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Sulodexide and Alzheimer's Disease: A Preliminary Prospective Study

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Abstract

The purpose of this prospective study is to determine the relative incidence of Alzheimer's disease in patients treated for at least three years, with sulodexide (n = 46, 76.48 ± 7.02 years old) or acenocoumarol (n = 47, 78.21 ± 6.66 years old) in order to prevent primary and secondary venous thromboembolism and atherothrombotic disease. In the sulodexide group, there was an apparent prevention of cognitive and behavioural impairment (relative incidence: 2.02) compared with acenocoumarol group (relative incidence: 4.86). The favourable results in sulodexide group may be related to their pharmacodynamic actions of inhibition of PAI-1, which may interfere with the pathogenesis of Alzheimer's disease, and to the role of glutathione and PAI-1 in the *β*-amyloid system in the brain.

Keywords

Sulodexide, Alzheimer's Disease, Glutathione, t-PA, PAI-1, Plasminogen, Plasmin

1. Introduction

Advanced age is the single most important risk factor known to be associated with cognitive alterations and neurodegenerative diseases. Among these conditions, the irreversible and incurable senile dementia known as Alzheimer's disease (AD) is included [1] [2].

From the anatomopathological point of view, the typical cerebral lesions of AD are characterized by the presence of *β*-amyloid (A*β*) peptides formed from the endoproteolysis of the amyloid precursor protein (APP) through the activity of the *β*-secretase enzyme (BACE 1) [3]-[9]. The A*β* peptide is mostly deposited in the cor-

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tex, hippocampus, and other regions of the brain in the form of amyloidal plaques or neurovascular infiltration [10]. The accumulated deposits of Aβ in the cerebral parenchyma have a neurotoxic effect and play a central role in the etiology of AD [11] [12].

The Aβ peptide is a substratum capable of being degraded, via beta-amyloidolysis [13], by various proteases known as AβDPs (Aβ-degrading proteases) [14]. Among all AβDPs that can degrade the Aβ peptides, for their clearing and cerebral elimination, such as neprilysin (NEP) [15]-[24], insulin-degrading enzyme (IDE) [16] [25]-[27], and plasmin [28]-[33].

The extent of accumulation of the Aβ peptides depends on an imbalance between their production, proteolytic degradation and cerebral elimination [34], being the relationship between glutathione (GSH or L-gamma-glutamyl-L-cysteinyl-glycine) and plasminogen/plasmin system of great importance for normal cerebral function, since the deficit of Aβ-degrading enzymes and the decrease of GSH affect the Aβ balance in aging, and are very important mechanisms in the brain accumulation of Aβ [13] [35]. Several groups of investigators have suggested the possibility that the amyloidal deposits may be amenable by these proteases. In fact, they play an important role in the regulation of Aβ brain accumulation, they may also represent a target of therapy with possibility of exercising pharmacological action to be able to prevent and to treat AD [16] [24] [36]-[40].

In the study a population of patients older than 65 years distributed in two groups receiving long-term treatment with the glycosaminoglycan sulodexide (SLX) y acenocoumarol (0A), a beneficial effect of prevention of decay of both cognitive state and behavior in SLX. This effect leads us to assume that it is achieved through those pharmacodynamic properties of sulodexide, consisting in the reduction of plasminogen activator inhibitor (PAI-1) activity and in the increase of tissue plasminogen activator (t-PA), as well as in its pro-fibrinolytic activities [41].

2. Material and Methods

In this prospective not randomized study, we included 93 patients all aged over 65 years who, from 2000 to 2010, had been treated for three or more years with sulodexide (n = 46) or acenocoumarol (n = 47) for prevention primary and secondary venous thromboembolic and atherothrombotic diseases.

Selection of the patients. The patients come from external consultations directed by family doctors of the Social Security of the Community (Logroño, La Rioja) and of our consultation of the CMH (C. Medicine Hematology, Logroño, La Rioja). All patients were recruited under the following conditions: 1) Patient of both sexes ≥ of 65 years old. 2) At the beginning of treatment, none of the patients in both groups presented signs of cognitive disorders or abnormalities that would have excluded them from the recruitment. 3) Treatment pharmacological with Sulodexide/Acenocoumarol for at least three years without interruption until the recruitment. 4) During the preventive treatment in both groups none of the patients had suffered hemorrhagic processes or thromboembolic systemic or cerebral processes. 5) The clinical follow-up of the patients was carried out by their own family doctors. 6) The final evaluation of cognitive evolution of the patients was performed by neurologists.

SULODEXIDE (SLX) group: was formed by 46 patients with an average age of 76.48 ± 7.02 years. In this group, 21 patients were women and 25 men. The average age of the women was 77.0 ± 7.89 years and that of men was 76.04 ± 6.33 years. Sulodexide was administered at a dosage of 300 LSU [lipasemic units (approximately corresponding to 30 mg)] every 12 hours.

ACENOCOUMAROL (OA) group: was formed by 47 patients with an average age of 78.21 ± 6.66 years. In this group, 24 patients were women and 23 men. The average age of the women was 79.00 ± 7.42 years and that of men was 77.32 ± 5.71 years. The patients were controlled in our unit (CMH) for the adjustment of the anticoagulant medication in a periodic way (≈every 21 - 25 days) maintaining an International Normalized Ratio (INR) (Protime 3) among 2.0 - 3.0. Age groups of the patients and age averages of patients are showed in **Figure 1** and **Figure 2** respectively.

Patients in both groups were suffering from various diseases common to their advanced age. These diseases are specified here below:

SLX group: cardiac pathology in 16 patients (34.7%), arteriovascular or venous diseases in 27 (58.7%), type 2 diabetes mellitus (T2DM in 8 (17.4%), dyslipidemia in 17 (36.9%), arterial hypertension (AH) in 21 (45.6%), hyperuricaemia in 3 (6.4%), and miscellaneous diseases in 8 patients (17.35%).

OA group: cardiac pathology in 31 patients (65.9%), arteriovascular or deep venous thrombosis (DVT) in l8

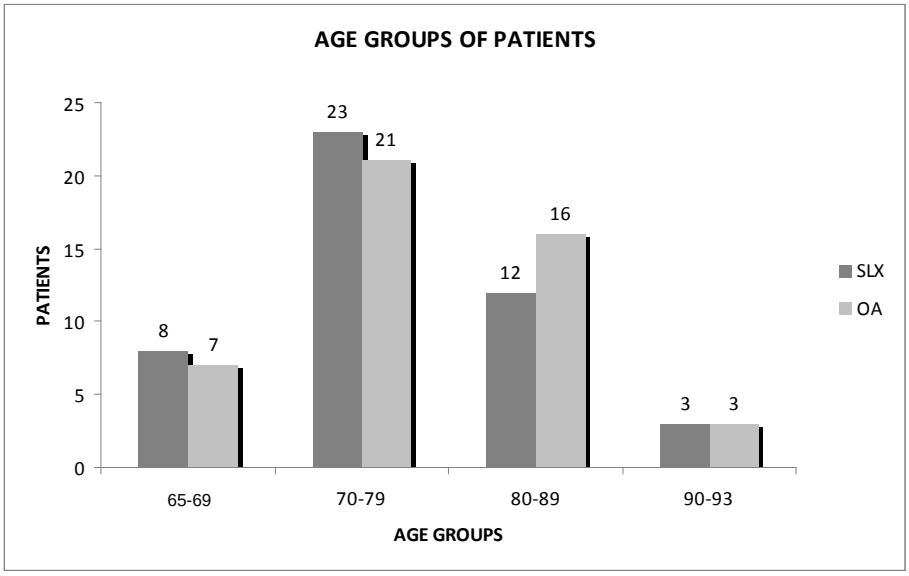

Figure 1. Age groups of the patients.

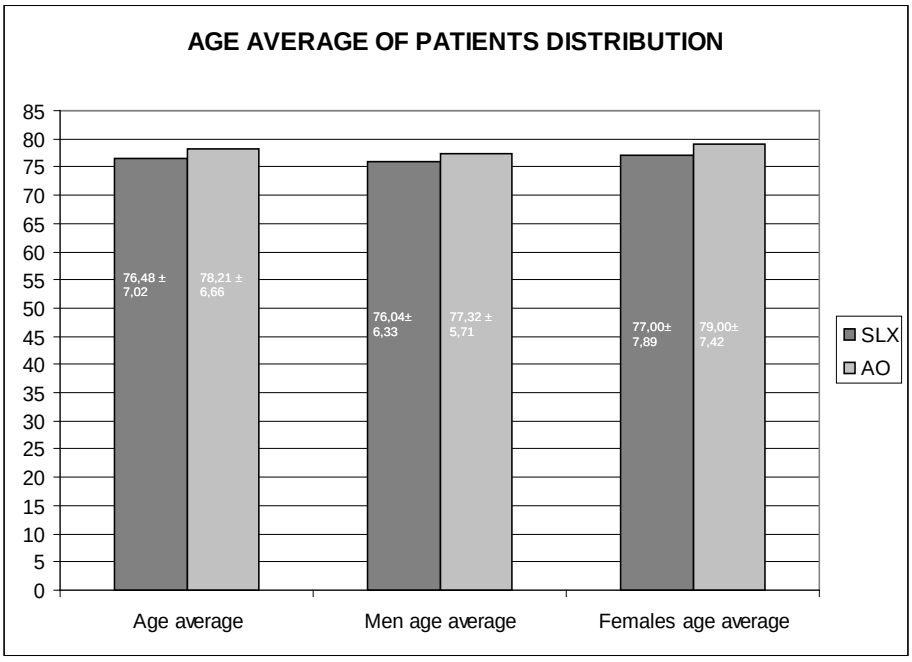

Figure 2. Age average of patients distribution.

(38.3%), type 2 diabetes mellitus (T2DM) in 10 (21.2%), dyslipidemia in 13 (27.7%), arterial hypertension (AHT) in 17 (36.2%), hyperuricaemia in 3 patients (6.4%), and miscellaneous diseases in 6 patients (12.8%) (**Figure 3**). The load of chronic illnesses for the patients in the group SLX was of 2.690 ± 0.9859 and for the group OA was 2.7021 ± 0.9536.

Associated medications: numerous medications were used based on the complex diseases of the patients in the study, according to their advanced age. The associated medications were the following: antihypertensives, diuretics, oral antidiabetics, dislypemics, cardiac tonics, ASA, allopurinol, NSAIDs, betablockers, sleeping pills and omeprazol. The load of medications for the group SLX was 3.80 ± 0.89/patient and for the group OA was 4.91 ± 1.60/patient.

Clinical evaluation of cognitive/intellectual state: it was carried out according to the criteria of the Mini Mental

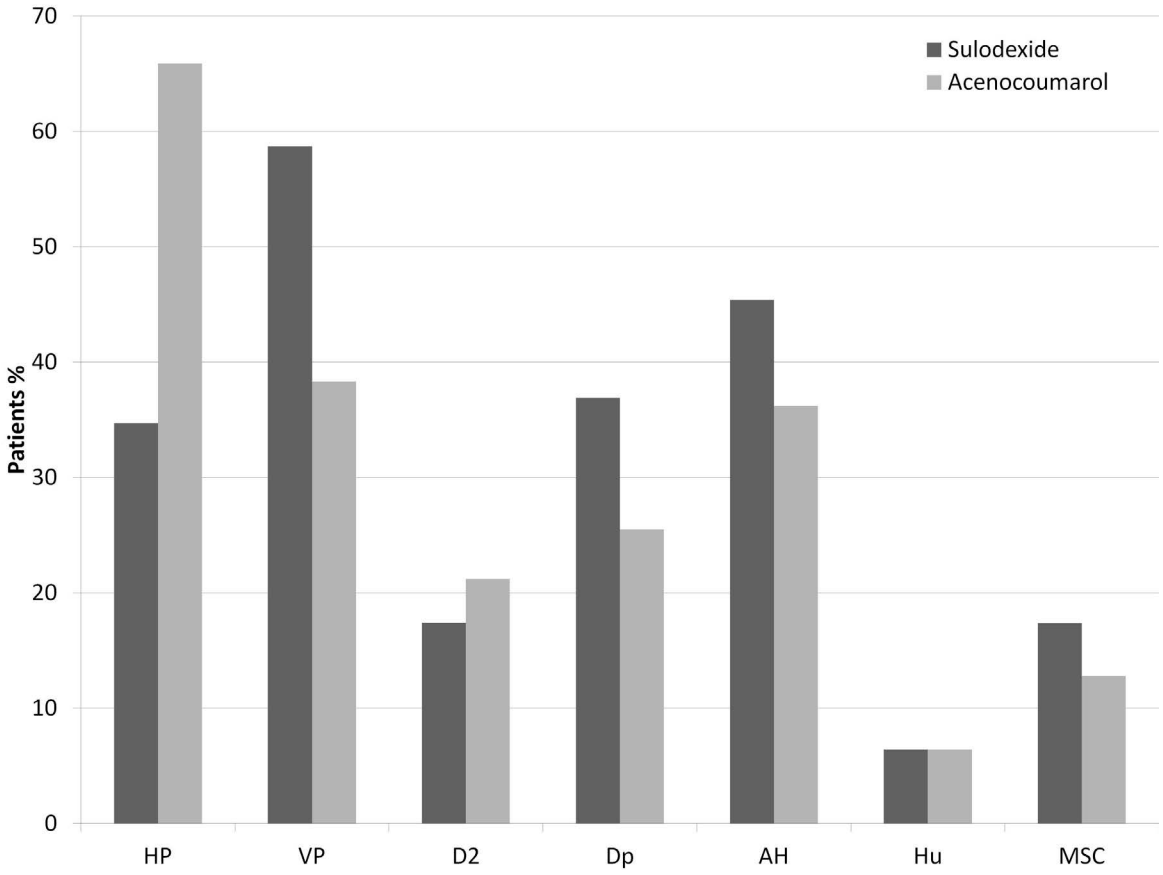

Figure 3. Associated pathology in groups of patients. HP: Cardiac pathology. VP: Vascular pathoology. D2: T2DM. Dp: Dyslipidemia. AH: Arterial hypertension. Hu: Hyperuricemia. MSC: Miscelanea.

State Examination (MMSE) and GENCD [42] [43]. The conclusion of the study was marked by a final evaluation of the patients' clinical symptomatology in areas related to cognitive state, such as actual memory loss, difficulties in orientation, and deterioration of self-sufficiency as well as deterioration of recognition of objects and people, irritability/aggression and disorganized language.

Nuclear Magnetic Resonance (NMR): not all the patients that showed signs of altered cognitive state were tested with NMR.

Statistical analysis: the data were examined in both groups for the estimate of their incidence rate [44].

3. Results

The study was carried out with the purpose of determining the relative incidence of Alzheimer's disease in two groups of patients under treatment for the primary or secondary prevention thromboembolic venous and atherothrombotic diseases.

The clinical valuation in both groups were determined by significant as initial symptom the loss current or short term as cognitive deterioration accompanied by the difficulty of new learning, as well as, the problem of the family coexistence. The patients' affections of the short term loss of the memory with bigger or smaller loss of the historical memory have been considered as Incipient Alzheimer disease (IAD). The pathological evolution of the clinic with new parameters such as recognition of objects and people, irritability or aggressiveness the patients are classified as Middle Alzheimer's Disease (MAD), and their hospital entrance with loss of the self-sufficiency and the necessity of a constant supervision the patients are considered as Serious Alzheimer disease (SAD).

SLX group. Patients in the sulodexide group were continuously treated with sulodexide for an average time of 6.37 ± 2.75 years. Among the 46 patients recruited, five patients are diagnosed of AD that they are exposed

next to the comorbility, that is to say, the diagnoses that exist simultaneously independent of the AD. Two females, one of 80 years old with AH and DVT who had an evident loss of memory and orientation difficulties which required assistance and whose NMR study showed areas of cerebral infarctions, and a woman aged 77 years with a history of an old cerebrovascular accident (CVA), AH and DVT are diagnosed as MAD. A 73 year-old man with AH, dyslipidemia and atherosclerosis and two women, both of 72 years, one with AH, dyslipidemia and DVT and the other one with T2DM and atherosclerosis.

Two woman died one of them at age 68 from colon carcinoma and circulatory inadequacy, and the other one t died at age 93 year old from diabetic coma after a complicated medical history of A MI, T2DM, hypercholesterolemia and DVT. Two patients were diagnosed of irritability without aggressiveness, one woman 73 years old with circulatory Inadequacy**,** AMI and hypercholesterolemia, and a man 85 years old with DVT and AH, both with the other parameters remained normal. The remaining patients showed no significant changes in the parameters tested.

OA group. In the group OA were continuously treated with acenocoumarol for an average time of 6.84 ± 3.1 years. The periodic controls of the anticoagulant treatment for their drug adjustment, showing 91.58% inside the range INR among 2.0 - 3.0, 7.22% > 3.0 (INR among 3.1 - 5.0) and 1.20% < 2.0 (INR among 1.9 - 1.6) The mean of the INR of the patients with diagnose of AD it is of 2.5135 ± 0.7804.

In this group 14 patients are diagnosed of AD: Six patients of SAD, two patients of MAD and six patients of IAD. The comorbility has been: Cardiac pathology, Atrial fibrillation (AF) 85.7%, others heart pathology, 10.1%, AH, 50%, DVT 42.8%, dyslipidemia, 35.7%, atherosclerosis 35.7, T2DM, 21.4%.

Of the 6 patients with diagnose of SAD, three died, two men 86 and 91 year-old and a woman of 90 years old respectively. Of the three remaining patients we found two women one of 80 years with AHT, hypercholesterolemia, DVT, and atherosclerosis, and another woman of 92 years old with AF, AH, and DVT, and a man of 69 years old with AF, AH and DVT. In two patients find lesion consistent with cerebral infarctions on NMR testing. Two patients of MAD are women of 87 years old with AF and DVT, and the other one 79 years old with AF, DM and venous disease. Six patients are of IAD, 4 women and 2 men. One woman of 83 years old with FA, AH, DVT and, T2DM, two men, one of them of 80 years old with DM and DVT, an another of 80 m years old with AF, AH, and IC. Tree women, one of them of 80 years old with AF,IC, another of 80 years ol with AF and the last one of 76 years old with AF, hypercholesterolemia, AH and IC.

Three patients, one woman of 84 years old with AF AH and T2DM died of AMI and two men, one of 62 years old with dyslipidemia and the other one 82 years old with AF and T2DM died of lung cancer and cardiac disease respectively.

The relative incidence AD for groups of ages, gender and cases/year/100 patients they are exposed in the **Table 1**.

Adverse effects caused by sulodexide or acenocoumarol during the course of the study don't required to stop the treatment.

4. Discussion

This preliminary study prospective seek to determine the relative incidence (RI) of Alzheimer's disease in two

Table 1. Relative incidence (RI) of AD in the group SLX and OA both sexes.

CASES/YEAR/100 PATIENTS

	SLX		OA	
Range years	RI	Cases M/FM	RI	Cases M/FM
65 - 69	0	-	2.78	1/0
70 - 79	3.31	1/3	1.45	0/2
80 - 89	1.58	0/1	7.07	3/5
90 - 93	0	-	18.75	1/2
All ages	2.02	1/4	4.86	5/9

AD: Alzheimer diseases; SLX: Sulodexide; OA: Oral anticoagulation; M: males; FM: females.

groups of patients ≥65 years receiving treatment for prevention of venous thromboembolic and atherothrombotic diseases.

An increment of the venous and arterial thromboembolic diseases has been observed in the development of the aging [45], being attributed at a state prethrombotic like shows for the hypercoagulability activity found in blood [46] [47]. Sulodexide (SLX) or vitamin K antagonist (AVK) (Warfarina, Acenocoumarol) in the old patients is a medication prescribed in first line, being indicated in the illnesses of thromboembolic risk and stroke [48]-[51]. Although thromboembolic disease is related to the great activity or concentration of some factors of the blood coagulation in the aging, there is some scientific evidence of a decrease of the systemic fibrinolytic activity [47] [52] due to an increase in the expression of PAI-1 main inhibitor of the plasminogen activator tissue [3] [46] [53] that play a very important role in the thromboembolic disease, metabolic disease, T2DM and AD associated clinical processes with GSH depletion [54]-[57].

The patients recruited for this preliminary prospective study with the mentioned characteristics previously, suppose two different methodologies of prevention of the thromboembolic diseases in a population of patient with a high risk and incidence of thromboembolic complications. The group SLX is subjected to treatment with Sulodexide oral with fixed dose that doesn't need to be monitored and whose main pharmacological effect is referred as an inhibitor PAI with an increase of the fibrinolytic activity, and the group OA in treatment with vitamin K antagonist (VKA) that requires periodic monitoring for the adjustment of the INR, being both effective drugs in the prevention of the thromboembolic disease [58].

In connection with the group OA made up with patient affections of AF in their biggest part, clinical impression exists among the specialists that it can have certain relationship among the INR of the patients with AF and the cognitive state, referred mainly to that the alteration of the cognitive function could be related with a smaller effectiveness of the anticoagulation. However, this clinical appreciation has not been enough documented [49] [59]-[62]. Our results show as 91.58% recruited patients have been inside an INR among 2.0 - 3.0 appropriate range for the anticoagulation to patient with AF [63] [64], and only a 1.2% of them have been below the range and 7.2% for above of recommended range. In the same line, the results of the INR of the patients with AO and diagnose of AD they have been inside the range 2.5135 ± 0.7804.

The patients in this study are representative of a population older than 65 years, and it is important to point out that the patients in both groups, due to their advanced age, had a great load of chronic diseases such as cardiac diseases, dyslipidemia, arterial hypertension, type 2 diabetes mellitus, etc. They were under continuous follow-up and treatment by their family doctors. These chronic diseases in these patient groups require some comments because many of diseases and conditions inherent to them have been considered as AD risk factors by some researchers. Cardiovascular disorders (AF, IMA), AH, dyslipidemia and T2DM of mild cognitive impairment syndrome with high risk of progression to AD [64]-[67]. Numerous studies show that AH is associated with an increment of AD incidence and that early treatment of AH could be very important for the AD prevention [68]-[77]. Dyslipidemia and more specifically hypercholesterolemia has also been considered as possible risk factor in the development of AD [78]-[82]. This suggests that the treatment of these conditions may also be important for the prevention and treatment of AD [68] [83]-[86]. Nevertheless, in some studies in dyslipidemia, hypercholesterolemia could not be closely associated with the risk of development of AD [86]-[90]. T2DM is associated with an increment of risk of AD [91]-[99]. A close relationship is even suggested between both diseases [100] [101]. The patients of both groups had been followed and treated by their family doctors and the treatment for these diseases may have had some beneficial effects on maintaining the cognitive and mental health, although the exact mechanism of these diseases as risk factors in AD has not yet been clarified [78] [82]-[84] [89].

Common AD is a chronic process of complex etiology, without any effective prevention and treatment just until now. The results found in our study show the difference in cognitive and behavior evolution between sulodexide and acenocoumarol groups (**Table 1**).

In our opinion, the clinical benefit that we have found in the sulodexide group of patients, might be attributable to the properties of this drug on the fibrinolytic system t-PA/plasminogen/plasmin at systemic level and, in hypothesis, on the corresponding cerebral β-amiloidolytic mechanism [13] that will be discussed below.

The pharmacodynamic activity of sulodexide in the fibrinolytic system [41] is due to the increase of t-PA activity and the inhibition of PAI-1 activity [102]-[110]. After a quick and progressive intestinal absorption following oral administration of sulodexide [111], a remarkable plasmatic concentration and a generalized distribution occurs mainly in the endothelial cells due to its affinity to this cellular layer [39] [112]-[115]. The sulodex-

ide property of increasing fibrinolytic/proteolytic capacity would suggest that its long-term administration would bring, after passing the blood-brain barrier (BBB) of the proteoglycans [114] [115], an equilibrium between production and degradation of amyloid material with a greater clearing and a lesser accumulation of amyloid material (this last crucial to the progression of AD) in the cerebral regions [39].

The cerebral plasminogen/plasmin system does not differ from the systemic plasminogen/plasmin system, since all the constituents of the systemic mechanism are present in the brain [116]-[118]. Several studies have demonstrated the importance of the plasminogen/plasmin mechanism in the central nervous system [14] [119] and its implication in AD [31] [32] [120]-[122].

Along the aging there is a progressive descent of fibrinolytic activity due to a decrease of plasmin as it was observed in the serum of patients with Alzheimer type dementia [123] and in healthy subjects [124]. This decrease of plasmin with an increase in the levels of PAI-1 entails a decrease of β-amiloidolytic activity in the brain, which leads to an increase in the accumulation and to a decrease in the clearing of Aβ, and represents a very important mechanism in the pathogenesis of AD [34] [35] [119] [125] [126] in close correlation with the GSH mechanism.

We reported, in fact, that the pharmacological effect that is obtained after the administration of buthionine sulfoximine (BSO) or dietil maleate in rabbits, is a significant decrease in the levels of GSH with the inhibition of fibrinolytic activity measured in the fibrin plates, due to a decrease of cellular t-PA release with a significant increase of its inhibitor PAI-1 [13] [127].

Therefore, this systemic decrease of GSH by BSO suggests the following hypothesis: if cerebral plasminogen/plasmin system does not differ from the systemic plasminogen/plasmin system, it will be possible that the decrease of cerebral GSH levels, that is a fact in the physiologic aging as well as in AD, it may be the origin of the alteration of the cerebral protein homeostasis (proteostasis) characterized by deficit of the different cerebral proteolytic systems as neprilysin (NEP), insulin-degrading enzyme (IDE), endothelin-converting enzymes (ECE 1 and 2), and plasmin, with increments of the inhibitor PAI-1 [17] [21] [22] [25] [128]-[136]. In this line, it was reported that amyloid deposition in the brain was increased in PAI-1 transgenic mice, suggesting that increased PAI-1 expression contributes to the development of amyloidosis in AD [25] [137]-[139]. These scientific evidences lead us to think that GSH can play an essential role in the regulation of the different components of the brain proteolytic system.

GSH plays very important parts in many biological activities in the homeostasis of the organism, standing out for its capacity to neutralize the free radicals that origin reactive species of oxygen (ROS), due to its great antioxidant activity [140]-[144].

Many of the cerebral functions are altered as consequence of the decrease of the intra- and extracellular levels of GSH [144]-[151] as a result of the inhibition of GSH synthesis, due to the reduction of the enzymatic capacity of glutamylcysteine synthetase (GCS) that catalyzes the synthesis of GSH, and to the increased consumption of brain GSH due to age [152]-[156].

Deficiency of GSH is found in neurodegenerative diseases, mainly Alzheimer's and Parkinson's diseases, [146] [153]-[159] in patients with obesity, metabolic syndrome, resistance to insulin, hyperglycemia and diabetes, clinical conditions very related with AD [160]-[165]. In fact, an important decrease of fibrinolytic activity, with a depletion of t-PA activity, an increase of PAI-1 and an enhanced production of ROS has been found in these metabolic diseases [166]-[177].

Transforming grow factor-beta 1 (TGF-β1) is a factor that plays an important role in the proteolytic mechanism plasminogen/plasmin through GSH. TGF-β1 induces PAI-1 expression and activity with inhibition of t-PA and plasmin activities, whereas supplementation with GSH restores t-PA and plasmin activities by inhibition of TGF-β1-induced PAI expression and activity [178]-[180]. *In vitro*, TGF-β1 reduces the intracellular concentration of GSH [178] in a similar way to BSO [127]. This effect leads to a decrease of the t-PA and plasmin activities and an increase of PAI-1. The normalization of the concentration of GSH after the suspension of the effect of BSO is accompanied by normal t-PA and plasmin activities [127]. There are elevated serum concentrations of TGF-β1 in obesity, metabolic syndrome, type 2 Diabetes mellitus and AD [180]-[183] which are pathogenic processes entailing increase of PAI-1 and decrease of the level of GSH [166]-[168]. In addition to this, an improvement of the fibrinolytic activity and a decrease of PAI-1 have been observed with the administration of GSH to patients with non-insulin-dependent diabetes mellitus (NIDDM) [184] [185]. Experimental data show that a small molecule, PAZ-417, which is an inhibitor of PAI-1, increases t-PA activity, generates plasmin and enhances the degradation of Aβ *in vitro* and *in vivo* [33]. In the same line, in an experimental study in AβPP/PS1

double transgenic mice, a model of familial AD, a diet containing the phenolic compound tert-butyl hydroquinone (TBHQ) reduced the brain Aβ load, which was associated with an inhibition of PAI-1 and TGF-α-induced PAI-1 expressions and an increase in the activity of t-PA, plasmin, and the concentration of GSH [139]. These scientific evidences support the central role that PAI-1 plays in metabolic and neurodegenerative processes, especially in the AD, and suggest that agents inhibiting PAI-1 increase the plasminic activity.

The result in the SLX group of an apparent prevention of cognitive deterioration compared to the OA group leads us to highlight the benefits of the inhibition of the overexpression of PAI-1 and of the increase of the t-PA activity following the sulodexide administration [123]. There is some clinical evidence to suggest that cognitive status can be improved by decreasing the concentration of Aβ peptide in the cerebrospinal fluid, and that short-term and long-term resistance to cognitive deterioration can be achieved by oral administration of sulodexide. In line with our study some researchers present some evidences of clinical improvement of the cognitive state after short-term and long-term oral administration of sulodexide. Clinical improvement of memory deficit is described [186] as well as improvement of dementia symptomatology [187] [188] and mental confusion, [189]-[191] and a remarkable improvement of psycho-sensorial disturbances, sleeping disorders [192] and beneficial effects in vascular dementia [193].

Finally, the clinical benefit found in the group of patients receiving long-term treatment with sulodexide suggests in hypothesis, that the pharmacodynamic activity of sulodexide inhibiting PAI-1 and activating t-PA which leads to a permanent increase of cerebral plasmin activity, favors the catabolism of the Aβ peptide and the inhibition of its excessive extracellular accumulation.

It is possible that the cerebral mechanisms of GSH and β-amyloidolysis, can be some fundamental pillars in the prevention of AD, because their normal function during the aging brings the subjects to become centenarians. In fact, in centenarians glutathione reductase activity (leading to GSH synthesis) is normal or high [194] [195] and t-PA/plasminogen/plasmin and PAI-1 mechanisms are normal with a paradoxical increase of secondary fibrinolytic activity with high levels of D-dimer and plasmin-antiplasmin complex which are demonstrative parameters of a bigger fibrinolytic activity [196] [197].

5. Conclusions

Sulodexide prevents the depth and the relative incidence of the cognitive deterioration in patients older than 65, in treatment for more than 3 years apparently.

This favourable result may be related to its pharmacodynamic actions of inhibition of PAI-1. PAI-1 is the origin of the decrease of systemic fibrinolytic and cerebral proteolytic activities and it causes some thromboembolic complications so frequent in these patients. The clinical benefit found in the group of patients receiving long-term treatment with sulodexide suggests us in hypothesis, that the pharmacodynamic activity of sulodexide inhibiting PAI-1 and activating t-PA which leads to a permanent increase of cerebral plasmin activity, favours the catabolism of the Aβ peptide and the inhibition of its excessive extracellular accumulation. The possible causal agent may be the decrease of GSH synthesis which may interfere with the pathogenesis of Alzheimer's disease. It is possible that the cerebral mechanisms of GSH and fibrinolysis/β-amyloidolysis, can be fundamental pillars in the prevention of Alzheimer disease.

Further prospective clinical trials are needed to evaluate the cognitive state of patients during long-term treatment with PAI-1 inhibitors, such as sulodexide, as well as to investigate more deeply the relationship of GSH with the different components of proteolytic cerebral system in common AD.

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Disclosure

The authors report no conflicts of interest in this work.

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