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Review

Alpha-linolenic acid: A promising nutraceutical for the prevention of stroke

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ABSTRACT

Stroke is a worldwide main cause of mortality and morbidity. Most of the preventive and neuroprotective treatments identified in preclinical studies failed in clinical trials. Although there is a consensus that nutrition is important for health, its role is underestimated in stroke. Indeed an increase consumption of salt and fatty foods may promote hypertension and obesity, which are well known risk factors of stroke. In contrast it is more difficult to identify a risk factor arising from a deficiency in an essential nutrient in the diet. Western modern diets are deficient in omega-3 polyunsaturated fatty acids, which are essential for brain health. Such deficiency may constitute by itself a risk factor for stroke. Furthermore, an imbalance in the consumption of omega-6 and omega-3 progressively took place in the past 40 years leading to omega-6/omega-3 ratios that are far above the WHO healthy recommendations. A consequence of this imbalanced ratio has been the fostering of elevations in and increased prevalence of inflammatory cardiovascular diseases and obesity. In this context, this review outlines a promising therapeutic opportunity by integrating a nutritional-based approach focusing on omega-3 alpha-linolenic acid as nutraceutical to prevent the devastating damage caused by brain ischemia.

Contents

Abbreviations: ALA, alpha linolenic acid; ANSES, Agence Nationale pour la Sécurité et la Santé; BDNF, Brain Derived Neurotrophic Factor; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MCAO, middle cerebral artery occlusion; PUFA, polyunsaturated fatty acids; SNAP-25, Synaptosomal-Associated Protein 25; VAMP-2, Vesicle-Associated Membrane Protein 2; VGLUT1, Vesicular Glutamate Transporter 1; VGLUT2, Vesicular Glutamate Transporter 2.

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1. Introduction

Stroke is a worldwide main cause of mortality and morbidity. It causes a significant socioeconomic cost and a marked increase in patient/family burden. More than 1000 molecules have demonstrated brain-protective properties in experimental models. More than 200 clinical trials have examined neuroprotection for ischemic stroke, arguably despite sufficiently persuasive preclinical justification. To date most of the preventive treatments and neuroprotective drugs identified in preclinical studies failed in clinical trials. Therefore testing alternative protective strategies to prevent stroke is of considerable importance. Although there is a consensus that nutrition is important for health, its role is underestimated in stroke prevention. It is recognized that an increase consumption of salt, fatty foods and alcoholic beverages may promote pathologies like hypertension, obesity and alcoholism, all of which are well known risk factors of stroke. In contrast it is more difficult to identify a risk factor arising from a deficiency in an essential nutrient in the diet. Western modern diets are deficient in omega-3 polyunsaturated fatty acids, which are essential for brain health. Such deficiency constitutes by itself a risk factor for cardiovascular and cerebral diseases, including coronary heart disease and stroke. Furthermore, an imbalance in the consumption of omega-6 and omega-3 PUFAs progressively took place in the past 40 years leading to omega-6/omega-3 ratios that are far above the World Health Organization (WHO) healthy recommendations. A consequence of this imbalanced ratio has been the fostering of elevations in and increased prevalence of inflammatory cardiovascular and neuronal diseases and obesity. In this context, nutritional products with health benefits represent a growing interest. Functional foods enriched in omega-3 polyunsaturated acids or omega-3 used as nutraceuticals may reduce the frequency of strokes through preservation of both arterial and neuronal function. This review outlines a promising therapeutic opportunity by integrating a nutritional-based approach focusing on the omega-3 alpha-linolenic acid (ALA) to prevent the devastating damage caused by stroke.

2. Stroke statistics and healthcare

2.1. Stroke statistics

Stroke is the third leading cause of mortality and disability in the world. It has been predicted that stroke will account for 6.2% of the illness total burden in the first nine years in 2000 [1]. The mortality rate at five years is approximately 50% and a stroke strikes every 40 s with one death every 4 min [2,3]. The total number of stroke deaths is estimated at 508,000 per year in European Union; among the elderly population of 15 European countries, surveys showed 2,700,000 prevalent cases, and 536,000 incident cases each year [4]. In the United States, data show a total of 5,800,000 prevalent stroke cases, with 780,000 being first occurrences or recurrent strokes expected each year. Stroke causes many impairments and half of stroke survivors are left to live with physical or cognitive disabilities. This gives rise to real issues with hospital organization, care and public health, invariably exerting a high cost and a burden to society and health systems [5]. Because stroke compromises patients' lives so severely, they will require high levels of assistance and support even for common daily activities, which in turn directly impacts their quality of life – and their supporters. Therefore, those indirect costs contribute to increase the economic burden associate with stroke. The total economic costs (direct and indirect cost) for stroke were estimated at $73.7 billion in 2010 [3]. The only current therapy against stroke is thrombolysis, which is only given to ~5% of patients because of (1) its numerous side effects, the major one being a 6–7% risk of bleeding [6] and; (2) the therapeutic window of 0–4.5 h required to obtain a therapeutic effect of the thrombolytic [7]. Generally, the majority of patients are not treated with rtPA because they arrive after that narrow time window of treatment of opportunity, leaving clinicians without any repertoire of therapeutic opportunities. It is somewhat ironic that clot busters is considered the best 'neuroprotectant', given that it mediates its effect through the vasculature, as opposed to exerting any direct protection in neurons. In a landmark analysis published in 2006, none of the 114 treatments (from more than a thousand treatments demonstrating neuroprotection against acute stroke since the 1960s at the preclinical level) achieved neuroprotection in clinical trials [8]. In addition, these drugs displayed poor adherence to the STAIR criteria (Stroke Therapy Academic Industry Roundtable), designed to increase the rigor by which neuroprotective agents were assessed at the preclinical level, in order to improve the odds of success in clinical trials [9]. This failure in translation from experimental models to clinical trials led to a major exodus of pharmaceutical companies from stroke, and also prompted a major re-evaluation of properties, which would constitute the "best-in class" therapeutics to be used against stroke, integrating several aspect of the pathology of stroke.

2.2. Stroke physiopathology

An ischemic stroke is the result of an occlusion within a blood vessel supplying blood to the brain. This type of stroke accounts for more than ~80% of all stroke cases. The current understanding of its pathophysiology has dramatically evolved over the past two decades mainly due to the animal studies. It is well known that the clot may either be formed locally in a small artery or may arise from the heart or from an injury in the wall of one of the cervical arteries (carotid and vertebral arteries). Occlusion of the middle cerebral artery (MCA) is one of the most widely used experimental models. Interruption of blood flow generated a hypoperfusion in the MCA territory that leads to a rapid decline in oxygen (hypoxia) and nutriments (glucose, ATP, energetic metabolites, etc.). The cut off the supply of oxygen and glucose prevents the brain from generating the ATP needed to support its considerable energy demands. After focal ischemia, this energy deficit is most severe in the core of the ischemic territory that displays the lowest residual flow, wherein cell death occurs rapidly. In the core periphery, termed ischemic penumbra, even if reduced collateral blood flow buffers the full effects of stroke, waves of peri-infarct depolarization lead to neurotransmitter release. In concert with impairment of glial reuptake, extracellular glutamate achieves neurotoxic concentrations. Within the entire ischemic territory, glutamate overload into the extracellular space results in an hyperactivation of its receptors (excitotoxicity) leading to accumulation of intracellular Ca^{2+}, which in turn sets off deleterious events including activation of lytic enzymes, mitochondrial dysfunction, and oxidative stress [9–11]. Irreversible damages are caused to neuronal membrane and compromise brain tissue survival. Initiation of these pathologic pathways differs in space and time (Fig. 1) and also depends of the cellular subtype (neuronal or vascular, for example) [12].

Historically, stroke research aimed to target one element of the deleterious cascade that takes place during stroke [8]. It failed to identify and validate an effective drug able to protect the neurovascular unit. Although restoration of cerebral blood flow can be successfully applied in a small 5% subset of patients by recombinant tissue plasminogen activator, there is still no therapeutic for stroke, underlining a pressing need to investigate additional strategies. Epidemiologic studies have demonstrated most patients presenting with a stroke possessed at least one risk factor. In addition, the pre-existence of certain risk factors in the