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Neuroprotective diets for stroke

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ABSTRACT

Stroke is one of the main causes of death and disability in the elderly. In the last few years, there has been increasing evidence that suggests the influence of the diet on the decrease of stroke risk. Probably, because of the presence of bioactive components with beneficial effects such as antioxidant or anti-inflammatory properties. This article reviews several dietary bioactive compounds from studies in models of cerebral ischemia that have obtained promising results decreasing cerebral damage. We propose that many of these compounds present in diet could be good candidates to test new neuroprotection approaches focused on reducing the damage and protecting the brain before stroke occurs.

1. Introduction

Vascular diseases, fundamentally represented by coronary artery pathology and cerebrovascular diseases, are the leading causes of hospitalization and death worldwide (Mozaffarian, 2016). According to the World Health Organization (WHO), cerebrovascular diseases are the second leading cause of death worldwide and the major cause of disability in adults (http://who.int/mediacentre/factsheets/fs310/en/). In fact, one in six people are at risk of suffering a stroke during their life. Due to the increasing incidence and prevalence of cerebrovascular diseases among the elderly people, it is expected that these pathologies will raise sanitary costs in the next decades. Stroke represents 3–4% of the health care spending in developed countries (Evers et al., 2004). Hence, this disease is considered a health emergency and a real vascular epidemic in high-income countries and it is rapidly raising in low-income countries, and therefore needs to be successfully controlled. Any action focused on the development of new therapies or the enhancement of preventive strategies is necessary.

Stroke is a neurologic disorder that occurs due to the occlusion or disruption of brain vessels. The vascular occlusion is mainly caused by an arterial clot that produces a severe metabolic stress and triggers the ischemic cascade. The ischemic cascade, a

ABBREVIATIONS: 4-VO, Four-Vessel Occlusion; ADNES, Advanced Neuroprotection Strategy; Akt, Protein kinase B; ALA, alpha-linolenic acid; ApoE4, Apolipoprotein E4; BCCAO, Bilateral Common Carotid Artery Occlusion; Bcl-2, B-cell lymphoma 2 (protein); CAT, catalase; CREB, cAMP response element-binding protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ERK, extracellular signal–regulated kinases; FOSHU, Foods for Specified Health Use; GSH, Glutathione; (GSH-PX, glutathione peroxidase; HO-1, hemeoxygenase-1; IL-6, Interleukin 6; MDA, malondialdehyde (MDA); MUFAs, monounsaturated fatty acids; Nrf2, nuclear factor erythroid 2-related factor 2; p38, p38 mitogen-activated protein kinases; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; pMCAO, Permanent Middle Cerebral Artery Occlusion; PREDIMED, *Prevención con Dieta Mediterránea*; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; SIRT1, NAD-dependent deacetylase sirtuin-1; SOD, Superoxide dismutase; tMCAO, Transient Middle Cerebral Artery Occlusion; tPA, tissue plasminogen activator; WHO, World Health Organization.

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sequence of cellular mechanisms (free radicals formation, glutamate release, intracellular calcium accumulation and inflammatory processes induction), leads to neuronal apoptosis or death and produces irreversible tissue damage (ischemic core). However, the zone of injury that surrounds the ischemic core (ischemic penumbra) could be potentially salvaged if a treatment is administered at the proper time. Nowadays, stroke treatment represents a health challenge because there is not any successful neuroprotective strategy to avoid the death of the tissue or the expansion of the lesion except the use of reperfusion strategies such as thrombolytic treatment using tissue plasminogen activator (tPA) or the mechanical intervention in order to restore blood flow within the first hours of stroke onset. In spite of the efficacy of these treatments, the strict inclusion criteria for eligibility (therapeutic window is time-limited after the symptoms onset) and the risk of hemorrhagic transformation, restrict the possibilities of tPA administration and consequently a small percentage of stroke patients can benefit from the thrombolytic treatment (Berkhemer et al., 2015; Hacke and Lichy, 2008).

The big social impact of stroke along with the lack of effective treatments generate the current interest in this field of research. Therefore, it is necessary to find new neuroprotective strategies in order to prevent the increase of new cases of this dramatic pathology or reduce the extension of the brain infarct and its sequelae (if this damage, unfortunately, occurs). Several strategies are being handled in the field of stroke prevention; one of them is focused on the development of health policies (e.g. reduction of the salt and fat content in food) and other strategy, in which we are interested in, is based on the identification of groups of patients with high risk of stroke in order to avoid the ischemic event or minimize the effects of stroke, if it takes place. This second approach has been recently proposed by our group and was defined as “Advanced Neuroprotection Strategy” (ADNES) (Ayuso and Montaner, 2015). The objective of standard neuroprotective therapies is to have impact and restrict the effects of the ischemic cascade in order to avoid or reduce the damage and neuronal death in the ischemic penumbra, preserving the maximum extension of viable brain tissue after the event occurs and the mechanisms of damage were induced. However, ADNES differs from the classical therapies since this strategy is aimed on the preservation of brain before the onset of stroke and the ischemic cascade begins. Consequently, the main goal of ADNES would be to avoid the activation of the ischemic cascade inducting an early protection which would minimize the damage. These beneficial events would be directly associated with the presence of the neuroprotective compounds in the system prior to the ischemic event occurs. Interestingly, there are neuroprotective compounds (oleic acid, omega-3 fatty acids, flavonoids, etc.) with a safe profile that can be part of the diet in order to be administered for long cycles of time before the ischemic event occurs. Therefore, nutritional intervention (Mediterranean Diet, omega-3 or polyphenols enriched diets) combined with ADNES strategy could be a therapeutic tool able to modify vascular risk factors as well as modulate the extension of the brain damage. This approach would be applicable to patients with high risk of stroke in order to improve the functional outcome when the insult takes place (Ayuso and Montaner, 2015).

2. Mediterranean diet

As mentioned above, the type of diet can contribute to neurovascular disease. Thus, a recent study noticed that stroke patients have an unhealthy diet and exhibited less intention to adopt healthy nutritional habits (Rodriguez-Campello et al., 2014). Consequently, to bet on nutritional approach versus neuroprotective pharmacological interventions could be one of the most effective and low-cost strategy to reduce the burden of many diseases and their associated risk factors. In addition, the nutritional approach offers an opportunity for a safe and long-term intervention.

It is widely known that the type of food can impact on the evolution of vascular pathology. In 2012, Misirli et al. found, in a cohort of 23,601 people, an inverse association of adherence to the Mediterranean diet with cerebrovascular disease incidence and mortality (Misirli et al., 2012). Recently, the beneficial effects of the Mediterranean diet have been demonstrated in a clinical trial conducted in Spain [*Prevención con Dieta Mediterránea* (PREDIMED Study)]. The Mediterranean diet supplemented with extra-virgin olive oil or nuts, decreased the risk of myocardial infarction, stroke or cardiovascular death by 30% (Estruch et al., 2013; Sala-Vila et al., 2016). Interestingly, Tuttolomondo and collaborators also found that ischemic stroke patients with lower adherence to Mediterranean diet are significantly more likely to suffer an atherosclerotic stroke (Tuttolomondo et al., 2015). The components of the diet determine the beneficial effects of each diet. Diets with high-fiber foods and with low fat or low glucose content have been associated with a decrease in cardiovascular risk (Buil-Cosiales et al., 2016; Kernan et al., 2014; Mozaffarian et al., 2011). The typical Mediterranean diet includes high content in fruits, legumes, vegetables and whole grains; moderate intake of fish, seafood, poultry, eggs and milk; olive oil as the main fat and a moderate wine intake during meals (Bach-Faig et al., 2011; Willett et al., 1995). The components of Mediterranean diet are foods rich in bioactive compounds such as fatty acid, vitamins and polyphenols. Bioactive compounds confer antioxidant properties and appear to be responsible for the beneficial effects of consumption of these foods in the diet, participating in protection against cardiovascular disease and reducing oxidative phenomena associated with the aging of the organism. Thus, the diet would be a factor that could modify the extension of the lesion when the ischemic insult occurs. Following this idea, Dhungana and collaborators studied the effect of high-fat diet in mice expressing human E4 isoform of apolipoprotein (ApoE4) that were subjected to a permanent occlusion of the middle cerebral artery. The expression of human ApoE4 in mice fed with a western-type diet (high-fat diet) was related to the increase of functional deficits observed after stroke. These mice also presented an increased cyclooxygenase-2 immunoreactivity and plasmatic IL-6 levels, accompanied with altered neurogenesis and astroglial activation (Dhungana et al., 2013). This work showed the relationship between high-fat diet and stroke models with comorbid conditions and its importance in order to understand the role of the diet in human stroke.

3. Oleic acid and omega-3 fatty acids

Oleic acid is a nonessential monounsaturated fatty acid (MUFA) found in high amounts in many vegetable oils such as olive oil and sunflower oil. As previously commented, the consumption of olive oil is associated with a lower risk of suffering an ischemic stroke (Estruch et al., 2013), suggesting a neuroprotective effect in case of cerebrovascular disease (Martinez-Gonzalez et al., 2014; Schwingshackl and Hoffmann, 2014). Recent studies on rodent models of cerebral ischemia have shown that olive oil protects from neuronal death (Zamani et al., 2013) and reduces infarct volume (Mohagheghi et al., 2010; Rabiei et al., 2012). Moreover, these oils are important sources of polyphenols and other antioxidant compounds such as Vitamin E that can also exert beneficial effects combined with oleic acid (Martin-Pelaez et al., 2013).

The brain is one of the organs with the highest concentration of omega-3 fatty acids after adipose tissue. In fact, the presence of omega-3 fatty acids in the diet is necessary for the proper

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