Vascular dementia and aliamides: A new approach for the future

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Abstract
Vascular dementia (VaD) is the first usual cases of dementia after Alzheimer’s disease, causing approximately 15% of instances. Yet, unlike Alzheimer’s disease, there are no treatments to diminish the inflammatory process correlated to vascular dementia. Palmitoylethanolamide (PEA) was discovered more than five decades ago and has been proved to counteract peripheral inflammation and mast-cell degranulation, as good as to exert neuroprotective and antinociceptive effects in rats and mice experimental model. Luteolin (Lut) is an important flavone that has advantageous neuroprotective impacts both in vitro and in vivo. This mini-review gives a little outline of current information of PEA and Luteolin impact on various experimental model and the novel possible PEA-Lut use for the treatment of VaD.

Background
Vascular dementia (VaD) is a dynamic disorder that influences psychological capacities that were caused by lessened blood stream to the cerebrum [1]. VaD patients may suffer both distinctive subjective impedance, for example, discouragement and tension and additionally the loss of executive capacities [1]. Until today, no other medication, excluding cholinesterase inhibitors and memantine, has demonstrated a particular advantage in the treatment of VaD, anyway they are dubious clinical criticalness; likewise Cerebrolysin has indicated advantageous impacts on VaD patients, notwithstanding, an ongoing meta-examination presumed that there is as yet lacking confirmation to prescribe it as a normal treatment for VaD [2,3]. Therefore is required to test constantly new particles, in order to find a treatment that is able to stop the progression of this pathology.

Neuroinflammation and oxidative stress (OS) has been widely correlated to be involved in the pathogenesis of both Alzheimer’s disease (AD) and VaD. Experimental evidence suggests that after stroke, the microglia acquires a M2 phenotype, which step by step changes into a pro-inflammatory M1 phenotype in the peri-infarct area [4]. The pathologic mechanism, for example, oxidative/nitrosative stress and apoptosis can stimulate the release of a proinflammatory mediators by receptive glial cells (microglia and astrocytes), and this impact can be exacerbated by an enlargement in BBB permeability, in this manner empowering the penetration of proinflammatory factors, for example, interleukins (IL-1, IL-6) and TNF-α and prompt neurodegeneration and cell passing in various cerebral locales, including those associated with psychological capacities, for example, the hippocampus [1,5-7].

Developing confirmation exhibited that OS isn’t just connected to VaD, yet additionally to all its hazard factors, for example, diabetes, hypercholesterolemia and hyperhomocysteinemia [8-10]. The importance of OS in such a significant number of neurodegenerative issue the brain is highly susceptible to reactive oxygen species (ROS), since it is wealthy in unsaturated fats, which are sensible to peroxidation, moreover it has not a powerful antioxidant activity, and considering that it expends a ton of oxygen it is presented to a vital free-radicals amassing [11,12].

Several researches have been directed with a specific end goal to explore whether antioxidant and neuroprotective exerts a role in the prevention and treatment of VaD. In fact, in the last year, more than fifteen author all over the world, have focused their attention on the link between vascular dementia and neuroinflammation/oxidative stress relationship (Table 1).

One of the most widely studied families of molecules in recent years in the field of neuroinflammation is the family of ALIAmides. ALIAmides stands for Autacoid Local Injury Antagonist amides (ALIAmides) and represent a group of endogenous bioactive acyl ethanolamides that include the renowned palmitoyl ethanolamide (PEA), stearoyl ethanolamide (SEA), and oleoyl ethanolamide (OEA) and that are involved in several biologic processes such as nociception, lipid metabolism and inflammations [13]. Several mechanisms describe the anti-inflammatory, anti-hyperalgesic and neuroprotective effects of PEA. In particular, PEA down-regulates mast cell activation and prevent

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Table 1. Last year publications on vascular dementia an oxidative stress

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<td>Zhu et al.</td>
<td>Anti-oxidative and Anti-apoptotic Effects of Acupuncture: Role of Thioredoxin-1 in the Hippocampus of Vascular Dementia Rats.</td>
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<td>Zhao et al.</td>
<td>Ling-Yang-Gou-Teng-decoction prevents vascular dementia through inhibiting oxidative stress induced neurovascular coupling dysfunction.</td>
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<td>Du et al.</td>
<td>Acupuncture inhibits TNXIP-associated oxidative stress and inflammation to attenuate cognitive impairment in vascular dementia rats.</td>
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...their degranulation, modulates the activation of nuclear factor kB (NF-κB) and the synthesis of pro-inflammatory enzymes and promotes the activation of a cell surface cannabinoid CB2-like receptor, or a nuclear receptor of the peroxisome proliferator-activated receptors (PPARs) family [14]. However, the PEA does not have direct antioxidant action to prevent oxidative stress and counteract injury to proteins and DNA.

For this reason during the years, PEA was associated with different antioxidant molecules such as a (trans)resveratrol glucose(s), polydatin [15-18] and (trans)polydatin [19-23] as well as a flavonoid luteolin [24-38].

Luteolin (Lut), like PEA, exerts a variety of pharmacological activities and anti-oxidant properties related with its great ability to scavenge oxygen and nitrogen species. Luteolin has been appeared to constrain cytokine expression and modulates NF-κB and TLR4 signalling at micromolar concentrations in immune cells, including mast cells [39-41]. Moreover, luteolin has been shown to attenuate microglial activation and mediate BDNF-like behavior both in-vitro and in-vivo [42,43]. Until today, luteolin has been shown a protective effect on several experimental model such as epilepsy [44-48], autism spectrum disorders [26,49-60], AD [61-65] and Parkinson Disease [63,66-68].

Until now, the only work that has analyzed the antioxidant, neuroprotective and anti-inflammatory of the PEA and luteolin in an experimental model of vascular dementia was made by Siracusa et colleagues [25].

In this work co-ultraPEALut, a compound based on the association of PEA an Luteolin in a ratio of 10:1, was able to improving the behavior and histopathological features in mice after VaD-induction ameliorating cognitive and social function VaD-reduced, modulating the NF-κB and apoptotic pathway, decreasing iNOS and COX-2 expression VaD-induced and increasing BDNF and NT-3 expression.

Conclusion
Growing evidence has indicated that oxidative stress and neuroinflammation plays a key role in the progression of VaD. Disparity between antioxidant enzyme activities and ROS generation will cause lipid peroxidation, protein oxidation and nuclear and mitochondrial DNA damage, resulting in brain damage. PEA possess a very important capacity to counteract inflammation but intriguingly, has no antioxidant property per se, however its co-ultramicronization with luteolin is more efficacious than both molecule alone. This could be represents a complementary therapeutic treatment to manage VaD-associated neuroinflammation.

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