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Treatment of the Lesser Ailments of Aging: Phosphodiesterase Type 5 Inhibitors

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Abstract

Along with various major illnesses or chronic afflictions, the elderly may also have minor complaints. These include general muscle weakness, cold intolerance; transient memory lapses for a name or word, wrinkled skin, and the slow healing of cuts and bruises. These five symptoms and signs are grouped together here because they may have a common vascular basis, which is the reduction of capillaries throughout the body in the elderly. This reduction is due to diminished levels of angiogenic growth factors, as reported in both aged people and animals. Recombinant forms of these factors given parenterally have elicited capillary production (angiogenesis) in numerous experimental studies and if chronically administered to the elderly, might, in theory, ease their lesser ailments. Angiogenesis has also been elicited in animal tissues by type-5 phosphodiesterase inhibitors - sildenafil (Viagra) and tadalafil (Cialis). These are widely prescribed orally for their vasodilatory effect. Tadalafil is discussed here as a potential pro-angiogenesis agent for modulating the lesser ailments of aging and possibly influencing the clinical course of senile dementias, such as AD.

Keywords: Lesser ailments; Aging; PDE-5 inhibitors; Angiogenesis; Capillary density

Introduction

Apart from occasional accidents (falls and other injuries), elderly people experience a triad of health issues of differing severity: major illnesses (cancer, strokes, heart attacks, Alzheimer's disease, etc.), chronic afflictions (obesity, diabetes, arthritis, hypertension, atrial fibrillation, Parkinson's disease, etc.) and minor health complaints. Among the last are the 'lesser ailments of aging' (LAA), which include three symptoms (mild muscle weakness, cold intolerance and momentary memory lapses for names or a word) and two physical signs (wrinkled skin on the hands and face and the slow healing of cuts and bruises) [1,2]. The LAA have not been considered collectively before but are grouped together here because they may have a common, treatable cause - i.e., a reduced microcirculation, which is commonly expressed as 'a reduced capillary density' (CD). In theory, therapies promoting angiogenesis (AG) should restore a reduced CD and thus might relieve or delay onset of the LAA. Other minor health issues of the aged (fading hearing, urinary incontinence, constipation, dysphagia, thinning/gray/white hair) are not so clearly linked to diminished capillaries.

Three of the LAA - muscle weakness, wound healing, and possibly memory lapses - are directly affected by capillaries nourishing muscles, wound tissue, and the brain, respectively. Cold intolerance and wrinkled skin are influenced indirectly by the microcirculation, for capillaries maintain subcutaneous fat which insulates the body and smoothens the skin. Such fat cells (adipocytes) are regulated by angiogenic growth factors (AGFs), which determine the growth and maintenance of all capillaries [3].

Normal brain function obviously depends on an adequate cerebral blood flow. In 1993, de la Torre and Mussivand first proposed that an impaired cerebral circulation may be an underlying cause of a neurological condition most common in old age - Alzheimer's disease (AD) [4]. Along with various risk factors (obesity, diabetes, hypertension, etc.), he incriminated the atheromatous pathology in arteries. The focus of this present essay is on the microcirculation during old age. Capillaries in the brains of aged persons and those with AD become deformed by kinking and twisting, as described in numerous reports [5,6]. But more significant here may be the age-associated reduction in capillary numbers.

A reduced capillary density in old animals and aged persons (including those with AD) has been documented in over 47 reports and found in eight organ systems - i.e., brain, muscle, skin, larynx, colon, kidney, lung and vasa vasorum. These data have been summarized in the tables of my earlier papers [2,7,8].

Capillaries in people and higher animals are generated and maintained by angiogenic growth factors (AGFs), whose levels, like many hormones, are genetically programmed during early development and throughout life [9]. Among the AGFs are vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), angiopoietins (Ang) and many others discussed in detail elsewhere [10,11]. During old age, their levels fall, resulting in a reduced capillary density in tissues. The decline of such factors in aged persons and animals also occurs throughout the body (like the reduced CD) and has been described in seven reports and found in five organ systems - i.e., the brain, muscles, kidney, mononuclear cells and vein wall. See the tables of earlier papers [2,7,8].

These 47 reports on reduced CD and the seven on declining AGFs have led to the angiogenesis hypothesis, which proposes that such changes in elderly persons account in part for their lesser ailments. A corollary states that the ailments may be relieved or delayed by proAG therapy - e.g. recombinant forms of angiogenic growth factors (e.g. VEGF, FGF, etc.) or other agents promoting angiogenesis (see later).

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The microcirculation in the brain may affect medical conditions other than the momentary memory lapses of LAA. Major dementias, like Alzheimer's disease, may be "triggered by poor blood flow to the brain", as advanced again by de la Torre in 2017 [12]. I suggest that independent of its primary cause/causes, the subsequent clinical course of AD may be affected by a reduced cerebral CD and would be favorably influenced by pro-AG therapy.

In Defense of the Angiogenesis Hypothesis

The close association in time of these two changes in the body - i.e., a reduced CD and emerging LAA - does not establish that one causes the other. The body is also subject to environmental influences (e.g. nutritional) and other genetic ones (e.g. hormonal). While there are ample aggregate data showing a reduced CD and AGFs in the aged compared to values in younger adults, there are no figures showing a gradual reduction with time of CD/AGFs in parallel with a gradual accumulation of lesser ailments - i.e., there is no reciprocal temporal correlation, which is often useful in establishing cause and effect in other situations.

Support for AG hypothesis would come from showing that pro-angiogenesis therapy or prophylaxis in people can relieve or delay onset of the LAA. Such evidence has yet to be obtained and would involve a longitudinal clinical study lasting many years. Assessment of the lesser ailments would be difficult and would rely mainly on subjective self-evaluations. Muscle strength could be measured, but other potential influences than the microcirculation (e.g. hormones) would complicate any interpretation. Testing an animal model of aging with AGFs would also require several years, but biopsy and autopsy data on CD in animals would be more readily available than in human trials. Nevertheless, support for the hypothesis can be inferred from past human studies and animal experiments described next.

Three sets of human studies are relevant here. 1) Men with intermittent claudication were given bilateral femoral artery infusions of FGF-2 which resulted in a slightly increased walking time when assessed 90 days later [13]. 2) Subjects with impaired cardiac function received VEGF-A_{165}, FGF1 or FGF2 by intracoronary artery or intra-myocardium administration. None of the above trials measured CD by histological means but assumed that angiogenesis had occurred based on initial clinical improvement. While no long-lasting clinical benefits were achieved in either of these two short term studies, the safety of recombinant factors was established [14,15].

3) Studies begun in 1984 by Goldsmith would later show that increased endogenous angiogenesis improved cognition in subjects with AD [16]. He had observed that angiogenic activity is produced in rabbit corneas injected with a lipid extract from cat omentum [17]. The rat omentum contains 884 pg/mg of VEGF protein, which is 8-fold higher than in any other rat tissue [18]. Thus the human omentum, which cushions the abdominal viscera, is also a likely natural source of AGFs. Goldsmith surgically transposed an omental pedicle under the anterior abdominal skin and stretched it subcutaneously up the chest and neck to reach and cover part of the brain surface in 25 elderly subjects. He reported that ten subjects showed slight cognitive improvement, while "nine demonstrated marked cognitive increases" [19]. Presumably, the human pedicles supplied additional endogenous AGFs to the brain, thus improving the cerebral microcirculation.

Animal experiments employing recombinant forms of AGFs are another support for the hypothesis. For example, six studies simulated age-linked muscle weakness by occlusion of the femoral artery in the hind limb of various animals which evoked local ischemia. Injections of AGFs produced an improved local capillary bed and a return of the affected limb's strength. In another six studies, wound healing in mice, rats, rabbits, and pigs was promoted by administering various AGFs. The above 12 studies have been summarized and referenced in an earlier review paper [8]. Thus counterparts in animals of two lesser ailments in people - muscle strength and wound healing - showed improvement with pro-AG therapy.

Numerous studies of experimentally induced focal cerebral ischemia in rats and mice have shown new capillaries around the infarct area after administering VEGF [20-24]. In 2011, Wang et al. reported that daily intraperitoneal injections of VEGF led to improved learning and memory in mice tested in a Morris water maze [25]. They found an increased CD in the hippocampus up through the second week.

Reports of PDE-5 Inhibitors Producing Angiogenesis and Increased CD

Besides the recombinant AGFs used in the above studies, several newly developed drugs in wide clinical use have been shown to elicit angiogenesis. They are phosphodiesterase type 5 inhibitors (PDE-5), such as sildenafil (Viagra) and tadalafil (Cialis). These are prescribed to treat various medical conditions - erectile dysfunction (ED), benign prostatic hyperplasia (BPH) and pulmonary arterial hypertension (PAH) [26]. 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. These PDE-5 inhibitors regulate a key intermediate in metabolic pathways leading to capillary formation, as described later.

There are six reports in the experimental literature showing that sildenafil and tadalafil produce an increased capillary density in various organ systems rendered hypoxic before treatment [27-32]. These studies raise the issue of whether such drugs might ease the lesser ailments in elderly persons by restoring to some degree the widespread reduced CD. Thus the angiogenic action of these new drugs may have important medical implications in the elderly apart from ED, BPH and PAH. Below are synopses of these six reports (Table 1).

1. Li et al. produced strokes in rats by embolic occlusion of the middle cerebral artery. Sildenafil 10 mg/kg was then injected subcutaneously for six days, and the rats were autopsied six weeks after the stroke [27]. CD in the ischemic boundary area was measured on Day 42 using endothelial barrier antigen immunostaining and found to be c.480 in the control rats and c.570 in the treated ones. (The c. before a number indicates that it was extrapolated from a figure in the paper cited; other numbers cited here are the precise figures presented in the text of other papers.)

2. In 2005, Zhang et al. examined the embolic area created by occlusion of the middle cerebral artery in aged and young rats [28]. Some rats from each age group were given 10 mg/kg sildenafil subcutaneously for six consecutive days. All rats were autopsied on Day 30. CD was measured in the ischemic boundary areas using von Willebrand antigen immunostaining. The CD was c.40 in the young control/untreated rats and c.70 in young sildenafil-treated rats. Old rats showed lower control and treated values - i.e., c.32 in the controls versus c.48 in the treated ones, suggesting that aged rats had a "reduced expression of VEGF."

3. Ulusoy et al.'s group prepared dorsal skin grafts in rats for

Li et al. [27]	Rat brain embolic stroke...sildenafil 10 mg/kg SQ qd × 6 days			
	CD in ischemic boundary area examined 6 weeks after stroke			
		Control	10 mg/kg	
	CD, Day 42:	c.480	c.570	
Zhang et al. [28]	Rat brain embolic stroke...sildenafil 10 mg/kg SQ qd × 6 days			
	CD in ischemic boundary area examined on Day 30			
		Control	10 mg/kg	
	CD, Day 30: young rats	c.40	c.70	
	CD, " " : old rats	c.32	c.48	
Ulusoy et al. [29]	Dorsal skin flaps in rats…sildenafil 2.5 mg or 10 mg/0.5 ml			
	In slow release fibrin glue applied before closure by sutures			
		Control	2.5 mg	10 mg
	CD, Day 7:	77.8	91.8	92.5
Senthilkumar et al. [30]	Hind limb ischemia in mice...sildenafil oral ad lib × 7 days à			
	10 mg/kg/day...gastrocnemius muscles examined on Day 7 and 21			
		Control	10 mg/day	
	CD, Day 7:	c.0.3	c.0.6	
	CD, Day 21:	c.5.8	c.8.8	
Koneru et al. [31]	Rat heart occlusion...sildenafil 0.7 mg/kg IV 1x before			
	Occlusion...peri-infarct area examined on Days 2, 4, 7			
		Control area	Peri-infarct area	
	CD, Day 2:	3298	4617	
	CD, Day 4:	3449	4978	
	Arteriolar Density, Day 7:	2.16	5.4	
Zhang et al. [32]	Rat brain...cerebral occlusion...tadalafil oral ad lib × 6 day			
	Ischemic boundary area examined on Day 30			
		Control area	2.5mg/ml	10 mg/ml
	CD, Day 30:	c.400	c.500	c.580

Table 1: Lesser ailments Rx.

early closure by sutures. Circulation to the tissue in the flaps was greatly reduced [29]. Before closure, the inside of some skin flaps was treated with sildenafil citrate (2.5 mg/0.5 ml or 10 mg/0.5 ml) in slow-release fibrin glue. Control rats had skin flap treated with only the glue. On Day 7, the flaps were examined histologically for CD. The average CD in the three groups - 0 mg, 2.5 mg and 10 mg - was 77.8, 91.8 and 92.5, indicating increased angiogenesis in the two treated groups.

4. Senthilkumar et al. subjected mice (ages 2-3 months) to chronic ischemia of the left hind limb by ligating the left femoral artery on Day 0 [30]. They measured the CD in gastrocnemius muscles (right and left) on Days 7 and 21. Mice were given sildenafil in their drinking water ad lib for seven days, which resulted in a dose of 10 mg/kg/day. The CD values on Day 7 were c.0.3 (right, control) and c.0.6 (left, ischemic) and on Day 21 were c.5.8 and c.8.8, respectively. This indicates an increased angiogenesis in the ischemic limb over that of the normal limb.

5. Koneru et al. occluded the left anterior descending artery in rat hearts and assessed the microcirculation in control areas and peri-infarct areas on Day 2, 4 and 7 [31]. All rats were treated with sildenafil 0.7 mg/kg IV before occlusion. The CDs were measured in control areas and per-infarct areas and on Day 2 were 3298 and 4617 and on Day 4 were 3449 and 4978, respectively. The arteriolar densities on Day 7 were 2.16 and 5.4, respectively. Thus increased angiogenesis was induced in the hypoxic peri-infarct area of the hearts by sildenafil.

6. In 2006, Zhang et al. induced strokes in rats by occlusion of the middle cerebral artery and then provided tadalafil in the drinking water at 2.5 mg/ml and 10 mg/ml for 6 days [32]. Control rats received no drug. CD was measured in the ischemic boundary area on Day 30 using a monoclonal antibody to the endothelial barrier antigen. The CD values were c.400 (no drug), c.500 (2.5mg/ml) and c.580 (10 mg/ml).

In summary, the first five of the above reports tested sildenafil/Viagra, while the last one examined tadalafil/Cialis. The latter seems the more optimal agent, as explained later. The next two sections of this essay concern specialized aspects of PDE-5 inhibitors and can be passed over without losing the significance of them as pro-AG agents. The main narrative of this essay resumes with the section entitled The Importance of Half-lives of Pro-AG Agents.

Metabolic Pathways of VEGF and PDE-5 Inhibitors Leading to Capillary Formation

The pathways by which VEGF and PDE-5 inhibitors elicit capillary formation have been proposed by Pyriochou et al. and presented of their paper [33]. The following diagram outlines the proposed steps in the pathway leading to capillary formation, starting with VEGF.

VEGF → ↑NO → ↑**s**GC → ↑cGMP (from GTP) → ↑PKG1 → ↑p38 & ↑ERK1&2 → ↑CD

→ GMP (inactive)

VEGF functions at an early stage producing nitric oxide (NO). NO activates sGC (soluble guanylyl cyclases), which catalyze the formation of cGMP (cyclic guanylmonophosphate) from GTP (guanyltriphosphate). cGMP stimulates the remaining steps, which include a series of protein kinases - PKG1, p38 and ERK1 and 2 (Extracellular Regulated Kinases). The last steps induce angiogenesis with the migration and proliferation of endothelial cells and the formation of tube-like networks.

PDE-5 inhibitors induce angiogenesis as outlined in the following diagram.

PDE-5 inhibitors → ↓GMP → ↑cGTP (accumulation) → ↑PKG1 → ↑p38 & ↑ERK1&2 → ↑**CD**

Inhibitors of PDE-5 suppress the breakdown of cGMP to GMP and allow the accumulation of cGTP and the subsequent steps leading to angiogenesis.

In summary, VEGF stimulates production of cGTP, while PDE-5 inhibitors promote its accumulation by preventing its normal breakdown. The possible involvement of hypoxia inducible factors with VEGF was not included in the metabolic scheme proposed by Pyriochou et al. [33].

The Role of Ischemia in pro-AG

The widespread, general decline in levels of Angiogenic factors in the aging body is genetically programmed and presumably irreversible at that level. A practical issue with the therapeutic corollary of the AG hypothesis is whether a locally reduced CD represents a quasi-ischemia state responsive to pro-AG therapy. Most reports of pro-angiogenesis have involved responses in hypoxic tissues. For example, clinically directed pro-AG therapy in people has produced increased microcirculation under ischemic conditions, such as post-cerebral

infarct and myocardial insufficiency, as mentioned earlier. Similarly, most animals studies which tested antigenic growth factors have involve ischemic organ systems - ischemic hind limb from ligated femoral artery and ischemic brains from occluded middle cerebral artery [8,34]. The six animal studies with sildenafil and tadalafil, outlined above, found that PDE-5 inhibitors elicit capillary formation in areas of experimentally induced ischemia. Senthilkumar et al. wrote that "sildenafil therapy preferentially alters ischemic tissue response without nonspecific effects on non-ischemic tissue" [30].

But the following pro-AG studies examined normal animals and normoxic tissue sites.

1. Puumala et al. infused FGF-2 into the left lateral cerebral ventricle of healthy rats six times over 26 days and on Day 30 found increased CD in the left cortex (315/mm^2) but no increase in the brains of sham injected rats (261/mm^2) [35].
2. Rosenstein et al. infused VEGF by an osmotic minipump to a 3 mm depth in the rat brain near the coronal-lateral sutures for 7 days at 1 μl/h and found the infusion site filled with "remarkably vascular tissue" [36].
3. Wang et al. gave transgenic AD mice intraperitoneal VEGF for three days and reported "new blood vessel formation" in the hippocampal by the 7th and 14th days after treatment [25].
4. Two studies from the same lab using rats showed "site directed growth" of new blood vessels in an area of the normal heart (between aorta and myocardium of the left ventricle) treated for nine weeks with FGF-1 in a sponge or in a fibrin glue [37,38]. But a separate study by Banai et al. involved dogs whose normal hearts were treated with epicardial sponges containing α-FGF for four weeks. Here there was no evidence of smooth cell hyperplasia in the treated area [39].

Normoxic conditions prevailed in tissue culture experiments with various angiogenic growth factors and PDE-5 inhibitors. As reviewed below, endothelial cell replication and capillary tube like formation have been observed.

5. Pepper et al. treated cultures of "microvascular endothelial cells" of bovine adrenal origin with VEGF and bFGF under normoxic conditions and observed formation of capillary-like tubules [40].
5. Wilting et al. treated chick chorioallantoic membranes under normoxic conditions with VEGF165 and found that "many new blood vessels emerged from the precapillary arterioles" [41].
5. Pyriochou et al. observed in a chorioallantoic membrane model under normoxic conditions that sildenafil produced "a more robust migratory response than that produced by a saturating VEGF concentration" [33].

In conclusion, the issue of whether pro-AG therapy with a PDE5 inhibitor may correct the age-linked reduced CD in people has support in the experimental literature but can be definitely decided only by the clinical responses in appropriate human trials.

The Importance of Half-lives of Pro-AG Agents in the Elderly

The restitution of an optimal, 'healthy' capillary density throughout the body may require low level therapy daily in order to counter the genetic-determined, age-linked decline. Dor et al. used a tetracycline-regulated transgenic mouse model "for conditional switching of VEGF expression" and found that administering VEGF for 30 days led to long term persistence of vascular gains in the liver while a 15 day treatment did not [42]. The inference is that pro-AG therapy may need to continue for a long time, perhaps for the remainder of a person's life.

Thus in a clinical situation, the half-life of potential pro-AG agents would seem to be important. Takeshita et al. [43] reported a 6 min half-life for VEGF, while de la Riva et al. listed 50 min [44]. Viagra has a 4 h half-life, while Cialis has a 17.5 h half-life and continues to act for 36 h after a single dose [27]. Cialis would seem to provide the best continuous pro-AG therapy. Also, like other PDE-5 inhibitors, it is effective when given orally, while angiogenic growth factors are destroyed in the GI tract and have always been introduced parenterally.

Clinical Evaluation of Proposed Pro-AG Therapy

The administration of tadalafil (Cialis) may not only promote angiogenesis but may also elevate levels of testosterone. This was shown to occur with sildenafil (Viagra) in a double blind study with men age 40 to 70. Their mean total serum testosterone levels before and after a four-week course of sildenafil was 254 ng/dL and 338 ng/dL [45]. If the same androgen response occurred with tadalafil, this might cloud the interpretation given here to its effect on the muscle strength of LAA and suggest an indirect one via the increased androgen. Thus tadalafil might act through the protein kinase pathway and also via some hormonal one.

As mentioned earlier, evaluating the clinical benefit of pro-angiogenesis therapy in the elderly would rest mainly on subjective self-appraisals, such as noting improved strength, near normal rates of healing on minor lesions, or fewer instances of lapsed recall of names or facts.

Simons mentioned the absence of any useful biomarkers for CD in subjects in a clinical trial and cautioned about a placebo effect [46].

Previously, the only objective quantitative measurement of CD has been histologic studies on muscle biopsies done on living subjects or on tissues obtained at autopsy. Ideally, non-invasive assessments might involve capillaries visualized under the fingernails, in the forearm skin or in the conjunctiva but such measurements have not been quantified sufficiently to evaluate small changes during any therapeutic trial. Recently, the 'angiogenic vasculature' has been visualized by magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and other imaging modalities [47]. These methods can localize sites of angiogenesis in "living tissue deep within the body" but generally cannot yet resolve vessels of the microcirculation [48].

In 2006 Jensen et al. reported on the capillary density in animal brains using a bolus intravascular injection of a paramagnetic contrast agent, but the dose necessary is too large for human studies [49]. The gadolinium-based contrast agent used produces severe side effect in human subjects [50]. The iron oxide nanoparticle Endorem, which is an intravascular contrast agent with a long plasma half-life, has been approved for human use in clinical studies [50].

Conclusion

One goal of studies on aging should be to identify treatments which may reduce or delay the body's decline and discomfort during old age. From a broad perspective, elderly people experience a triad of health problems: major illnesses, chronic afflictions and lesser complains. Since these involve deviations from healthy physiological conditions,

correcting one of them (e.g. an altered circulation) should ideally improve old persons' health and sense of well-being. Of the lesser complaints, the LAA may be due to a reduced CD. Pro-AG therapy may relieve or delay the five particular ailments discussed here and thus ease some part of the lesser discomfort experienced by the elderly. While recombinant VEGF and FGF have been administered safely in clinical trials involving several ischemic conditions, to my knowledge these experimental growth factors have not been tested in other human situations or considered for 'treating' the medical issues of aging.

Recombinant AGFs have been administered parenterally because of their being destroyed in the intestinal tract. They are metabolized in the liver and have short half lives in the circulation. However, they escape 'first pass loss' in the liver - "hepatic presystemic disposition" - when given by sublingual route or by nasal drops or snuff, as explained elsewhere [8,51]. These might be practical routes for continuous daily treatment with recombinant AGFs.

The observation that phosphodiesterase 5 inhibitors induce angiogenesis in animals suggests they may have a therapeutic potential in situations of reduced CD in the elderly. One such agent - tadalafil (Cialis) - is promising because it has a relatively long half-life in vivo and is effective via the oral route. It is now widely prescribed for various medical condition (ED, BPH, PAH). In 2014, 16.2 million prescriptions for tadalafil were filled in the United States [51]. A large number of people are still taking Cialis daily and have done so over many months. Such a 'cohort' might provide a preliminary hint of whether the drug relieves any of the LAA. But a convincing answer would involve a long term, double blind clinical trial directed specifically to this issue.

Earlier in this essay, I suggested that pro-AG therapy might affect the clinical course of Alzheimer's disease. It would be difficult to determine whether the above 'Cialis-cohort' has a reduced incidence or slower progression of AD or other neurological diseases of the elderly, such as Parkinsonism. But this possibility might be kept in mind when designing any clinical trial with tadalafil.

References

1. Ambrose CT (2017) Capillaries, old age and Alzheimer's disease. J Alzheimer's Dis Parkinsonism 7: 309.
2. Ambrose CT (2016) The role of capillaries in the lesser ailments of old Age and in Alzheimer's disease and vascular dementia: The potential of pro-therapeutic angiogenesis. J Alzheimers Dis 54: 31-43.
3. Lyons ME, Parker KJ (1988) Absorption and attenuation in soft tissues. II. Experimental results. IEEE Trans Ultrason Ferroelectr Freq Control 35: 511-521.
4. de la Torre JC, Mussivand T (1993) Can disturbed brain microcirculation cause Alzheimer's disease? Neurol Res 15: 146-153.
5. Hassler O (1967) Arterial deformities in senile brains. The occurrence of the deformities in a large autopsy series and some aspects of their functional significance. Acta Neuropathol 8: 219-229.
6. Fischer VW, Siddiqi A, Yusufaly Y (1990) Altered angioarchitecture in selected areas of brains with Alzheimer's disease. Acta Neuropathol 79: 672-679.
7. Ambrose CT (2015) A therapeutic approach for senile dementias: neuroangiogenesis. J Alzheimers Dis 43: 1-17.
8. Ambrose CT (2015) Muscle weakness during aging: A deficiency state involving declining angiogenesis. Ageing Res Rev 23: 139-153.
9. Ohlsson C, Wallaschofski H, Lunetta KL, Stolk L, Perry JR, et al. (2011) Genetic determinants of serum testosterone concentrations in men. PLoS Genet 7: e1002313.
10. Edelberg JM, Reed MJ (2003) Aging and angiogenesis. Front Biosci 8: s1199-1209.
11. Klagsbrun M, D'Amore PA (1991) Regulators of angiogenesis. Annu Rev Physiol 53: 217-239.
12. de la Torre JC (2017) Are major dementias triggered by poor blood flow to the brain? Theoretical Considerations. J Alzheimers Dis 57: 353-371.
13. Lederman RJ, Mendelsohn FO, Anderson RD, Saucedo JF, Tenaglia AN, et al. (2002) Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): A randomized atrial. Lancet 359: 2053-2058.
14. Annex BH, Simons M (2005) Growth factor-induced therapeutic angiogenesis in the heart: Protein therapy. Cardiovascular Res 65: 649-655.
15. Wagoner LE, Merrill W, Jacobs J, Ginger C, Boehmer J, et al. (2007) Abstract 2048: Angiogenesis protein therapy with human fibroblast growth factor (fgf-1): Results of a phase 1 open label, dose escalation study in subjects with CAD not eligible for PCI or CABG. Circulation 116: II_443.
16. Goldsmith HS (2002) Treatment of Alzheimer's disease by transposition of the omentum. Ann N Y Acad Sci 977: 454-467.
17. Goldsmith HS, Griffith AL, Kupferman A, Catsimpoolas N (1984) Lipid angiogenic factor from omentum. JAMA 252: 2034-2036.
18. Zhang QX, Magovern CJ, Mazck CA, Budenbender KT, Ko W, et al. (1997) Vascular endothelial growth factor in omentum: Mechanism of the omentum-mediated angiogenesis. J Surg Res 67: 147-154.
19. Goldsmith HS (2014) Benefit of omental blood flow in Alzheimer's disease: Effect on deteriorating neurons. J Alzheimers Dis 42: S277-280.
20. Hayashi T, Abe K, Toyama Y (1998) Reduction of ischemic damage by application of vascular endothelial growth factor in rat brain after transient ischemia. J Cerebral Blood Flow Metab 18: 887-895.
21. Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, et al. (2000) VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. J Clin Invest 106: 829-838.
22. Sun Y, Jin K, Xie L, Childs J, Mao XO, et al. (2003) VEGF-induced neuroprotection, neurogenesis and angiogenesis after focal cerebral ischemia. J Clin Invest 111: 1843-1851.
23. Kanya D, Gürsoy-Özdemir Y, Yemisci M, Tuncer N, Aktan S, et al. (2005) VEGF protects brain against focal ischemia without increasing blood-brain permeability when administered intracerebroventricularly. J Cerebral Blood Flow Metab 25: 1111-1118.
24. Wang Y, Galvan V, Gorostiza O, Ataie M, Jin K, et al. (2006) Vascular endothelial growth factor improves recovery of sensorimotor and cognitive deficits after focal cerebral ischemia in the rat. Brain Res 1115: 186-193.
25. Wang PI, Xie ZH, Guo YJ, Zhao CP, Jiang H, et al. (2011) VEGF-induced angiogenesis ameliorates the memory impairment in APP transgenic mouse model of Alzheimer's disease. Biochem Biophys Res Commun 411: 620-626.
26. Moon DG (2016) AB030. Evolution of phosphodiesterase type 5 inhibitors. Trans Androl Urol 5: ABO30.
27. Li L, Jiang Q, Zhang L, Ding G, Gang Zhang Z, et al. (2007) Angiogenesis and improved cerebral blood flow in the ischemic boundary area detected by MRI after administration of sildenafil to rats with embolic stroke. Brain Res 1132: 185-192.
28. Zhang L, Zhang RL, Wang Y, Zhang C, Zhang ZG, et al. (2005) Functional recovery in aged and young rats after embolic stroke: treatment with a phosphodiesterase type 5 inhibitor. Stroke 36: 847-852.
29. Ulusoy MG, Uysal A, Koçer U, Karaaslan O, Cuzdan SS, et al. (2005) Improved flap viability with site-specific delivery of sildenafil citrate using fibrin glue. Ann Plast Surg 55: 292-296.
30. Senthilkumar A, Smith RD, Khitha J, Arora N, Veerareddy S, et al. (2007) Sildenafil promotes ischemic-induced angiogenesis through a PKG-dependent pathway. Arterioscler Thromb Vasc Biol 27: 1947-1954.
31. Koneru S, Varma Penumathsa S, Thirunavukkarasu M, Vidavalur R, Zhan L, et al. (2008) Sildenafil-mediated neovascularization and protection against myocardial ischaemia reperfusion injury in rats: Role of VEGF/angiopoietin-1. J Cell Mol Med 12: 2651-2664.
32. Zhang L, Zhang Z, Zhang RL, Cui Y, LaPointe MC, et al. (2006) Tadalafil, a long-acting type 5 phosphodiesterase isoenzyme inhibitor, improves neurological functional recovery in a rat model of embolic stroke. Brain Res 1118: 192-198.
33. Pyriochou A, Zhou Z, Koika V, Petrou C, Cordopatis P, et al. (2007) The phosphodiesterase 5 inhibitor sildenafil stimulates angiogenesis through a protein kinase G/MAPK pathway. J Cell Physiol 211: 197-204.

34. Hayashi T, Abe K, Suzuki H, Itoyama Y (1997) Rapid induction of vascular endothelial growth factor gene expression after transient middle cerebral artery occlusion in rats. Stroke 28: 2039-2044.

35. Puumala M, Anderson RE, Meyer FB (1990) Intraventricular infusion of HBGF-2 promotes cerebral angiogenesis in Wistar rat. Brain Res 534: 283-286.

36. Rosenstein JM, Mani N, Silverman WF, Krum JM (1998) Patterns of brain angiogenesis after vascular endothelial growth factor administration *in vitro* and *in vivo*. Proc Nat Acad Sci USA 95: 7086-7091.

37. Schlaudraff K, Schumacher B, von Specht BU, Seitelberger R, Schlosser V, et al. (1993) Growth of "new" coronary vascular structures by angiogenetic growth factors. Eur J Cardiothorac Surg 7: 637-643.

38. Fasol R, Schumacher B, Schlaudraff K, Hauenstein KH, Seitelberger R (1994) Experimental use of a modified fibrin glue to induce site-directed angiogenesis from the aorta to the heart. J Thorac Cardiovasc Surg 107: 1432-1439.

39. Banai S, Jaklitsch MT, Casscells W, Shou M, Shrivastav S, et al. (1991) Effect of acidic fibroblast growth factor on normal and ischemic myocardium. Circ Res 69: 76-85.

40. Pepper MS, Ferrara N, Orci L, Montesano R (1992) Potent synergism between vascular endothelial growth factor and basic fibroblast growth factor in the induction of angiogenesis *in vitro*. Biochem Biophys Res Comm 189: 824-831.

41. Wilting J, Christ B, Weich HA (1992) The effect of growth factors on the day 13 chorioallantoic membrane (CAM): A study of VEGF165 and PDGF-BB. Anat Embryol 186: 251-257.

42. Dor Y, Djonov V, Abramovitch R, Itin A, Fishman GI, et al. (2002) Conditional switching of VEGF provides new insights into adult neovascularization and pro-angiogenic therapy. EMBO J 21: 1939-1947.

43. Takeshita S, Zheng LP, Brogi E, Kearney M, Pu LQ, et al. (1994) Therapeutic angiogenesis. A single intraarterial bolus of vascular endothelial growth factor augments revascularization in a rabbit ischemic hind limb model. J Clin Invest 93: 662-670.

44. de la Riva B, Sánchez E, Hernández A, Reyes R, Tamimi F, et al. (2010) Local controlled release of VEGF and PDGF from a combined brushite-chitosan system enhances bone regeneration. J Control Release 143: 45-52.

45. Spitzer M, Basaria S, Travison TG, Davda MN, Paley A, et al. (2012) Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: A parallel, randomized trial. Ann Intern Med 157: 681-691.

46. Simons M (2005) Angiogenesis: Where do we stand now? Circulation 111: 1556-1566.

47. Mulder WJ, Griffioen AW (2010) Imaging of angiogenesis. Angiogenesis 13: 71-74.

48. McDonald DM, Choyke PL (2003) Imaging of angiogenesis: From microscope to clinic. Nat Med 9: 713-725.

49. Jensen JH, Hanzhang L, Inglese M (2006) Microvessel density estimation in the human brain by means of dynamic contrast-enhanced planar imaging. Magnetic Res Med 56: 1145-1150.

50. Ullrich, RT, Jikeli JF, Diedenhofen M, Böhm-Sturm P, Unruh M, et al. (2011) *In vivo* visualization of tumor microvessel density and response to anti-angiongeic treatment by high resolution MRI in mice. PLoS ONE 6: e19592.

51. Sood S, Jain K, Gowthamarajan K (2014) Intranasal therapeutic strategies for management of Alzheimer's disease. J Drug Target 22: 279-294.

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