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Capillaries, Old Age and Alzheimer's Disease

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Abstract

Many of the minor complaints of old age may have a common etiology and are grouped together here under the term 'the lesser ailments of aging' (LAA). This essay proposes that they are due in large part to an age-linked reduced microcirculation. Capillary density (CD) in the tissues is determined by levels of angiogenic growth factors (AGFs). Over 47 studies have reported a reduced CD and/or waning AGFs throughout the bodies of aging animals and people. More convincing than such a generalization are the 80 sets of data comparing these two parameters in adult vs. the aged. These data have led to a hypothesis whose corollary proposes a specific treatment for the LAA.

While genetically controlled, the waning levels of AGFs theoretically could be countered by pro-angiogenesis therapy and thus might ease the LAA or delay their onset. Therapies mentioned here include recombinant AGFs and inhibitors of type 5 phosphodiesterases, such a tadalafil/Cialis. Finally, Alzheimer's disease (AD) is generally an illness of the elderly and may have a single or multiple causes. However, its clinical course may be influenced secondarily by conditions affecting the LAA. Therefore, any effective treatment of them may influence favorably the clinical course of AD.

Introduction

Diminished blood flow to the brain and other organ systems may result from an impaired microcirculation due to pathological changes in the capillaries or reduced numbers of capillaries. The former are reflected in twisting, kinking, and looping of capillaries in the cerebral cortex [1-3]. Whether these changes progress to reduced capillary numbers by cellular atrophy has not been demonstrated and is not considered further here. However, the widespread reduced capillary density (CD) found in aged animals and people has been correlated with diminished levels of angiogenic growth factors (AGFs) [4-6].

The association between CD and AGFs during old age is the focus of this essay, which advances two ideas. 1) The reduced CD of old age may be the main, primary cause of many symptoms and signs of the elderly, i.e., the 'lesser ailments of aging'. 2) A reduced CD may also be an underlying, secondary condition for other diseases associated with aging and may facilitate the action of factors postulated to cause them -- e.g. amyloid plaques, neurofibrillary tangles, etc. of Alzheimer's disease (AD) or Lewy bodies, proposed malfunctioning mitochondria, etc. of Parkinson's disease (PD).

The Lesser Ailments of Aging

People die from accidents and major diseases. The rest live on through old age with generally two sorts of complaints: chronic afflictions and/or lesser ailments. The former involve arthritis, diabetes, atrial fibrillation, Parkinson's disease, or other distressing illnesses and are not a concern here. The latter, the lesser ailments, include minor symptoms, such as general muscle weakness, cold intolerance, memory lapses for names or words, and momentarily dozing, especially during the evening hours [6]. Also included are physical signs, such as wrinkled skin on the face and dorsum of the hands and the slow healing of bruises and abrasions. These symptoms and signs may share a common etiology which is the reduced capillary density that develops throughout the body during old age.

As discussed elsewhere, a reduced CD in aged persons and animals has been described in over 40 reports and noted in many organ systems -- i.e., brain, muscle, skin, larynx, lung, colon, kidney and vasa vasorum [5,6]. Capillaries are formed and maintained by angiogenic growth factors (AGFs), whose levels are genetically programmed during early development and throughout life. A decline in AGFs in the aged has been described in seven other reports and noted in five organ systems -- i.e., the brain, muscles, kidney, mononuclear cells, and vein wall [5,6]. Among the AGFs are vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), and other such factors. For this essay, the important aspect of these AGFs is that during old age their levels decline, resulting in a reduced capillary density in the tissues. Thus, the lesser ailments reflect a deficiency condition of AGFs, much like the reduced testosterone levels in elderly males.

In the literature little mention has been made that the decline in the levels of AGFs in the elderly is genetically programmed. Whether amyloid plaques or other factors can also influence capillary density is unclear.

The Importance of Data

In theory from the above analysis, the lesser ailments should be relieved or delayed by pro-angiogenic therapy -- e.g., recombinant forms of VEGF, FGF, or other angiogenic agents. This is a novel idea which must be introduced with persuasive data to be seriously considered by students of aging.

Merely listing a large number of papers sharing a common effect does not convey so convincingly their importance as does showing the relevant data. Age-linked changes are presented here in the form of 'data pairs' -- i.e., values of CD or AGFs in adult animals or people vs. those in their aged counterparts. For example, Amenta et al. measured the capillary density in three areas of the brain of rats age 12 months vs. 18 months old and reported reduction of the CD as follows -- frontal cortex: 122 vs. 71, occipital cortex: 130 vs. 82 and hippocampus: 113 vs.

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58 [7]. Similarly, Haidet et al. compared the CD in three muscle areas of beagle dogs ages 2-3 years vs. 10-14 years and found the following -- gastrocnemius: 886 vs. 718, semitendinosus: 895 vs. 658, and triceps: 959 vs. 805 [8]. These six sets of data are more persuasive than a generalization that papers by Amenta and Haidet show an age-linked reduce CD.

As noted above, an examination of the research literature on aging and angiogenesis has disclosed 47 studies concerning CD and levels of AGFs. They have provided 80 data pairs showing age-linked reduced CD and declining AG. These paired figures have been presented elsewhere in tables and are the basis for a hypothesis that the reduced capillary numbers in the elderly account in part for their lesser ailments [4-6].

Cause and Effect

The mere temporal association of two events -- here, a reduced CD throughout the body with aging and the age-linked development of LAA -- does not establish by itself cause and effect. Definitive proof would be showing that pro-angiogenesis therapy relieved or delayed onset of the lesser ailments. This proof has yet to be established. However, many experimental studies employing recombinant forms of AGFs support the hypothesis, as discussed in detail elsewhere [6,9]. For example, injection of VEGF or FGF into the normal cerebral cortex or ventricle of animals elicits cortical angiogenesis [10,11]. Occlusion of the femoral artery in an animal's hind limb evokes ischemia there, which is relieved by local injections of AGFs [12]. Pro-angiogenesis treatment produced suggestive clinical improvement in subjects with intermittent claudication or cardiac insufficiency [13,14].

The natural course of AGFs during animal/human life offers inferential support to the angiogenesis hypothesis. During early life, the rising levels of AGFs and the maturing microcirculation determine the development of various organ systems and account for the healthy functioning of the body. During old age, the waning levels of AGFs and the declining CD parallel the falling organ function and may logically account for the emerging symptoms and signs of aging -- notably the general muscle weakness of the lesser ailments.

Alzheimer's Disease

Alzheimer's disease is a dreaded development during aging in many persons. A reduced CD in subjects with AD is documented in five reports with 11 data pairs. Table 1 lists the CD in AD patients compared to values in an adult group or an aged group. Since all AD subjects here were elderly, a reduced CD found in them might merely reflect their age and not a specific effect on the AD aspect of their state of health. However, four data pairs suggest a slightly greater reduced CD in AD subjects compared with similarly aged persons -- e.g., reports #1 (entorhinal cortex), #3, and #4.

Other studies on AD patients suggest an impaired cerebral microcirculation. 1) Farkas et al. [15] postulated that capillary dysfunction occurs in both Alzheimer's diseases and Parkinson's disease, based on finding a 2-fold increase in basement membrane deposits in these two conditions. 2) Hunter et al. found elevated numbers of degenerated string capillaries in AD brains but no overall reduced CD. However, the "total brain mass, determined at autopsy, was significantly less in AD compared to ND [non-demented] control groups" [16]. Cortical shrinkage may mask any reduced cerebral capillary counts, as discussed elsewhere [4]. 3) Sweat and Jicha reported that "capillary length-density was greater in AD...in the frontal neocortex" but postulated atrophy of the brain "as responsible" [17]. 4) Miners et al. reported a reduced CD and diminished levels of VEGF in cases of dementia with Lewy bodies [18]. 5) Parenthetically, Mateo et al. reported lower serum VEGF levels in subjects with Alzheimer's disease [19].

Some gerontologists contend that AD involves a reduced cerebral microcirculation and have considered pro-angiogenesis therapy to aid this condition. For example, in 2004 Ward and LaManna wrote that "we now know angiogenesis is involved in Alzheimer's disease" and several other neurological disorders [20]. They suggested that "controlling angiogenesis may also provide novel therapeutic approaches for treatment of these disorders." In 2011, Wang et al. also wrote that "that VEGF should be pursued as a novel therapeutic agent for treatment of AD" [21]. These latter authors had found that therapeutic angiogenesis ameliorated the memory impairment in APP transgenic mouse model of Alzheimer's disease. And in 2015, Baloyannis considered that "protection of the brain capillaries at the initial stages of the disease" might reduce "the pathological alterations" in AD [22].

Pro-Angiogenesis Therapy

Three therapeutic approaches for easing the lesser ailments warrant consideration.

Authors	Adults	Aged	AD
Mean capillary density mm/mm^3	av. 38year (5)	av. 74 year (5)	av. 78 year (5)
Entorhinal cortex	148	124	111
Overall of 6 zones	124	102	101
Av. Capillary density mm/mm^3	12-54 year (8)	67-95 year (8)	63-92 year (10)
Visual cortex, lamina 1	141	99	97
Visual cortex, av. of 6 laminae	251	212	206
% capil, surface area of total cortical field area	49 year (1)	av. 79 year (3)	av. 80 year (7)
Cortical areas	26.32%	18.95%	16.50%
Capillary density in test grid method		73 ± 4 year (6)	79 ± 12 year (8)
Frontal cortex		c. 28	c.21
Parietal cortex		c. 28	c.20
Vascular density index	23-90 year (6)		76-92 year (16)
Prefrontal cortex	94.6		75.4
Basal forebrain	86.8		42.7
Hippocampus	82.3		50.2
Motor sensory cortex	94.3		83.1

Note: c=value extrapolated from figure listed; other values listed here are cited in text; ( )=number of subjects

Table 1: Cerebral capillary density in adults/aged and AD subject.

1) Employing recombinant angiogenic growth factors (VEGF, FGF or others) has been discussed at length in previous papers [4-6]. Their weaknesses for clinical use include being destroyed in the intestinal tract when administered orally and a short half- life in the circulation. These problems could be overcome in part by nasal administration in snuff or nose drops, as suggested and explained elsewhere [4,23].

2) Physical exercise evokes production of VEGF by striated muscles [5]. The released endogenous factor may enhance muscle function locally with new capillaries but also might reach the brain via the blood, increase the cerebral microcirculation, and improve memory and cognition. Exercise has been popularly recommended to improve mental sharpness [24].

3) A recent option is testing a long acting inhibitor of the type 5 phosphodiesterase (PDE5), such as tadalafil/Cialis.

Besides angiogenic growth factors (VEGF, FGF, etc.), several newly developed drugs in wide clinical use have been shown to elicit angiogenesis. They include sildenafil (Viagra) and tadalafil (Cialis), which are prescribed to treat various medical conditions, including erectile dysfunction (ED), benign prostatic hyperplasia (BPH), and pulmonary arterial hypertension (PAH) [25]. The drugs' intended effect in patients is to produce vasodilation, but in animal studies both have been shown also to induce capillary formation in ischemic tissues/organs [26-31]. These drugs regulate a key intermediate in metabolic pathways leading to capillary formation, as outlined elsewhere [32]. They are effective when administered orally. For promoting angiogenesis, Cialis would be the superior PDE5 inhibitor because it has a longer biological half-life -- 17.5 h for Cialis vs. 4 h. for Viagra.

Conclusion

This short commentary has been a defense of the angiogenesis hypothesis of aging and the grouping together of the lesser ailments of aging (LAA). More difficult to support or prove is the idea that a reduced CD may facilitate the mechanisms or agents which have been proposed to cause AD and PD. It seems logical to believe that brain nutritionally impaired by a reduced cerebral microcirculation may be more vulnerable to specific pathological insults -- e.g., amyloid plaques, Lewy bodies, etc. But the reciprocal consideration suggests that a well-nourished brain may slow the onset of the genetically fated cognitive decline. Thus pro-angiogenesis treatment seems a tenable approach for dealing with the LAA and indirectly with AD and PD.

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