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# Alzheimer's Disease, Early Diagnosis

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## Abstract

**Aim:** In this review paper we propose a method to make an early diagnosis of the Alzheimer's Disease (AD), the most common form of neurodegenerative dementia. **Background:** Glymphatic System (GS) is the main means of eliminating waste substances in the central nervous system (CNS); if it does not work properly, waste substances accumulate in CNS until to cause AD. Basal Forebrain is the most important component of a much broader system of cholinergic cells distributed throughout the Central Nervous System (CNS). This structure regulates attention, learning and memory and its destruction is considered responsible for the cognitive AD alterations. The characteristics of AD patients, that interest us most, are the lack of Acetylcholine, and the Orexin excess; we think that the hypothalamus produces more Orexin to stimulate cholinergic cells, indispensable for a correct CNS functioning. We want to identify these patients by detecting the Orexin excess. Early Diagnosis Model. Of course we could take a cerebrospinal fluid sample and dose Orexin but this method is risky and painful for the patient's health, therefore unsuitable for large numbers of patients. We propose a fairly simple method for the early diagnosis of AD: if we temporarily eliminate the Orexin excess, with Dual Orexin Receptor Antagonist (DORA), *i.e.* Suvorexant, we can intercept the Orexin increase and demonstrate the decrease in Acetylcholine with a Functional Magnetic Resonance or a Polysomnography, many years before the AD symptoms occur.

## Keywords

Glymphatic System, Acetilcholine, Adenosine, Orexin, Dual Orexin Receptor Antagonist

## 1. Background

Alzheimer's Disease (AD) is the most common form of degenerative dementia [1], characterized by widespread neuron destruction, a sharp decrease in Ace-

tylcholine in patients' brain, and the accumulation of a protein called beta-amyloid ($\beta$A) in the extracellular environment and of anomalously phosphorylated Tau protein, within neurons. Especially important in AD are the Basal Forebrain Cholinergic (BFC) neurons, whose destruction is considered the main cause of the patients' memoryloss. We know that the genetic mutations responsible for the genetic forms of AD often interfere with the correct function of the main cleaning mean of our Central Nervous System(CNS), and the Glimphatic System (GS) [2] [3] [4]. We think that this happens in the sporadic forms of AD, also, for other reasons, which often involve the breaking of the Blood-Brain-Barrier integrity, above all, aging [5].

## 2. The CNS Clearance and the Glymphatic System

The waste products, deriving from the cellular activity of neurons, are partly eliminated within the same cells by intracellular clearance mechanisms; the substances that are not eliminated inside the neurons, are expelled in the extracellular matrix and eliminated through the Glymphatic System, the main instrument for removing extracellular waste substances in the CNS [6].

## 3. Intracellular Clearance Mechanisms

The main AD genetic alterations slow the clearance mechanisms that, within neurons, are performed by the Ubiquitin-Proteasome System (UPS) or by autophagy, a process by which superfluous or potentially dangerous cytoplasmic material is delivered to lysosomes for degradation. We know three types of autophagy:

- Microautophagy, in which the cytosolic material is directly engulfed by lysosome invaginations.
- Chaperone-Mediated Autophagy (CMA), in which chaperone proteins lead the waste to the lysosome.
- Macroautophagy (autophagic-lysosomal network or ALN), which involves the seizure of cytosolic material in autophagosomes that provide their content to lysosomes for digestion [7] [8] [9].

The laboratory findings show that in Alzheimer's Disease, UPS, CMA and ALN, are compromised, often due to gene alterations in APOE4, PS1, PS2, APP, PICALM, TREM2, among the main recognized genes responsible for Alzheimer cases [10].

Naturally the substances not removed by the endocellular mechanisms are expelled by neurons, in the extracellular environment.

## 4. Extracellular Clearance Mechanism: Glymphatic System

The main tool for removing extracellular waste substances is Glymphatic System [2] [3] [4] [6]. The clearance of soluble proteins, waste products and extracellular fluid excess is achieved through the convective flow of the interstitial fluid, facilitated by the presence of channels called aquaporins (AQP), located in the

astrocyte membrane [11], which play acrucial role in water flow regulation in and out of cells. AQPs facilitate cell's water permeability up to 30 times [12]. The main AQP types, expressed in the CNS, are: aquaporin-1 (AQP1), which is expressed by the epithelial cells of the choroid plexus, and aquaporin-4 (AQP4), which is expressed by astrocytes [13] [14].

The AQP4 in astrocytes is present above all in their terminal processes (end feet) that cover the encephalic vessels. Up to 50% of the surface of these feet is occupied by AQP4 [11] and the glinfatic system is critically based on astrocytic AQP4.

Deficiencies in this pathway have been shown to contribute to AD, and a perivascular AQP4 reduced number is associated with AD diagnosis and pathology [15].

In case of glinfatic system deficiency, the clearance of the $\beta$-amyloid protein is altered [16] and thus that of Adenosine, present above all in the Basal Forebrain (BF) [17]. The key factor in the GS functioning, therefore in the pathogenesis of AD, is sleep. GS works up to 60% better during sleep and especially during the N3 phase of NREM (deeper sleep) [18]. Several studies have indicated that limited sleep increases the level of $\beta$-amyloid and of Tau protein neurofibrillary tangles [19] [20] [21].

Sleep Deprivation (SD) simulates what can happen as a result of some factors, such astrauma, stress and, above all, aging, which can alter the control of the endoplasmicreticulum on protein quality and lead to an "Unfolding Protein Response" (UPR), which causes the production of "Misfolding" proteins, *i.e.* poorly aggregated and hyperphosphory [22]. In SD, adenosine levels are greatly increased (+140%) in the cholinergic BF; adenosine, a small purine molecule that constitutes the central element of adenosine triphosphate (ATP), the main energy source of all our cells, including neurons.

This molecule is produced everywhere, in the CNS, but accumulates only in the basal Forebrain [23], where it inhibits cholinergic neurons by stimulating its A1 receptors; this induces drowsiness and reduces the waking state [24].

The Glymphatic system also plays an important role in the transport of extra-synaptic glutamate excess, which, if not eliminated, can cause excitotoxicity, perhaps the most important cause of neuron loss in AD. Some drugs (e.g. memantine) are effective (but not decisive) in the AD care [21].

The GS may encounter difficulties in functioning following Traumatic Brain Injury [25], in Depression [26], following general anesthesia [27], in Diabetes [28], following Stroke [29] and above all with the aging [30]. In all these cases there would be substance accumulation, both in the extracellular and in the intracellular environment.

## 5. Neurotransmitters

A clearance system that does not function optimally will, above all, penalize the cells with high activity. Therefore, the cells of ARAS nuclei, which perform many

functions, even the most disparate, must present a remarkable metabolism. In fact, in addition to the Tau and A$\beta$ proteins in AD, some of the most important neurotransmitters (NT) in our body, such as Serotonin, Norepinephrine, Histamine and Dopamine and above all Acetylcholine are involved (reduced in quantity) [31] [32] [33] [34] [35].

Orexin (OX) is an exception: the number of orexinergic neurons decreases with age [36], but the Orexin concentration in CSF of AD patients is increased [37] [38] [39] [40] [41].

## 6. Basal Forebrain Cholinergic System

It constitutes the most important component of a much broader system of cholinergic cells distributed throughout the CNS, from the rostral portions of the Striato until, caudally, to the spinal motor neurons. This structure regulates phenomena such as attention, learning and memory and is implicated in the cognitive alterations present in different neurological pathologies such as AD. BFC neurons also project towards the preoptic nuclei (VLPO and MnPO) and Tubero Mammillari (TMN) of the Hypothalamus and, through these projections, participate in wake/sleep modulation [42] [43]. Cholinergic neurons present many Adenosine receptors [44].

## 7. Orexin

The cellular bodies of neurons expressing the orexin/hypocretin neuropeptides, present only in the lateral hypothalamus and in the contiguous perifornical area, provide diffuse projections towards the basal forebrain which increase the cortical Acetylcholine release [45] [46] [47]. Orexin has a strong and direct excitatory effect on BFC neurons, contributes to cortical activation associated with wakefulness [48] [49], more than all the other NTs that promote wakefulness [50] [51] and works in concert with cholinergic ones [48] [52].

## 8. Discussion, Pathogenetic Hypothesis and Early Diagnosis Model

If the GS does not work well, as with aging, diabetes, lack of sleep etc., at the Basal Forebrain level, there is an increase in adenosine, which inhibits cholinergic cells. Acetylcholine production is expected to decrease but the hypothalamus produces more Orexin and stimulates the remaining cholinergic cells to produce enough Acetylcholine to make CNS work properly. When the cholinergic cells number decreases too much, the AD symptoms begin. Orexin determines the vigil and there is a sleep mechanism alteration with daytime sleepiness, due to the excess of Adenosine and nocturnal vigil, caused by the excess of Orexina. The GS becomes less and less effective causing a further Acetylcholine deficiency, in a vicious circle that leads to the AD. Adenosine, $\beta$-Amyloid and TAU protein are not disposed of by the glymphatic system and accumulate: this causes further loss of BFC, the Ach decreases further and the OX increases further: the

AD. Thus, in AD, while many neurons die and all other ARAS Neurotransmitters decrease in quantity, the OX increases and we can use this detail for an early diagnosis. The OX increase is a very important fact because it causes an acceleration of the neurodegeneration (due to sleep loss) and is AD specific. This is probably the reason for which AD is the main neurodegenerative disease, and we can use this increase to make an early diagnosis of the disease. The orexinergic "compensation" of Ach deficiency can mask the disease for years but could allow us to intervene for an early diagnosis.

Early Diagnosis Model: Of course we could take a cerebro-spinal fluid sample and dose Orexin but this method is risky and painful for the patient's health, therefore unsuitable for large numbers of patients.

Hanazawa T and Kamijo Y [53] have administered suvorexant to four AD patients, all four patients with nocturnal delirium successfully fell asleep rapidly, suggesting that the resolution of delirium may be related to the effects of suvorexant on sleep dysregulation. In all four cases, suvorexant drastically resolved delirium symptoms and improved their sleep. The nocturnal delirium recurred almost immediately following the discontinuation of suvorexant. The effect of suvorexant on nocturnal delirium was thus suggested to be reproducible. The medical history of these patients, showed a progressive and gradual decline in cognitive function, neuroimaging results including computed tomography of the brain, cognitive tests, and laboratory data all satisfied the DSM-5 criteria for AD with a high level of evidence. The administration of suvorexant for the purpose of managing nocturnal delirium, in several elderly patients with dementias other than AD, had no effects at all. Then the administration of suvorexant allows us a differential diagnosis between AD and other similar neurodegenerative diseases [53]. We know that the orexin, besides being important for the maintenance of wakefulness, is fundamental for the stabilization of the wakefulness-sleep switch [54]; and we also know that nocturnal delirium depends on Acetylcholine deficiency [55] [56] [57] [58] [59] and that by administering an anticholinergic we can cause hallucinations and delirium (Atum M, 2020), while, with the administering an acetylcholinesterase inhibitor, which increases the amount of Acetylcholine, we can stop these hallucinations and delirium [60]. So if we administer a Dual Orexin Receptor Antagonist (DORA) and the delirium ceases it means that this patient has Ach deficiency and, of course, excess of Orexina. DORA eliminates the excess of Orexina and the patient sleeps: hallucinations and delirium are due to the complex: too much Orexina, that does not make the patient sleep and little Acetylcholine, which, during insomnia, causes delirium. During sleep (NREM sleep) it is normal, however, that there is little Acetylcholine. If we administer a DORA, to an awake patient, the effects of Orexin will be zeroand, if that patient is an asymptomatic Mild Cognitive Impairment, the Ach will show its real levels, low. We can administer a DORA to the suspect patient and perform an instrumental check: e.g. a Functional Magnetic Resonance Imaging (fMR). If the BFC does not have a sufficient amount of Acetylcholine its $O_2$ consumption will be significantly reduced and we will see it in the neuroimaging

that will present signs of impaired hippocampus function and of other CC areas, particularly related to cholinergic innervations. In case of doubt we can perform the same analysis, after a few time, without DORA and compare the two results [61]. Furthermore, in the AD patient, the DORA administration will increase both the amount of total sleep and the NREM [62] [63]. REM sleep, instead, will decrease, both in quantity (time) both, above all, in quality, due to the inability of BFC cells to support it, proportionally to the gravity of the situation, with disappearance of posterior dominant alpha rhythm and the diffuse slowing in EEG, specifically a reduction of power in the alpha (8 - 15 Hz) and beta (16 - 31 Hz) bands and an increase in the theta (4 - 8 Hz) and delta (0.5 - 4 Hz) bands [64] [65]. This because the BFC system, which is impaired in Alzheimer's disease, is more crucial for the activation of REM sleep EEG than it is for wakefulness 110 - 120 [66] [67]. The phenomena related to sleep, in AD, are very early and present for the entire duration of the disease [68] [69]. We could make a first Polysomnographic (PSG) check on the "suspect patient", evaluate the various parameters and above all the quantity and quality of the REM. Perform a second PSG after DORA administration to the patient and rechecking the values obtained, especially the REM, again [64] [65] [67] [70]. If we administer DORA during waking state and subject the patient to AD tests (Mini Mental State Examination, Clock Drawing Test etc.) its performance will be poor, similar to those of a patient frankly AD or MCI, Finally, to be sure of the diagnosis we can make more invasive examinations (e.g. Cerebrospinal Fluid control).

After making a diagnosis, as early as possible, we must first try to investigate the possible causes: ageing, genetics, diabetes, depression, stroke, etc. and try to intervene on these. We must try to restore optimal functioning of the Glymphatic System by acting on the lifestyle, especially with regard to the quantity and quality of sleep. The use of drugs such as Suvorexant itself which [71], by eliminating the effect of OX excess will improve sleep and, therefore the function of the Glymphatic system, and also some antihistamines such as Pitolisant, an H3 receptor agonist/inverse antagonist of histamine, which has been shown to be effective in AD, probably improving sleep [72]. We can improve the action of Ach with cholinesterase inhibitors (if Ach increases, less Ox will be produced and sleep will improve [73]. All this will improve the clearance made by the Glymphatic System which will reduce the amount of A$\beta$, Tau etc. taking care, in fact, of the causes of the AD. Furthermore, the patient can keep himself constantly under control by monitoring his sleep.

The ethiopathogenetic AD model we presented is very simple and shared by many other authors: the cleaning system (GS) in our CNS does not work properly and the waste accumulates. There is a great loss of neurons, especially of cholinergic ones, while the Orexin production increases. Despite many similarities, the increase in Orexin is not present in other neurodegenerative diseases. We can demonstrate the decrease of Acetylcholine by eliminating the excess of Orexina with specific drugs and make an early diagnosis, even many years before the symptoms of this disease, Alzheimer's, appear.

## 9. Conclusion

We strongly believe in the pathophysiological model we propose because it explains many characteristics of this disease, but if it were wrong, the system for early diagnosis, that we have devised, would work anyway. The administration of Suvorexant, in asymptomatic patients, allows us an early diagnosis, a differential diagnosis and a more targeted therapy, both with Suvorexant itself and with cholinesterase inhibitor drugs. This model of early diagnosis is not invasive; it is very simple, very fast and to our knowledge; there are no better ones.

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## Conflicts of Interest

The authors have no affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript.

The undersigned, Dr. Giovanni Andrisaniand Dr. GiorgiaAndrisani, declare that we have no conflict of interest.

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## List of Abbreviations

5-ht—Serotonin

A1—Adenosine 1

Ach—Acetylcholine

AD—Alzheimer's Disease

AGP—Aquaporin

ALN—Autophagic-Lysosomal Network

APOE—Apolipoprotein E

APP—Amyloid Precursor Protein

ARAS—Ascending Reticular Activation System

ATP—Adenosine Triphosphate

$\beta$A—Beta Amyloid

BF—Basal Forebrain

BFC—Basal Forebrain Cholinergic neurons

Ca—Calcium

CC—Cerebral Cortex

CMA—Chaperone-Mediated Autophagy

CNS—Central Nervous System

CSF—Cerebro Spinal Fluid

DA—Dopamine

DORA—Dual Orexin Receptor Antagonist

DR—Dorsal Raphe

EEG—Electroencephalogram

GABA—Aminobutyric Acid Gamma

GIRK—Potassium Channels Coupled with Inward Radical Proteins

GS—Glymphatic System

H—Histamine

K—Potassium

KirNB—Inward Rectifier $K^+$ Channel of the Basal Nucleus

LC—Locus Coeruleus

LDT—Latero-Dorsal Nuclei of the Tegmentum

LGN—Lateral Geniculate Nucleus

MnPO—Median Preoptic

NA—Norepinephrine

NREM—Movement for Non-Rapid Eyes

NT—Neurotransmitter

OX—Orexin

PB—Parabrachial Area

PICALM—Clathrin Assembly Protein Binding the Inositol with Phosphatidyl

PPT—Peduncolo-Pontine del Tegmentum

PS—Presenilin

P2X7—Purinoceptor 7

REM—Rapid Eyes Movement

SCN—Suprachiasmatic Nucleus

SD—Sleep Deprivation

SLD—Sub Laterodorsal Core

TMN—Tuber-Mammillary Nuclei

TREM—Trigger of Receptors Expressed on Myeloid cells

UPR—Explanable Protein Response

UPS—Ubiquitin-Proteasome System

VLPO—Pre-Optic Ventro-Lateral Nucleus