Aging: Thromboembolic Disease, Metabolic Syndrome, Type 2 Diabetes Mellitus, and Alzheimer’s Disease

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Abstract

Aging can be interpreted as an unavoidable process whose end point is the death. Aging entails, in the hemostasis field, some changes that favour blood hypercoagulability. Both the plasminogen activator inhibitor (PAI-1), specific inhibitor of the tissue plasminogen activator (t-PA), accompanied by the oxidative stress and the marked decrease of the main antioxidant—glutathione are fundamental in the bases of elderly pathologies which can cause death. There is some scientific evidence of the relationship between aging, neuro-degenerative diseases, an excessive production of reactive oxygen species and the decrease of proteolysis in brain. The cerebral plasminogen/plasmin system represents the essential proteolytic mechanism that degrades amyloid peptides (β-amyloidosis) for action of plasmin with effectiveness. This physiologic process is being considered as a preventive neurodegenerative mechanism. At the same time, the decrease of glutathione levels in aging entails a decrease of cerebral plasmin activity and a progressive descent of t-PA activity due to a descent in t-PA expression and an increase in PAI production. All of them entail an increment of amyloid beta peptides (Aβ) production and a lower level of their clearance. Both mechanisms, oxidative stress, direct consequence of the oxygenate metabolism of aerobics cells, and changes in the systemic fibrinolysis and cerebral b-amyloidolytic activity, play a very important role in thromboembolic disease, metabolic syndrome—obesity, insulin resistance, hyperglycemia—, type 2 Diabetes Mellitus and Alzheimer’s disease, clinical processes that accompany the aging. In this revision we show the importance of the interaction between glutathione, proteolytic t-PA/plasminogen/plasmin system, and the inhibitor PAI-1 in aging physiopathology, whose results suggest the hypothesis of the importance of a therapeutic strategy using the inhibition of

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PAI-1 as a goal, because it is increased in the different aging pathologic processes.

Keywords
Aging, Alzheimer’s Disease, T2DM, PAI-1, Glutathione

1. Introduction
Aging can be interpreted as an unavoidable process whose end point is the death. Longevity, consequence of an improvement of environmental, social, sanitary conditions and of quality of life along the XX century involves a morbidity and mortality reduction with an increment in the life expectancy [1]-[3]. There is some scientific evidence that 27.6% of European population will be 65 or more years by 2050 [4]. This longevity has created a centennial society with a less burden of disease that frequently appears in the development of aging and often causes death of younger people [5].

There are many definitions of aging. It is possible that it refers to a normal process, as a consequence of organism metabolism with a formation of toxic substances that damage cellular structures, proteins and nucleic acids, explains the most frequent pathologies in the senility and could be considered the most right one.

Among the substances that modify the normal physiologic operation, oxidative stress—direct consequence of the oxygenate metabolism of the aerobic cells [6]-[10], hemostatic changes in systemic fibrinolytic mechanism, changes in cerebral b-amyloidolytic mechanism, an increase in the expression of plasminogen activator inhibitor (PAI-1)—main inhibitor of the tissue plasminogen activator (t-PA) [11]-[13], play a very important role in the thromboembolic disease, metabolic syndrome (MS), (obesity, hyperglycemia, insulin resistance (IR)), type 2 Diabetes Mellitus (T2DM) and Alzheimer’s disease (AD). These diseases are associated to clinical processes with glutathione (GSH) depletion and oxidative stress that accompany the aging. According to epidemiologic and pathogenic studies, these entities possibly share physiopathological factors as much in their progression as in their etiology [14]-[21].

In this study, we focus on the clinical importance of the pathogenic processes, such as obesity, type 2 Diabetes Mellitus, metabolic syndrome, Alzheimer’s disease and thromboembolic disease, because of their prevalence in the aging, and because all of them have a glutathione depletion [22] [23] and an increment of PAI-1 expression [11][13] [24] [25]. Glutathione is the most important antioxidant in aging, and PAI-1 is the main inhibitor of tissue plasminogen activator. For this reason, an increment of glutathione or a reduction of PA1-1 could be a useful way to prevent these diseases which accompany the aging process.

2. Thromboembolic Disease and Aging
An increment of the venous and arterial thromboembolic diseases has been observed in aging [26]-[30]. It is though that it can be attributed to fibrinogen, factor VIII and factor IX increments, molecular and anatomical changes of vascular wall and an increase of platelet activity. In fact, a state prothrombotic is created as shows the hypercoagulability found in blood [26]-[28] [31]-[35]. Nevertheless, in spite of the great activity or concentration of some blood clotting factors, the high incidence of thromboembolic diseases in aging can be related to the decrease of systemic fibrinolytic activity [26] [27] [33]-[37]. The study of the different components of fibrinolytic system in aging shows an increase of t-PA antigen with a marked depletion of its activity (t-PA) and an increase of PAI-1. It is suggested that the tendency of diminishing the t-PA activity for their inhibitor PAI-1 can be related with the increase of thrombosis incidence in the elderly [14] [37]. The potent inhibitor PAI-1 is not only increased in aging but it is also enhanced, in a significant way, in the pathogenesis of processes very related to aging, such as myocardial infarction, atherosclerosis, thromboembolic disease, MS (obesity, RI, hyperglycemia), T2DM and neurodegenerative diseases including AD and Parkinson disease (PD). These processes are accompanied by oxidative stress and an enhanced production of reactive oxygen species (ROS) with marked decrease of GSH [19] [38]-[47], by an impaired fibrinolysis due to elevated PAI-1 levels, principal regulator of fibrinolysis [48] [49], a descent in t-PA activity as answer to a GSH decrease [50] and they could play a very important role in the pathogenesis of thrombotic disorders in the MS in the elderly [12].
3. Systemic and Cerebral Glutathione System in Aging

GSH is the most abundant non-protein thiol in mammal cells, being mainly located in mitochondria, nucleus and endoplasmic reticule and in a very low concentration in extracellular spaces [51] [52]. GSH synthesis is generated in two steps: the first one is the combination of cysteine with glutamate in presence of ATP and γ-glutamyl-cysteine synthetase enzyme to form glutamylcysteine. The second one is the combination with glycine to produce GSH (gamma-glutamyl-cysteinyl-glycine) [53]-[55].

ROS are generated continuously during oxidative metabolism. GSH system is fundamental for cellular defense against ROS. A GSH decrease or a ROS increase cause oxidative stress and metabolic alterations. The GSH anti-oxidant action stands out among its multiple physiologic activities. It is due to its capacity of neutralize free radicals. GSH deficit involves oxidative stress [51] [52] [55]-[64] and it has been suggested that GSH plays a role in the apoptosis regulation [65]. High GSH concentrations are associated to high levels of physical health [66].

There is some scientific evidence of a GSH reduction in aging and a decrease of gamma-glutamylcysteine synthetase gene [67] [68] in some age-related diseases. It makes the organism be more vulnerable to oxidative stress. An increment of free radicals causes harmful effects in many chronic pathologies in the elderly [52] [64] [66] [68]-[78]. The decreased GSH levels in the healthy elderly predispose them to suffer metabolic alterations, detoxification mediated by GSH [71], a decreased proteasomal activity [63] [79]-[81], mitochondrial alterations [82], a ROS increase [83] and a great quantity of clinical entities in the field of the medical pathology [66] [84] [85].

GSH system in brain is the most important component of the anti-oxidant mechanism in chronic pathological entities associated with aging [76] [83] and it develops a fundamental role in xenobiotic detoxification “in situ” within the central nervous system [86]. The high cell specialization confers a significant capacity to generate free radicals on human brain as consequence of high oxygen requirement, 20% of the total consumption of the organism, in spite of being less than 2% of the body weight in adults [87].

Astrocytes and neurons maintain a cellular language in a very specific way about GSH neuronal synthesis and brain protection against oxidative stress [76]. In this line, neurons are considered to contain less GSH than astroglial cells [76] [88]. Nevertheless, the concentration varies with the region from which the cells have been prepared. In cortex cultures, neurons contain less GSH than astroglial cultures [89]. Nevertheless, neurons maintain GSH levels taking up cysteine provided by glial cells [90]-[92] being astrocytes the main GSH supplier to microglia and neurons in the brain [93].

A GSH deficit is observed in neurodegenerative diseases, mainly AD and PD [64] [77] [84] [94]-[99], obesity, MS and T2DM [74] [85] [100]-[102]. It is important to indicate that GSH deficit by pharmacological synthesis inhibition with buthionine sulfoximine (BSO) or diethyl maleate in animal models involves an inhibition of systemic fibrinolytic activity with a marked decrease of t-PA and an increase of PAI-1 [13] [50] [58]. Thus, PAI-1 would play an important role in aging pathology, cardiovascular diseases, thromboembolic diseases, and in systemic vascular atherothrombotic and cerebral complications, which are so frequent and cause death.

4. Metabolic Syndrome

MS is a group of physical and metabolic abnormalities. It is a clinical complex process characterized by an alteration of glucose metabolism, an increase of blood pressure and a deposit of abdominal fat, finding a defined group of risk factors such as hyperglycemia, IR, low HDL levels, and high LDL levels. It is associated with an increased cardiovascular morbidity and mortality, even in absence of baseline cardiovascular disease or diabetes [103] [104] and their treatment and prevention are their primary medical care [105].

Likewise, there is some evidence that a higher prevalence of MS [106] and higher PAI-1 concentrations [107] in male patients with depression symptoms. It has been well documented that android obesity, the most important factor in SM [108] [109] increases the risk of venous thromboembolism, atherothrombotic disease, cardiovascular disease, stroke, T2DM, and AD [22] [103] [105] [110]-[122]. MS is associated with hypofibrinolysis, with a decreased plasmin activity by increased PAI-1 levels [123]-[129].

Although MS is a complex process, there are some in vitro and in vivo studies that show PAI-1 can be involved in the metabolic process of the obesity [127] [130] [131], causing thrombotic events in obese people [11] [12] [132] [133].

Obesity has been considered as the central factor of MS [115], and it is associated with a decrease of fibrino-
lytic activity by a very significant increment of PAI-1 [126] [130] [134]-[136], the main t-PA inhibitor and a well-known risk factor for venous thrombotic or arterial complications [133] [137]. In this line, obesity and PAI-1 are considered as risk factors of cardiovascular illnesses and they play a very important role in the development of the atherothrombosis associated with impaired fibrinolysis [123] [126] [134] [138]-[140].

At experimental level, high PAI-1 levels have been observed in adipose tissue in mice as well as in obese animals [132] [141] [142]. Although the main sources of plasma PAI-1 are liver, endothelial cells and thrombocytes [143] [144], some studies in human adipose tissue put in evidence that adipocytes are a source of PAI-1. Therefore, adipose tissue may directly contribute to increase circulating PAI-1 levels in human [123] [126] [130] [145]-[149]. Likewise, at experimental level it has been observed that PAI-1 inhibitors can neutralize the increment of PAI-1 in pre-adipocyte cultivations [150].

IR is another metabolic factor of MS and it represents an inductor factor of T2DM and it is associated with the oxidative stress process [151] [152]. IR can precede the beginning of T2DM for years [153] [154]. There is some scientific evidence of the probable association between neurodegeneration and IR [111]. SM is closely related to T2DM. RI, a risk metabolic factor of SM and a hallmark of T2DM, it is also expressed in AD [155] and it is considered the major regulator of PAI-1 expression, a common denominator in the physiopathology of these processes [155]. In diet-induced IR, IR promotes amyloidogetic beta-amyloid Aβ 1-40 and Aβ 1-42 peptide generation and a production of amyloid plaques in the brain of mice Tg2576 [156] [157]. IR reduces the clearing of Aβ through descending the insulin-degrading enzyme expression, increasing Aβ deposits in AD models [156]-[158]. IR is associated to an increase of development of cardiovascular illnesses [159]-[161] strongly related to a decreased fibrinolytic activity due to a marked increase of PAI-1 [22] [38] [128] [162]-[167].

5. Type 2 Diabetes Mellitus and Alzheimer’s Disease

T2DM and AD are the two clinical processes more prevalent in aging. Along more than 20 years T2DM is being discussed to be an AD risk clinical factor. Prospective studies carried out in Rotterdam Study [168], Rochester (Minnesota) [169], Rotterdam [170], and Estokolmo [171], revealed an increased dementia risk in people with T2DM. Community multi-ethnic studies report a weak association between diabetes and AD and a strong association between diabetes and stroke-associated-dementia. It was significantly higher in Blacks and Hispanics than in Whites [113]. In another study, the Honolulu-Asia-Aging Study, diabetes was associated with vascular dementia and AD in Japanese American men. There was a particularly strong association between diabetes and AD in people who carrier apolipoprotein E (APOE) ε4 allele [114]. Finally, a systematic review and a meta-analysis with 15 epidemiology studies report positive association between T2DM and AD [172].

Although the nature of the association is not yet known, it is interesting to point out that multiple common features of clinical processes that accompany the aging can influence the relationship between T2DM and AD [153] [172]-[174]. The association between diabetes mellitus and impaired cognitive function suggests that diabetes mellitus may contribute to increase the development of dementia rate in AD two to three times [175]. T2DM is associated with a decreased cognitive function in adults and the elderly [169] [176]-[183]. The insulin receptor insulin/insulin-like growth factor-1 might represent a molecular link between T2DM and AD [184]. Likewise, an interrelation among these two clinical entities has been suggested by the following reasons: the risk of developing the both processes in aging, its association with APOE, tau formation, oxidative stress, a decrease of glutathione concentration, IR, hyperinsulinemia, alterations of both systems: insulin growth factors and transforming growth factors, hyperphosphorization of tau protein, amyloid-β deposition, hypo-proteolysis, elevated PAI-1, stroke and brain atrophy [18] [111] [114] [168] [170] [185]-[197]. Likewise, in relation to metabolic alterations in T2DM, they are an impaired glucose tolerance and hyperinsulinemia in brain AD, and for this reason some researchers refer to AD as the type 3 diabetes [198]-[204].

In recent years, some scientific evidence supports the concept that AD is a metabolic disease as result of the inability of the use of glucose and IR in brain, characterizing AD as brain-type diabetes [184] [205].

Nevertheless, several researchers consider oxidative stress like the primary pathogenic mechanism, AD progenitor [77], considering this process as a possibility of the development of potential preventive treatment of AD [46] [206] [207]. There is a lot of scientific evidence that oxydative stress is increased in diabetes due to an increase of ROS production and a decrease of GSH [74] [194] [208]. A decreased synthesis and an altered metabolism of GSH levels have been found in hyperglycemia and diabetes. GSH concentration is diminished in erythrocytes and plasma in diabetic patients and in patients with MS, who have a high risk of suffering diabetes [85]
Several clinical studies have demonstrated a strong correlation between circulating PAI-1 levels and cardiovascular events and mortality [209]. 80% of patients with diabetes mellitus die from a thrombotic process, mainly from a cardiovascular process [16]. In this line, most of epidemic studies have demonstrated an increment of thromboembolic risk in diabetic patients [210]-[213]. Thromboembolic risk seems to be elevated in both clinical entities, type 1 and type 2 diabetes mellitus [211] [214]. In T2DM, hypercoagulability is attributed to a hypofibrinolysis with high PAI-1 levels [185] and a marked decreased plasmin activity. That is demonstrated as a prolongation of clot lysis time that expresses the systemic fibrinolytic activity [214]-[220].

Situations with proteolytic deficit are very frequent. Its maximum expression are systemic hypercoagulability and cerebral hipo-β-amiloidolysis, processes that go settling down during aging in a progressive way, and whose pathology is responsible for venous and arterial thromboembolic complications and accumulation of the peptide beta-amyloid cerebral, that characterize the more frequent pathology in aging (Table 1).

Some studies about the relationship between the proteasome activity and the age show that enzymatic activity of urokinase, plasmin, and thrombin were inversely correlated with age, suggesting certain relationship between the normal process of aging and AD pathology [221].

AD histopathology is characterized by brain accumulation of extracellular amyloid plaques [222]-[228] and intracellular neurofibrillary tangles, which are mainly composed of an abnormally hyperphosphorylated Tau protein [229]-[235]. T2DM is characterized by loss of beta cells and a deposition of islet amyloid derived from islet amyloid polypeptide. They are initially formed in an intra cellular level and they are released to extra cellular space by exocytosis [18] [236]-[239]. Amyloid deposition in brain and pancreas has some strong pathophysiological similarities. Neurodegeneration in pancreatic islet has been less studied than in AD but it may also occur [240]. Nevertheless, in pathological studies in brain and pancreas, amyloid islets are more frequent in patient with AD than in controls and they are more common in brain in patients with T2DM than in no diabetics [18]. In autopsy studies it is shown that above 96% of patients with T2DM present islet amyloid [241] [242]. Likewise, other neurodegenerative processes, such as Huntington’s disease, Friedreich’s ataxia, Werner’s disease and Myotonic dystrophy, are associated with the development of T2DM [243]-[245].

**Table 1.** Mechanism t-PA/plasminogen/plasmine and glutathione in aging pathology and in centennials. Experimental design.

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>GSH</th>
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The mechanism of the incremented Aβ accumulation in common AD has not been completely clarified. It has been well documented the importance of oxidative stress in aging. A progressive increase of oxidative stress in the aging development plays an important role in AD pathology, mainly in the neuronal death and Aβ accumulation in the brain [13] [246]-[248]. In this line, it is of interest to point out as oxidative stress, a metabolic characteristic of the pathological processes that accompany the development of the aging, involves an increased PAI-1 expression [19] [249], which is considered as a pharmacological target by different authors, mainly in AD. Indeed, the inhibition of PAI-1 activity with specific inhibitors reduces brain Aβ burden and reverses cognitive deficit in the AD model in mice [250] [251]. It is of great interest to point out the results found by Liu and collaborators [251] with administration of the fenolic compound Tert-Butyl Hydroquinone (TBHQ) in the diet to mice. This is an effective anti-oxidative used in food and cosmetic products as a preservative. These authors took account the evidence of the increase of PAI-1 expression in the development of the amyloidosis in AD. Two groups AβPP/PS1 double transgenic mice were fed with either a control or 1% TBHQ-containing diet for 6 weeks. This study showed that TBHQ administration significantly reduced the brain Aβ load in AβPP/PS1 mice getting an inhibition of PAI-1 expression and an increase in the activities of tissue and urokinase types plasminogen activator, plasmin and an increase of GSH level in brain of AβPP/ps mice. These results lead us to consider that GSH could play an essential role in regulation of the different components of the fibrinolytic system in the brain [50].

The experimental rehearse through the decrease of cerebral GSH levels with BSO allows us to value its effect in the cerebral anti-oxidative mechanisms. A widely used approach to study the physiological function of glutathione has been the depletion of its intracellular levels with BSO [57] [58]. The induction of pharmacological depletion of GSH causes neurodegenerative alterations [252]. Furthermore, GSH depletion is found in the neurodegenerative diseases associated with oxidative stress [98]. GSH depletion can affect the severity of the cerebral attack induced by ischemia [253]. These results show that the intensity of the cerebral attack is related to the reduction of GSH levels in the injured area of the cerebral cortex.

6. PAI-1 Inhibition

Some clinical studies about antithrombotic treatments have demonstrated that the inhibition of the PAI-1 produces an endogenous increase of the fibrinolytic activity [254]-[257]. In our experience we have observed that the treatment with sulodexide, an inhibitor of PAI-1 activity, in the prevention of secondary thrombosis in AD in long term produces positive results due to its pharmacological effect [258] [259]. These clinical observations suggest the hypothesis that aging develops a sequence of processes such as obesity, MS, as well as clinical entities such as T2DM and AD, with a common denominator, the increase of the PAI-1. PAI-1 is the origin of the decrease of systemic fibrinolytic and cerebral proteolytic activities and it causes the thromboembolic complications so frequent in these processes that are the main cause of death in these patients. The possible causal agent is the decrease of GSH synthesis, and, in hypothesis, its pathogenic relationship with T2DM and AD.

At clinical and experimental level, this increase of PAI-1 with decreased proteolytic activity is normalized with the restoration of cellular GSH synthesis [50]. It suggests possible benefits with treatments with PAI-1 inhibitors [260]-[264], such as glycosaminoglycans [265] [266], sulodexide [258] [267], GSH administration at systemic level to normalize the cell concentration [268] [269] or with their precursors to activate the GSH synthesis at cerebral level [270] [271]. It is possible that cerebral mechanisms of GSH and fibrinolysis/β-amyloidosis, can be fundamental pillars in the prevention of aging pathology (TED, MS, T2DM and AD). Their normal function during the aging brings the subjects to become centenarians. In fact, in centenarians, the glutathione reductase activity (leading to GSH synthesis) is normal or high [272] [273] and t-PA/plasminogen/plasmin and PAI-1 mechanisms are normal, but there is an increase of secondary fibrinolytic activity paradoxically [24] [25] [274].

7. Conclusions

This revision shows like a concatenation of processes sustained by the intractable problem of aging such as TED, MS, T2DM, and AD; they are closely united for two pathophysiological situations, a) decrease of GSH and b) depletion of proteolytic systems: systemic fibrinolytic system and β-amyloidolytic system in the brain, and all of them present increased PAI-1 levels.

Oxidative stress is a present process in the development of aging, which accompanies its pathology and it is
responsible for the deterioration of the anti-oxidative mechanism. It is demonstrated by the GSH descent, as much as systemic level as in the brain. At the same time there is a PAI-1 increase, central factor that accompanies the aging and their pathologies, creating a systemic hypofibrinolysis/hypobeta-amyloidolysis in brain, responsible for systemic thromboembolic complications, stroke, as well as, for the beta-amyloid deposits in T2DM and AD.

PAI-1 inhibition involves an endogenous increase of the fibrinolytic activity. PAI-1 inhibitors treatments would produce positive results due to its pharmacological effect. It is suggested that aging develops a sequence of processes such as obesity, MS, as well as, clinical entities such as T2DM and AD, with a common denominator—the increase of the PAI-1. PAI-1 is the origin of the decrease of systemic fibrinolytic activity and cerebral proteolytic activity and it causes the thromboembolic complications. The possible causal agent is the decrease of the synthesis of the GSH, and, in hypothesis, its pathogenic relationship with T2DM and AD.

At clinical and experimental level, this increase of the PAI-1 with decreased proteolytic activity is normalized with the restoration of the cellular GSH synthesis. It suggests possible benefits with PAI-1 inhibitors treatments, such as glycosaminoglycan, sulodexide, GSH administration or GSH precursors. It is possible that the cerebral mechanisms of GSH and fibrinolysis/beta-amyloidosis can be fundamental pillars in the prevention of aging pathology (TED, MS, T2DM and AD). In fact, in centenarians, glutathione reductase activity (leading to GSH synthesis) is normal or high and t-PA/plasminogen/plasmin and PAI-1 mechanisms are normal but paradoxically there is an increase of secondary fibrinolytic activity.

As final reflection, some clinical evidence suggests the necessity to propose prospective studies in the different pathologies that accompany aging using PAI-1 inhibitors as pharmacological procedures, to corroborate the clinical benefits in the different processes in aging in the short term.

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**List of Abbreviations**

Abbreviation | Description
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Aβ | Amyloid beta peptides
AβPP/PS1 | Amyloid-β protein precursor/presenilin-1
AD | Alzheimer’s disease
APOE | Apolipoproteina E
BSO | Buthionine sulfoximine
GSH | Glutathione = gamma-glutamyl-cysteinyl-glycine
HDL | High Density Lipoproteins
IAPP | Islet amyloid polypeptide
IR | Insulin Resistance
LDL | Low Density Lipoproteins
MS | Metabolic Syndrome
PAI-1 | Plasminogen activator inhibitor
PD | Parkinson disease
ROS | Reactive oxygen species
TBHQ | Tert-Butyl Hydroquinone
t-PA | Tissue plasminogen activator
TED | Thromboembolic disease
T2DM | Type 2 Diabetes Mellitus