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Review

The nutraceutical potential of omega-3 alpha-linolenic acid in reducing the consequences of stroke

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ABSTRACT

Stroke is a worldwide major cause of mortality and morbidity. Preclinical studies have identified over 1000 molecules with brain-protective properties. More than 200 clinical trials have evaluated neuroprotective candidates for ischemic stroke yet, to date almost all failed, leading to a re-analysis of treatment strategies against stroke. An emerging view is to seek combinatory therapy, or discovering molecules able to stimulate multiple protective and regenerative mechanisms. A pertinent experimental approach to identify such candidates is the study of brain preconditioning, which refers to how the brain protects itself against ischemia and others stress-inducing stimuli. The recent discovery that nutrients like alpha-linolenic acid (ALA is an essential omega-3 polyunsaturated fatty acid required as part of our daily diet), may be an efficient brain preconditionner against stroke fosters the novel concept of brain preconditioning by nutraceuticals.

This review stresses the underestimated role of nutrition in preventing and combating stroke. Although there is a consensus that increased 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 – few risk factors are attributed to a deficiency in an essential nutrient in the diet. The ALA deficiency observed in the Western modern diets may itself constitute a risk factor.

This review outlines how ALA supplementation by modification of the daily diet prevented mortality and cerebral damage in a rodent model of ischemic stroke. It also describes the pleiotropic ability of ALA to trigger responses that are multicellular, mechanistically diverse, resulting in neuronal protection, stimulation of neuroplasticity, and brain artery vasodilation. Overall, this review proposes a promising therapeutic opportunity by integrating a nutritional-based approach focusing on enriching the daily diet in ALA to prevent the devastating damage caused by stroke.

1. Stroke is a worldwide main cause of mortality and morbidity, lacking therapeutic options

Stroke is a devastating disease in developed and 3rd world countries, due to its high incidence, its brutal impact on the patient and its relatives, and the lack of therapeutic options. On average, someone has a stroke every 40 and 90 s in the United States and Europe, respectively [1,2]. Annually, 15 million people worldwide suffer a stroke. The total number of stroke deaths is estimated at a half million people per year in European Union and is three time higher in the U.S. Of these, 30% die and another 30% are left permanently disabled, placing a tremendous burden on family and community. The estimated cost of stroke for 2010 was $74 billion and €64 billion in the U.S and Europe, respectively [2,3].

For the public, stroke is better known as brain attack, because it strikes in 85% of the cases by disrupting the blood flow to part of the brain due to occlusion of a blood vessel feeding the brain. Stroke is therefore a hypoxic-ischemic injury, whose pathophysiology involves glutamate, the major physiological excitatory neurotransmitter in the brain. The lack of oxygen and glucose causes a massive release of glutamate from neurons, and the

Abbreviations: ALA, alpha-linolenic acid; ANSES, Agence Nationale pour la Sécurité et la Santé; BDNF, brain derived neurotrophic factor; CVD, cardiovascular diseases; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linolenic acid; LC omega-3, long-chain omega-3 (eg, mainly EPA and DHA); 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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overactivation (excitotoxicity) of ionotropic glutamate receptors, predominantly the *N*-methyl-D-aspartate (NMDA) glutamate receptor subtype. These results in accumulation of intracellular calcium, which in turn triggers deleterious cascades including activation of lytic enzymes, mitochondrial dysfunction, oxidative stress and inflammation [4] in two regions that coexist within the infarct: the necrotic core and the ischemic penumbra, an area surrounding the core where neurons remain on the brink of survival or death for hours [5].

The progresses in understanding its complex interplay of multiple cellular and signaling pathways that alter the neurovascular unit integrity within differentially affected territories allowed identification in preclinical studies of neuroprotective targets or/and drugs blocking the neurotoxic ischemic cascade. Nevertheless, of those tested in clinical trials, all have failed, leaving patients and clinicians without any repertoire of therapeutic opportunities exerting direct protection of the neurons [6]. Consequently, the only approved therapeutic exerts its benefits through the restoration of the blood flow to the brain by blood clot disruption. It is performed by recombinant tissue plasminogen activator (tPA) treatment administered to approximately 5% of stroke patients. On the positive side, three definitive points are worth noting: 1) Efforts have been made over the past decades in high-income countries to control major risk factors like hypertension, diabetes, and high cholesterol, strides which have contributed to stroke mortality reduction. This success is associated with a global improvement in population health. It should be monitored cautiously as it probably represents the tip of the iceberg because stroke mortality represents, at the maximum, a third of the annual first-ever strokes; 2) The failure in translation from experimental models to clinical trials has lead to revisiting the research of strategies against stroke, resulting in a set of drug development criteria, collectively known as the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations [7]; and 3) There is an acceleration in the study of unconventional therapies, with a major theme being to interrogate how the brain protects itself [4,8].

To summarize, considering the multifactorial nature of stroke, in order to be considered as a good candidate for a clinical trial, a treatment should exhibit multimodal actions on the multiple cell types composing the neurovascular unit. Consequently, an emerging view is that we should preferentially seek and test for drug combinations or multi-therapy, or discovering molecules able to stimulate multiple protective and regenerative mechanisms to fight stroke [9,10]. A pertinent experimental approach to identify such candidates came from our experience on brain preconditioning through the study of how the brain protects itself against ischemia and others stress stimuli.

2. The study of the brain preconditioning opens new rational against stroke

The idea of developing a treatment against stroke inspired by this endogenous protective process is appealing. Preconditioning depends on the stimulation of protection and regeneration against stroke through direct and/or indirect mechanisms, involving multiple cell types, rather than through inhibition of single deleterious events, or targets of most of the conventional neuroprotective approaches. Indeed, brain preconditioning refers to a sublethal toxic stimulus eliciting an endogenous response, which renders the brain remarkably tolerant to a subsequent, normally lethal stimulus of the same insult. Since its original description in the brain [11], the discovery that non-ischemic preconditioners (Fig. 1) including various sublethal insults like epilepsy, endotoxins, anoxia, hyperthermia and spreading depression also promote tolerance to ischemia – a phenomenon known as "cross-tolerance" [8,12,13] – definitely established that the protective response to brain preconditioners is pleiotropic in nature. A major conceptual roadblock for clinical translation – the requirement of bringing neurons to the 'brink of death' during the sublethal preconditioning challenge [14] – can be circumvented based on the demonstration that brain preconditioning may be pharmacologically/chemically induced by drugs like adenosine or K_{ATP} channel agonists [15]. Finally, the recent discovery that nutrients like polyunsaturated fatty acids and lysophospholipids that form part of our daily diet may be efficient brain preconditioners against stroke [16,17] gave birth to the novel concept of brain preconditioning based on nutraceuticals against stroke [18].

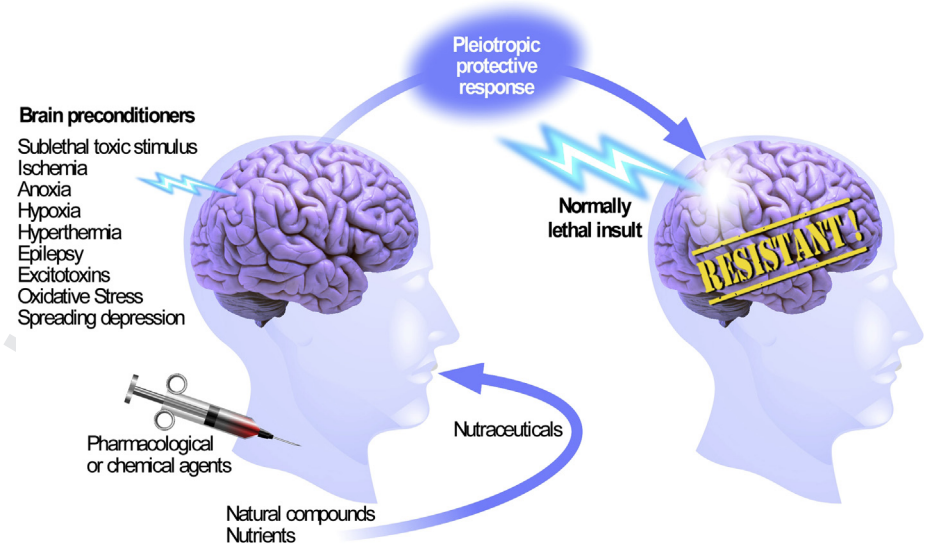

Fig. 1. The different natures of brain preconditioners and their perspectives against stroke. Originally, brain preconditioning refers to an endogenous response to a sublethal stimulus in the brain, which develops tolerance to a subsequent, normally lethal stimulus of the same insult. The protective response to brain preconditioners is pleiotropic in nature. Non-ischemic preconditioners include various sublethal insults, pharmacological/chemical agents and natural compounds including nutrients that are part of our daily diet. The diet aspect provides the rationale of supplementation with a non-ischemic preconditioner that could be a natural product – a nutrient defined as a nutraceutical.

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