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Mini Review

Cholinesterase Inhibitors as a Disease-Modifying Therapy for Alzheimer's Disease: The Anticholinergic Hypothesis

Hori K[1,2]*, Hosoi M[2], Konishi K[3], Sodenaga M[1], Hashimoto C[1], Sasaki O[1], Suzuki I[1], Maedomari M[1], Tadokoro M[1], Tsukahara S[1], Kamatani H[4], Kocha H[1], Tomioka H[2] and Hachisu M[5]

[1]Department of Neuropsychiatry, St. Marianna University, Japan

[2]Department of Psychiatry, Showa University Northern Yokohama Hospital, Japan

[3]Tokyo Metropolitan Tobu Medical Center for Persons with Developmental/ Multiple Disabilities, Japan

[4]Department of Psychiatry, Kawasaki Memorial Hospital, Japan

[5]Department of Pharmaceutical Therapeutics, Division of Clinical Pharmacy, Showa University, Japan

***Corresponding author:** Koji Hori, Department of Neuropsychiatry, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamaeku, Kawasaki City, Kanagawa, Japan

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Abstract

In this mini-review article, we summarize our previous results and discuss whether cholinesterase inhibitors (ChEIs) should be considered a disease-modifying therapy for Alzheimer's disease (AD). First, we reiterate that the acceleration in AD progression is related to the endogenous appearance of anticholinergic activity (AA) and that one of the two possible pathways generating amyloid peptides in AD is related to acetylcholine downregulation. Second, we compare the kinetics of ACh between the mild cognitive impairment stage and normal stage according to the hypothesis of AA in AD. Third, we differentiate among ChEIs according to the classification of AD stage based on AA and also speculate that ChEIs might be useful as disease-modifying therapies.

Keywords: Anticholinergic activity; Acetylcholine; Alzheimer's disease; Choline acetyltransferase; Disease-modifying therapy; Mild cognitive impairment; Pharmacotherapy

Abbreviations

AA: Anticholinergic Activity; ACh: Acetylcholine; AD: Alzheimer's Disease; BuChE: Butyrylcholinesterase; ChAT: Choline Acetyltransferase; ChEI: Cholinesterase Inhibitor; MCI: Mild Cognitive Impairment; NMDA: N-methyl-D-aspartate

Introduction

Antidementia agents such as cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists are not considered disease-modifying therapies but symptomatic treatments. However, based on our theory of the endogenous appearance of anticholinergic activity (AA) in Alzheimer's disease (AD) [1,2], we believe that ChEIs and NMDA receptor antagonists should be considered both disease-modifying therapies and symptomatic treatments [3].

Therefore, in this mini-review article, we discuss why ChEIs should be considered a disease-modifying therapy based on our previous work. First, we summarize why the acceleration in AD progression is believed to be related to the endogenous appearance of AA in AD [1] and why one of the two pathways generating amyloid peptides in AD is related to ACh downregulation [2]. Second, we reiterate our hypothesis that the mild cognitive impairment (MCI) and mild stages of AD can be explained by the hypothesis of endogenous AA in AD [1,2] and hypothesize that the kinetics of ACh are altered in MCI stages compared with the normal stage. Third, we differentiate among ChEIs according to the classification of AD stage based on AA levels and speculate that ChEIs are disease-modifying therapies.

Classification of AD based on the hypothesis of endogenous AA in AD

ACh is related not only to cognitive function but also regulation of inflammation [4-7]. AD patients show ACh downregulation [8,9], which might possibly up regulate the inflammation found in the brains of AD patients. This inflammation might induce the release of cytokines with AA. Therefore, we previously hypothesized that AA both in the central nervous system and peripheral tissue might appear endogenously in the moderate stage of AD [1,2]. At this stage, the depression of the cholinergic system reaches a critical level, with increased NMDA receptor expression causing hyperactivity of the inflammatory system and leading to AA. Accordingly, we proposed our hypothesis of endogenous AA in AD [1,2]. AA is considered not only to depress ACh by antagonizing its binding to the ACh receptor but also to induce amyloid production [10,11]. Thus, we speculated that AD progresses more rapidly at the moderate stage than at the mild stage due to endogenous AA [12].

We therefore believe that there are two amyloidogenic patterns in AD. The first pattern (P1 pattern) is pathological and is unrelated to the ACh downregulation observed in MCI or mild AD. The second pattern (P2 pattern) is also pathological but is related to the ACh downregulation observed in moderate AD. The P1 pattern probably begins when the AD pathology occurs and is likely to be misdiagnosed as normal aging due to the slow decline in cognitive function. However, the P2 pattern is related to ACh downregulation and is clearly prominent, and it can be readily diagnosed as AD at the moderate stage when AD patients present with clinical symptoms such as memory disturbance, disorientation, aphasia, delusions,

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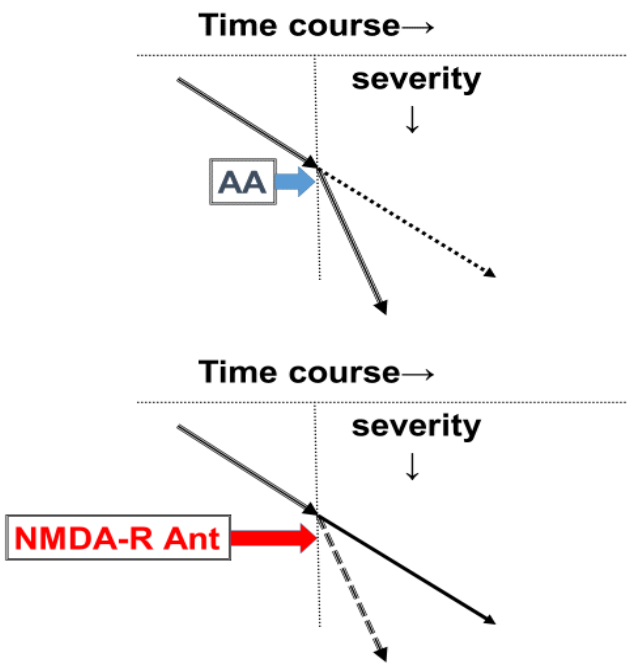

Figure 1: In moderate-stage AD, AA appears endogenously and the progression of AD is accelerated (upper panel). This process involves NMDA receptor hyperactivity. Therefore, NMDA-R Ant can abolish AA and reduce the speed of AD progression to that of the mild stage (lower panel). This figure is reproduced from Hori, et al. [13]. AA: Anticholinergic Activity; AD: Alzheimer's Disease; NMDA: N-methyl-D-aspartate; NMDA-R Ant: NMDA Receptor Antagonist.

hallucinations, and diurnal rhythm disturbance [3,13]. The decline is also more rapid at the moderate stage than in patients with MCI or mild AD [12]. Therapeutically, we recommend that ChEIs and NMDA receptor antagonists be prescribed for the prevention and treatment of the appearance of AA and the rapid progression of AD, respectively [3]. Thus, ChEIs and NMDA receptor antagonists should be considered both disease-modifying therapies and symptomatic treatments [3]. As for NMDA receptor antagonists, these medications abolish AA due to hyperactivation of ACh and slow the progression of AD (Figure 1) [13,14].

Moreover, we also speculate that there might be a compensatory mechanism in relatively early-stage AD. Generally speaking, AD pathology causes the degeneration of cholinergic neurons [6,7]. However, although the activity of choline acetyltransferase (ChAT, the enzyme that produces ACh) is down regulated in the mild and moderate stages of AD, increased ChAT activity has also been reported in patients with MCI or early AD [15-17] and in the tau rat model [18]. Hara, et al. [18] reported that acetylcholinesterase upregulation in the septum may result in the selective degeneration of the septohippocampal cholinergic pathway in the tauopathy mouse model. Our group and other group also previously speculated that this upregulation of ChAT is related to a compensatory mechanism [15-17,19]. This mechanism ensures that the ACh level is relatively normal and that cognitive function remains largely intact. This compensatory reaction to the onset of AD may be attributable to hyperactive presynaptic cholinergic neurons. If this compensatory mechanism works, then the cholinergic system remains intact,

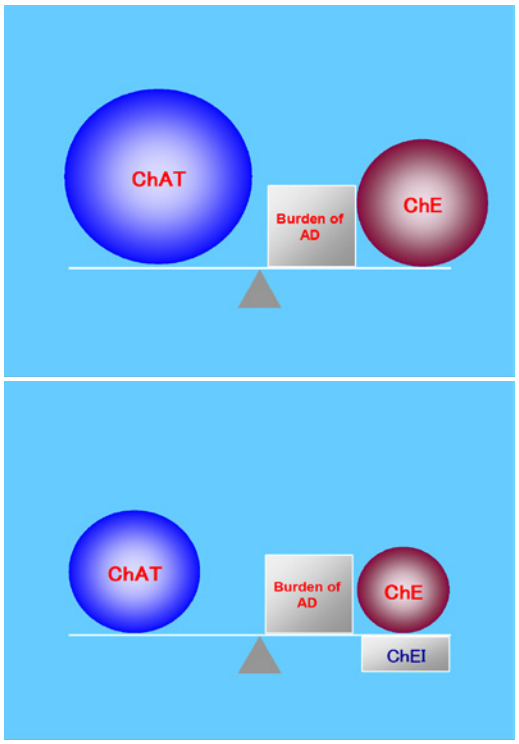

Figure 2: In the MCI stage, ChAT is hyper activated to compensate for the AD burden and to maintain ACh at a normal level. However, this ChAT upregulation causes early degeneration of ACh neurons (upper panel). Therefore, it is important to down regulate ChE activity to maintain a normal ACh level without ChAT upregulation. For this reason, we should prescribe ChEIs to patients with AD, even those with MCI (lower panel). These figures are reproduced from Konishi, et al. [19], with the permission of Karger, Basel, Switzerland.
ACh: Acetylcholine; AD: Alzheimer's Disease; ChAT: Choline Acetyltransferase; ChE: Cholinesterase; ChEI: Cholinesterase Inhibitor; MCI: Mild Cognitive Impairment.

rather than deteriorated. Thus, when clinical symptoms occur, the cholinergic system is burdened but functioning and the neurons are functional (i.e., not degenerated).

Based on these speculations, we hypothesize that, in the MCI stage, the AD pathology burdens the brains of AD patients, but that ChAT activity is up regulated, resulting in normal ACh levels. Moreover, we propose that ACh gradually decreases in mild-stage AD. The hyperactivity of presynaptic neurons may cause early and rapid neuronal degeneration and depress ChAT activity [15-17]. Therefore, we consider it important to maintain the compensatory reaction as long as possible. To do this, it is important to down regulate cholinesterase so as not to up regulate ChAT activity and hyper activate ACh (Figure 2) [19].

ACh kinetics in the MCI and normal stages and the differences among ChEIs

The compensatory mechanism might succeed in the MCI stage and support the cholinergic system. However, there might be two situations in which ACh is down regulated or overburdened in MCI that are not seen in the normal stage. One occurs when patients with AD at the MCI stage relax, at which time the ACh level is lower than normal. In this situation, these patients show apathy (e.g., when

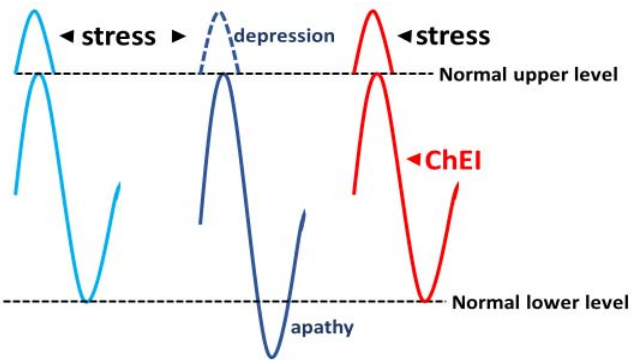

Figure 3: There might be two situations in which ACh is down regulated or overburdened in MCI (middle) that are not seen in the normal stage (left). One occurs when patients with AD at the MCI stage relax, at which time the ACh level is lower than normal. In this situation, these patients show apathy (e.g., when they watch television, they fall asleep). The other situation is when they are more stressed than usual. In this situation, their cholinergic system cannot be up regulated any further because ChAT is already activated and does not permit further upregulation. When ChEIs are prescribed, ACh upregulation is possible, even if another AA-inducing factor is present, to compensate for other AA inserts and ameliorate stress (right).
AA: anticholinergic activity; ACh: Acetylcholine; AD: Alzheimer's Disease; ChAT: Choline Acetyltransferase; ChEI: Cholinesterase Inhibitor; MCI: Mild Cognitive Impairment.

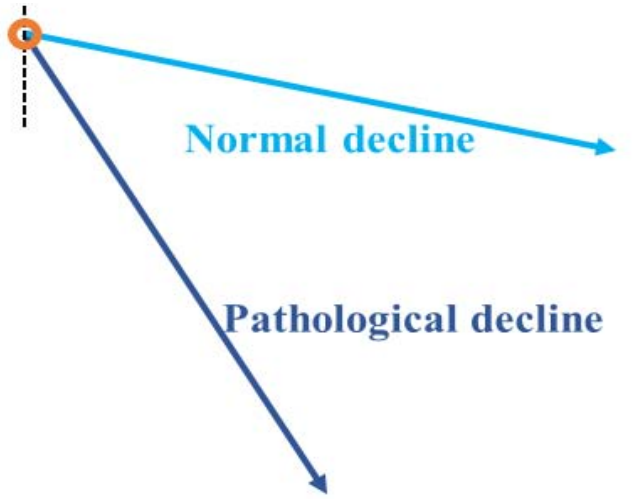

Figure 4: Cognitive functions in patients with MCI are relatively maintained. Therefore, in the clinical setting, patients obtain relatively high scores on the mental examination test battery. It is important to predict the speed of decline in these patients (orange circle). Patients showing apathy, depressive symptoms, or irritability even with good cognitive function will probably have a faster rate of decline (pathological decline; dark blue line) than during normal aging (normal decline; light blue line) and be diagnosed with AD. When patients show apathy when relaxed or depressive symptoms or irritability that is related to depressive symptoms in AD, they should be diagnosed with AD (at the MCI stage) even when they do not show cognitive impairment, permitting the early diagnosis of AD.
AD: Alzheimer's Disease; MCI: Mild Cognitive Impairment.

they watch television, they fall asleep). The other situation is when they are more stressed than usual. In this situation, their cholinergic system cannot be up regulated any further because ChAT is already activated and does not permit further upregulation (Figure 2). We have discussed this mechanism above. When the ACh system is intact

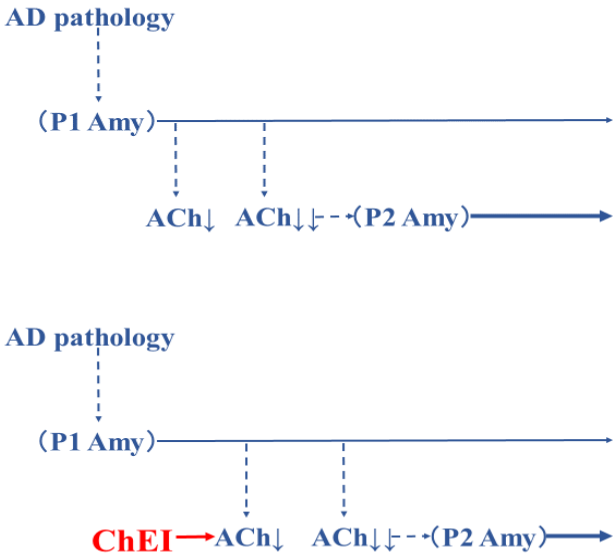

Figure 5: There may be two steps by which amyloid is generated. The first pattern (P1 pattern) is caused by AD pathology and induces ACh downregulation. The second pattern is another pathological pattern (P2 pattern) and is related to the ACh downregulation. When the downregulation of ACh caused by the P1 amyloid pattern reaches a critical level, the P2 amyloid pattern develops, accelerating the progression of AD (upper). If ChEIs are prescribed, the time to the critical ACh downregulation and the initiation of the P2 amyloid pattern is delayed. Therefore, ChEI is a symptomatic treatment for the P1 amyloid pattern and is also a disease-modifying treatment of P2 amyloid (lower). These figures were produced based on Hori, et al. [3].
ACh: Acetylcholine; AD: Alzheimer's Disease; Amy: Amyloid; ChEI: Cholinesterase Inhibitor.

and not depressed or overloaded, upregulation of ACh is possible, even in the presence of another AA-inducing factor (e.g., medication [20], febrile illness [21], or mental stress [22]. Consequently, the inflammatory system is not up regulated and AA does not appear. Even if ACh downregulation does not reach a critical level, when another AA-inducing factor is present and the ACh system is depressed or overloaded, the inflammatory system is up regulated and AA appears [23].

Alternatively, when the ACh system is intact and not depressed or overloaded, it can compensate for the effects of other AA inserts and stress is ameliorated. However, when the ACh system is overloaded, such as in the MCI stage, it cannot compensate for other AA inserts and the stress continues, causing depression. In this situation, ChEI prescription may enable ACh upregulation by boosting ChAT (Figure 3). The other implication of this hypothesis is that patients who show apathy when relaxed or who show depressive symptoms or irritability related to depressive symptoms in AD could be diagnosed with AD (at the MCI stage) even when they do not show cognitive impairment, permitting early diagnosis of AD. Alternatively, the cognitive functions of patients with MCI are largely maintained. Therefore, in the clinical setting, patients get relatively high scores on the mental examination test battery. We would also be able to predict the speed of cognitive decline in these patients. If the patients show apathy, depressive symptoms, or irritability despite good cognitive function, we can speculate that the cognitive decline in these patients would be faster than that of normal aging and thus diagnose them with AD (Figure 4).

Finally, we should differentiate among the three ChEIs we prescribe. Because the cholinergic system is considered to be intact in the MCI stage, nicotinic receptor, amyloid, glia, and butyrylcholinesterase (BuChE) levels are also considered to be normal. Therefore, donepezil should be prescribed because it specifically inhibits acetylcholinesterase. In contrast, in mild-stage disease, particularly in the mild and moderate stages, we should consider prescribing rivastigmine or galantamine because this stage shows a gradual decrease in ACh that depresses ChAT activity due to cholinergic neuron degeneration and nicotinic receptor downregulation. Of course, BuChE is also up regulated because of the proliferation of amyloid peptides and glia cells [24]. When patients show marked apathy, we prescribe rivastigmine. Moreover, rivastigmine should be prescribed to younger patients because amyloid pathology is more predominant than the physiological aging process in these patients compared with older AD patients [25]. In contrast, when patients show marked depressive symptoms or irritability, we should prescribe galantamine [26].

Based on these hypotheses, we consider ChEIs to be not only a symptomatic treatment but also a disease-modifying therapy (Figure 5). NMDA receptor antagonists also have disease-modifying properties. It is vital to develop new pharmaceutical approaches to AD. However, we also consider it important to reevaluate already available medicines, namely, ChEIs and NMDA receptor antagonists, as disease-modifying therapies.

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