting that PUFAs level in the brain may be negatively correlated with the risk of PD [42]. They used the patient-reported outcomes in PD (PRO-PD) as the main outcome gauge of PD's severity, and food frequency questionnaires (FFQ) was used to gauge recent 6 months nutritional intake. After examining 1053 PD patients with an average age of 63,

researchers discovered that eating items including vegetables, nuts, non-fried fish, FO, and others was linked to slowing the progression of PD [66]. Besides, the consumption of fried food is associated with PD advancement; the cause may be the aldehydes (such as MDA) created by lipid peroxidation brought on by an increase in ROS in PD. MDA accumulates in DA neurons, inhibits proteasome action, results in α-syn modification and aggregation, and causes DA cell death, accelerating the development of PD [67].

However, others hold differing opinions regarding the impact on specific ω-3 subtypes. After an average follow-up of 6.0 years, a Rotterdam analysis of eating habits before the beginning of PD found that only ALA of the ω-3 PUFAs appeared to be associated with a decreased risk of PD [5]. Recently, a case-control research examined the plasma levels of PUFAs while also assessing dietary consumption using FFQ in the study with 38 PD patients and 33 controls. The findings demonstrated decreased plasma ALA levels in PD patients, and plasma ALA levels were adversely connected with the severity of motor in PD patients, while DHA was positively correlated with non-exercise symptoms [68]. This differs slightly from the outcomes of preclinical research. Several possible reasons are as follows: (i) Sample size is insufficient; (ii) patient recollection is the source of the FFQ data, which may lead to incorrect results.; (iii) PD is a chronic disease that evolves over time, and short-term dietary surveys only represent food intake for a short period of time.

Common non-motor symptoms of PD include depression, anxiety, cognitive decline, and others [69]. The use of ω-3 in the treatment of depressive symptoms in PD patients has also yielded encouraging results. In a double-blind, randomized controlled experiment, ω-3 capsules (720 mg EPA and 480 mg DHA) were given daily for three months to 31 PD patients with major depressive disorder and the average age of the patients was 64.4 years old. The outcome of the illness was assessed using the Montgomery-Asberg Depression Scale (MADRS). The findings suggested that ω-3 may be employed as an additional therapy since it alleviated depression symptoms in PD patients regardless of whether they were taking antidepressants [70].

4. The studies of ω-6 in PD

4.1 Preclinical studies

LA has also demonstrated encouraging outcomes in the treatment of PD. An article discovered that LA can both stop neurodegeneration and lessen the signal of neuroapoptosis in 6-OHDA-induced PD model mice. The pro-inflammatory markers TNF-α and COX-2 in SN were also found to be significantly lower in LA-treated PD mice [2], indicating a decrease in reactive astrocyte signaling. Reactive astrocytes can be brought on by CNS damage, and after CNS damage, activated microglia cause reactive astrocyte signaling by secreting inflammatory substances (such as TNF-α), which encourages neuronal death [71]. In vitro tests revealed that LA also encouraged nitrite decrease, it demonstrates that LA has some neuroprotective and anti-neuroinflammatory effects.

α-syn has been defined as a biomarker of PD, and its overexpression and aberrant aggregation are associated with the disease [72]. ARA can bind to Fatty acid-binding protein 3 (FABP3) and cause α-syn aggregation in neuro-2A cells. FABP3 is mostly expressed in DA neurons and can enhance α-syn oligomerization in the presence of MPTP. The application of a FABP3 ligand to bind to it reduces ARA-induced -syn aggregation, reducing DA neuronal degeneration, showing ARA's dependency on FABP3 [73-76]. The precise mechanism of α-syn oligomerization caused by the combination of ARA and FABP3 is uncertain.

Additionally, researchers shown that ARA is released by phospholipase A2 (PLA2) activity, boosting α-syn aggregation. PLA2 can release ARA from biomimetic phospholipid membranes like phosphatidylcholine and phosphatidylserine. Incubation of α-syn with ARA increases α-syn structural change and aggregation formation [77]. However, other researchers measure α-

syn aggregation rate and discovered that ARA and DHA seemed to increase α-syn aggregation rate and led to stronger cytotoxicity. Even though they had the different viewpoint to other researchers in that they thought ARA and DHA were both damaging to the human body [78], they still need more evidence to back up their claim, because they used a less rigorous control group.

4.2 Clinical studies

The identification of biomarkers, which serve as objective indicators, is advantageous for the diagnosis and assessment of disease. In a study with 30 people with PD and 55 healthy controls, it was discovered that ARA levels were significantly higher in the plasma of PD patients, making it a viable biomarker for the diagnosis of PD or the evaluation of the prognosis for PD [79]. What's more, ARA also emerged to be raised in the blood of PD patients in the other studies, and the blood level of ARA was found to be positively connected with PD [80]. At the meantime, in order to research the connection between specific unsaturated fatty acids in the diet and the risk of PD, researchers studied 249 PD patients and 368 controls. A diet history questionnaire was used to evaluate dietary practices during the previous month. They found that ARA intake was positively associated with the risk of PD, while other PUFAs, such as DHA, showed no evidence of an association between their intake and PD [81], we speculate that this is due to insufficient DHA intake, as people do not particularly supplement it on a daily basis. In addition, higher plasma ARA levels were related to more severe non-motor symptoms of PD, while lower plasma LA levels were associated with more severe motor symptoms of PD, according to an observational study by Dallah Yoo et al. that was previously noted in the article [68]. Overall, ARA appears to have a strong connection with PD as a pro-inflammatory substance and too much ARA in the body indicates the excessive growth of inflammation, thereby exacerbating the condition. In contrast, LA appears to be beneficial to the human body in ω-6.

5. Conclusions

Currently, levodopa, which is clinically utilized to reduce PD symptoms, and other DA agonists are used to replenish the brain's normal amounts of DA in PD treatment [82], however, its therapeutic efficacy is limited, and there is no effective treatment for PD. We are seeking for additional complementary treatments to help PD sufferers live better lives. Fatty acid is a nutrient present in cell membranes that is involved in substance formation and cell metabolism. A healthy diet and fatty acid intake are beneficial to brain lipid homeostasis. Nevertheless, PD is a chronic disease that can be delayed or prevented by making changes to our regular diet. PUFAs are classified as ω-3 and ω-6. ω-3 has antioxidant, anti-inflammatory, and neuroprotective properties on the human body, while ω-6, ARA, appears to increase α-syn aggregation and disease progression. As a result, we advocate increasing ω-3 intake, such as fish or fish oil supplements, while decreasing ω-6 intake, such as bacon, pork, fried foods, and so on. Diet intervention is not as effective as drugs, as mentioned above, PD is a chronic disease, to gradually delay the progression of the condition, we need to modify our eating habits in daily life. Diet intervention of PD requires more investigation. Likewise, we must focus on the molecular mechanisms of PD pathogenesis in order to identify new targets and insights for PD medication development.

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