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Hypothesis

The 5-Lipoxygenase as a Common Pathv Pathological Brain and Vascular Aging

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Abstract

Epidemiological studies indicate age as a strong risk factor for diseases. During the aging process, changes in the expression of these diseases. 5-Lipoxygenase (5-LO) by oxidizing fatty acids for inflammatory reactions, two key pathogenic events in both clinica cardiovascular as well as in the central nervous system, where its e it may be involved in their diseases of aging. The central theme biologic link between different stressors and the development of c hypothesize that the age-dependent upregulation of 5-LO represen in the brain, where a subsequent exposure to triggering stimu inflammatory reaction, and ultimately results in increased organ vu

1. Introduction

Consistent demographic data show that due to the improvements the number of older people (over 65 years) is fast increasing world

Since advancing age is the strongest risk factor for developing chr
increase several-fold over the next 15–20 years. This fact has cre
the population in view of the potential catastrophic socioeconomic
risk factor for atherosclerosis and chronic neurodegenerative disea
aging process is the most common feature of the postreproduc
organisms and is characterized by a progressive reduction in the e
decline translates to a reduced capacity to maintain homeostatic
increased organ vulnerability.

In experimental models, for example, aged animals have an exace
atherosclerosis even on a chow diet [3]. On the other hand, they a
potentiation, a form of synaptic plasticity that has been proposed
[4], and have impaired spatial learning in the Morris water maze [5

2. The 5-LO Pathway in the Vasculature and Central

5-Lipoxygenase (5-LO) is a member of a large family of enzym
esterified polyunsaturated fatty acids. 5-LO first introduces active
resulting in the formation of 5-Hydroxy-peroxy-eicosatetraenoic
reduced to 5-Hydroxy-eicosatetraenoic acid (5HETE), or converte
either as an intracellular intermediate in the synthesis of LTB4 a
subsequently be taken up by adjacent cells devoid of 5-LO act
synthase. LTs and the cysteinyl derivatives of LTs all have strong
Figure 1).

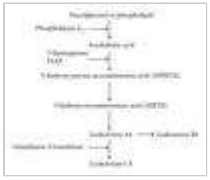

Figure 1: Schematic representation of the
Arachidonic acid is released from diacyglycer
Phospholipase . Once free, arachidonic acid
been activated by the Five-Lipoxygenase-Act
unstable 5-hydroxy-peroxy-eicosatetraenoic a
the more stable 5-hydroxy-eicosatetraneoic ac
leukotriene A4 (LTA4), which can serve either
LTB4 and LTC4, or may be released extracell
cells devoid of 5-LO activity but expressing LTA

5-LO is widely expressed in the cardiovascular system, that is, a
macrophages and neutrophils. Interestingly, its expression leve
compared with young ones [7]. This enzymatic pathway is also
(CNS), where it localizes mainly in neuronal cells of the hippocam
levels increase significantly with aging [8, 9].

The expression of 5-LO is susceptible to hormonal regulation,
melatonin deficiency and/or hyperglucocorticoidemia [10, 11], bo
Although in general upregulation of 5-LO might serve a physiolog
increase the vulnerability of the cardiovascular system and CNS t
subjects are at greater risk of health complications and mortality
functions, and aging, via the upregulation of 5-LO, can be an im
enzymatic pathway are of particular importance.

3. -LO, Aging and Cardiovascular Diseases

Recent studies have implicated 5-LO in the pathogenesis of ather
LO genotypes in subpopulations with increased risk of atherosclero

Age is an established risk factor for atherosclerosis. Among pri
extensive atherosclerosis than younger animals [17, 18]. Age-acc
result from increased oxidative stress, leading to inflammation ar
animals demonstrate increase generation of reactive oxygen spe
with age-associated remodeling changes, and oxidation of lipids,
and proatherogenic actions [20, 21]. Interestingly, in experimenta
be exacerbated by inflammatory stress such as lipopolysaccharide
receptor 4 (TLR4) on the surface of a variety of cell types sti
inflammatory leukotrienes derived from the 5-LO pathway [25]
enzyme or its genetic deficiency affords a significant protective
These facts, together with the upregulation of 5-LO in the ag
enzymatic pathway plays a functional role in the development of a

4. -LO, Aging and Neurodegenerative Diseases

In the CNS, aging, in general, is associated with an increased inci
among them, AD is the most frequent [27, 28]. From a biochemica
microglia activation and a diffuse and chronic brain inflammation ir
Interestingly, aged animals show greater increase in central infl
following both peripheral and central LPS administration [30, 31].
spatial working memory than is seen in young adult mice [32, 33]
Thus, as stress appears to sensitize the CNS to subsequent ins
sensitizes cells of the immune system to stress itself. Although t
responses and memory performance in elderly, however, the direc
unknown. In the aging brain, the prolonged stress-dependent infl
augmented neuronal vulnerability which often culminates in cell d
hypothesis, recent work has also highlighted a novel concept t
receptors as well as amyloid beta peptide metabolism, both of w
brain aging [34, 35].

5. Peripheral Stressors: Effect on Cardiovascular an

Stress is a risk factor for pathological aging because elderly indivic
to develop cardiovascular and/or neurodegenerative disorders th
Recent studies suggest that activation of peripheral immune sys
aged but, otherwise, healthy subjects compared with younger coh
aged individuals has been suggested as the basis for this abnorm
upregulation of 5-LO in the aging brain and vasculature by releasir
factor for these organs facilitating an abnormal inflammatory r
increased organ vulnerability and functional impairments (Figure 2

Figure 2: Hypothetical model whereby 5
pathological aging. During aging, peripheral
and/or the central nervous system find these
secondary to the upregulation of 5-LO in er
microglia, respectively. This fact facilitates an
which ultimately results in increased orga
development of pathology.

Importantly, while these responses are transient and reversible in and long-lasting in aged subjects.

In what follows, we briefly discuss two models of stress which hav mimick in vivo biologically relevant situations: LPS, as bacterial glucocorticosteroids (as it is typically observed in aging) [36, 37].

6. LPS

Administration of LPS has been widely used as a model to trigge [38–41]. These inflammatory responses, in part mediated by 5 accelerate vascular and neuronal vulnerability and subsequent cell endothelial cells and neurons, typical of the aging proce macrophages/microglia in these systems and sensitizes them to a response to stressors (Figure 2).

7. Glucocorticoids

Recent data suggest that glucocorticoid-sensitive mechanism(s) a the aging brain. Thus, high glucocorticoid levels appear to be a humans with prolonged elevated levels of cortisol exhibit reduced dependent memory tasks compared with normal cortisol contro neuronal survival [43] in vitro, and impairs cognition in vivo [44]. secondary to abnormalities in the hypothalamic-pituitary-adrenal a inflammatory reactions within the vasculature [45, 46]. In both sce further sensitize these organs to glucocorticoid-mediated detriment

In both cases, the hypothesis could be easily tested considering th enzymatic pathway, together with mice which are genetically defi with LPS or corticosteroids in the presence of the inhibitors, or a same stressors could provide us with important information suppor

8. Conclusions

Because of the projected aging of the human population, the burd dramatically over the next 20–25 years. The identification of a p these diseases and amenable of a therapeutic modulation would r life for this segment of the population but also in a significantly red fact that the 5-LO is significantly increased with aging, which ass well as neurodegenerative diseases, makes this enzymatic pathway

Several molecular mechanisms have been invoked for the 5-LO-risk, and most of them involve modulation of the inflammatory vas is known about the molecular mechanisms operating in the 5-LO-i 5-LO in regulating neuroinflammation, more recent works have p whereby this enzyme may be involved in pathological brain agin beta peptide metabolism.

Future studies are warranted to provide a more conclusive evidenc molecular mechanisms responsible for it.

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