Omega-3's Biological Actions

Subjects: Clinical Neurology

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Schizophrenia is a severe psychiatric disorder affecting more than 20 million individuals worldwide. According to the well-established clinical staging model, schizophrenia is a progressive illness that typically emerges during late adolescence and transitions through several evolving stages: early vulnerability, at-risk mental state (also called ultra-high risk, abbreviated UHR), first episode psychosis (FEP), and chronic schizophrenia. The transition from one stage to the other is not inevitable, and it has been observed that only one-third of UHR individuals convert to psychosis after a 3-year follow-up.

Keywords: antipsychotics ; omega-3 ; membrane lipids ; first episode psychosis ; ultra high-risk patients ; schizophrenia ; oxidative stress ; dopamine ; inflammation

1. Introduction

Schizophrenia is a severe psychiatric disorder affecting more than 20 million individuals worldwide [1]. According to the well-established clinical staging model, schizophrenia is a progressive illness that typically emerges during late adolescence and transitions through several evolving stages: early vulnerability, at-risk mental state (also called ultra-high risk, abbreviated UHR), first episode psychosis (FEP), and chronic schizophrenia. The transition from one stage to the other is not inevitable, and it has been observed that only one-third of UHR individuals convert to psychosis after a 3-year follow-up [2]. The factors leading to progression across these stages remain largely unknown, reflecting the need to uncover the mechanisms underlying the pathophysiology of schizophrenia. The aetiology of schizophrenia is not restricted to brain dysfunctions, and the disorder is currently conceptualized as a systemic disease that includes immune, cardiometabolic, and endocrine abnormalities [3]. In addition to dopaminergic and glutamatergic abnormalities [4], patients with schizophrenia also experience increased levels of oxidative stress [5], inflammation, and immune reaction [6] and have abnormalities in membrane lipid composition [7] and in one-carbon (C1) metabolism [8].

Omega-3 fatty acids (omega-3) play a central role in brain functioning and may be a promising therapeutical alternative for vulnerable individuals. Omega-3 is an unsaturated fatty acid composed of a carboxylic acid with a long hydrophobic aliphatic chain, which has a first double bond on its third carbon. Omega-3 belongs to monounsaturated (one bond) or polyunsaturated (up to six bonds) fatty acids (PUFA). α-linolenic acid (ALA) is an omega-3 PUFA that originates mainly from the diet and leads to the synthesis of other omega-3 PUFAs-through a series of metabolic cascades-including eicosapentaenoic acid (EPA) and the docosahexaenoic acid (DHA). In psychiatric disorders, a decrease in omega-3 levels has been uncovered in the neuron membrane of individuals with mood disorders and schizophrenia [9]. Research on lipid composition in cell membranes and in the serum of patients with schizophrenia has shown that higher levels of omega-3 are correlated with lower negative symptom severity, and with higher scores in cognition [10], although mixed results are found in the literature [11]. In UHR patients, lower levels of omega-3 and omega-3/omega-6 ratios (healthy ratio varies between 1-to-1 and 1-to-4) in erythrocyte membranes have been correlated with increased severity of depressive, psychotic, and general psychopathology symptoms and with increased cognitive impairment [12][13]. Thus, omega-3 supplementation has been proposed as a potential preventive treatment for UHR individuals as it might prevent transition to psychosis [14], and the supplementation appears to be safe and well tolerated [15].

2. Omega-3 Overall Actions and Shared Biological Pathways with Antipsychotics

As discussed in the first part of this review, omega-3 is involved in several biological pathways and could be considered a gateway to the complex pathophysiology of schizophrenia, which includes oxidative stress, inflammation, myelination, glutamate and dopamine signalling pathways, one-carbon metabolism, and endocannabinoid pathways. These biological pathways also interact with each other, further increasing complexity. Indeed, it has been established that inflammation is associated with oxidative stress and endocannabinoids, oxidative stress is associated with one-carbon metabolism, and

endocannabinoids are involved in glutamate and dopamine signalling pathways, To add to this complexity, there may be a time window that potentiates the action of omega-3, as it may play a role against the emergence of psychosis through its neuroprotective effects, especially during adolescence, when brain maturation takes place [16].

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