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Mini Review

Why Does the Progression of Alzheimer's disease Accelerate?

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Abstract

We have already reported that anticholinergic activity (AA) appeared endogenously in Alzheimer's disease (AD) serum, and may accelerate AD pathology. In this article we introduce the reasons for this. We comment on the roles of acetylcholine (Ach) downregulation and AA in AD, show two patterns of AD rapid progression associated with AA, and three putative patterns of amyloid pathology in AD. We speculate that ACh downregulation and AA may induce inflammatory hyperactivity in both the central nervous system and peripheral tissue, as well as among inflammatory cytokines that may have AA. This ACh downregulation in AD may extend the pathological processes in the central nervous system to peripheral tissues and vice versa, whereas AA in AD may be a final common pathway in the amyloid-producing process from various invasions. In addition, we discuss our proposed hypothesis of endogenous AA in AD and consider its implications. Therapeutically, we recommend that prescribing cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists are appropriate for the "prevention" and "treatment" of rapid progression of AD respectively. In this context, it is important to prevent iatrogenic overdosing or polypharmacy for patients with AD. Furthermore, it is important to ensure that patients with AD are not suffering from concurrent physical illness or mental stress because this may facilitate the rapid progression of AD. Finally, we consider the limitations of the proposed hypothesis of the endogenous appearance of AA in AD

ABBREVIATIONS

MCI: Mild Cognitive Impairment; **AD:** Alzheimer's disease; **SAA:** serum anticholinergic activity; **ACh:** Acetylcholine; **NMDA:** N-methyl-D-aspartate; **AA:** anticholinergic activity; **FAST:** Functional Assessment Staging; **MMSE:** mini-mental state examination; **BEHAVE-AD:** Behavioral Pathology in Alzheimer's Disease Rating Scale; **ChEIs:** Cholinesterase inhibitors; **ChAT:** Choline acetyltransferase

INTRODUCTION

Alzheimer's disease (AD) progresses irreversibly in a non-linear manner, and is characterized by abrupt changes in disease progression [1,2]. In general, progression is slow in mild AD and accelerates as it reaches a moderate stage. Although this difference in the speed of progression is not fully understood, we speculate that it is related to changes in anticholinergic activity (AA). AA refers to all substances that can bind to muscarinic acetylcholine (ACh) receptors [3]. Although aberrations in the cholinergic system can involve both agonists and antagonists of muscarinic receptors, most are antagonistic. Thus, AA elevations typically imply that there has been a deterioration of the cholinergic system, which is particularly relevant in patients with AD, in whom the cerebral cholinergic system is believed to be involved in the pathogenesis [4]. AA is considered to cause cognitive dysfunction in patients with AD, particularly in the memory domain [5,6]. ACh downregulation, a characteristic feature of AD [4], causes a similar pattern of dysfunction [7]. Therefore, both AA and ACh downregulation cooperate to cause the cognitive dysfunctions that are characteristic of AD. We have speculated that these interact with each other, with ACh

downregulation causing the endogenous appearance of AA, and vice-versa, thereby accelerating AD pathology [8-10].

In this article, we introduce our previous articles describing why AA may develop endogenously in AD, and comment on the roles of ACh downregulation and AA in AD. In addition, we describe two acceleration patterns and three amyloidogenic patterns associated with AD.

Proposed hypothesis of endogenous anticholinergic activity in Alzheimer's disease

We previously evaluated and reported the relationship between AA and clinical symptoms in AD. AA was measured using serum anticholinergic activity (SAA), a peripheral marker of AA [3], whereas clinical symptoms were assessed using Functional Assessment Staging (FAST) [11], the mini-mental state examination (MMSE) [12], and the Behavioral Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD) [13-15]. Among 76 patients with AD, 26 were positive for SAA, the mean SAA was 4.14 ± 2.70 nM, whereas the remaining 50 patients were SAA negative. The SAA positive group showed higher psychotropic medication use, more advanced AD, lower cognitive function, and more severe behavioral symptoms, including delusions, hallucinations, and diurnal rhythm disturbances. Logistic regression analysis revealed significant correlations between SAA, and delusion and diurnal rhythm disturbances [15]. The MMSE total score and the registration and recall domain score were significantly lower in the SAA positive group compared with the SAA negative group [14], consistent with previous reports. Many prescription medications have AA or may cause SAA [16] and increase cognitive dysfunction, particularly in the memory domain [5,6], as well as psychotic symptoms similar to delirium [17,18,19]. Central cholinergic deficiency was characterized clinically by neuropsychiatric symptoms rather than by cognitive impairment [20,21]. We observed two new findings in these articles. First, was the endogenous appearance of AA in AD [15], which we considered was caused by psychotropic medications and caused behavioral symptoms? Moreover, we postulated that because psychotropic medicines are often clinically prescribed for the psychiatric symptoms of agitation and psychosis in AD [22,23], there may be the cyclic relationships among these factors. We termed this the "vicious cycle of AA in AD (VCAA)" and because medicines are prescribed for the clinical psychiatric symptoms of agitation and psychosis in AD [22,23], there may be endogenous AA [15]. Second, ACh downregulation not only induced cognitive deterioration but also accelerated AD pathology through increased AA [8-10, 14]. Since our previous work suggested that memory domains were more vulnerable to AA in AD [5,6], we supposed that memory function was more highly dependent on cholinergic function than other MMSE domains. In general, medication-induced AA resolves following their cessation, and one would expect the associated cognitive impairment to reverse [24]. However, the recovery of cognitive impairment took longer was only partial in some cases, despite complete discontinuation [25]. Perry et al reported that amyloid plaque densities were 2.5-fold higher, and that pathology increased, in cases treated with long-term antimuscarinics (over 2 years) compared with untreated or short-term use (under 2 years) [26]. Lu and Tune also commented that chronic exposure of medications with AA accelerated the clinical course of AD [27]. Moreover, muscarinic 1 receptor agonists induced amyloid precursor proteins to nonamyloid protein (α-processing) [28,29]. Therefore, muscarinic 1 receptor antagonism (i.e., AA) induces the conversion of amyloid precursor proteins to amyloid, and worsens the cognitive function and exacerbates AD pathology by increasing amyloid plaques. The pathology of this amyloidogenic process with AA remains unclear. It is possible that long-term exposure to anticholinergic medications irreversibly changes the AD pathology and that AA endogenously appears in AD and contributes to accelerated AD pathologies [14,15].

Next, we reviewed the putative mechanisms of endogenous AA appearance in AD [8-10]. In general, AA primarily results from prescription drugs, particularly those with potent AA and a complex administration regimen [16], with endogenous AA occurring due to illness [30] and stress [31]. Flacker and Lipsitz reported that SAA disappeared without medication changes following the amelioration of acute physical illnesses and commented that SAA may reflect a nonspecific stress response to illness in the elderly [30]. Plaschke et al reported that SAA became positive from both extrinsic and intrinsic factors, and included stress (and raised cortisol) as a causal factor for SAA [31]. They comment that even if AA is induced by prescribed medications, intrinsic factors equally contribute. Therefore, the anticholinergic load cannot be inferred by an individual's medications. These two studies concluded that prescribed medications were not the only reason for AA, and that endogenous mechanisms existed.

Based on the work of Flacker and Lipsitz, we reviewed the relationship between ACh and inflammation and those between inflammation and AA [8]. We speculated that deficient cholinergic activity causes AA by way of inflammatory processes because AD is known to have reduced cholinergic neuronal activity due to degeneration [4]. When cholinergic deficiency reaches a threshold level, anti-inflammatory activity (the cholinergic anti-inflammatory pathway) [32,33] cannot inhibit the activation of inflammatory system cytokines that may contribute to AA. The possibility is that neuronal immunoreactions (inflammation) were induced by way of the reduction of ACh neuronal activity in the brain of patients with AD [8-10]. Hence we proposed the "endogenous anticholinergic hypothesis in Alzheimer's disease" (Figure 1; courtesy Hori et al. [9]. Here, ACh downregulation causes anti-inflammatory pathway downregulation, which in turn causes inflammatory upregulation and hyperactivity of inflammation-generated AA via N-methyl-D-aspartate (NMDA) receptors hyperactivity [32]. Regulation of the NMDA receptors was by way of nicotinic ACh receptors [32,33]. Because the characteristic feature of AD is ACh downregulation [4], when the level of ACh reaches a critical level, i.e., a moderate stage, AA is endogenously generated, which causes the rapid progression of cognitive decline. We refer to this vicious cycle as the "endogenous cascade of anticholinergic activity in Alzheimer's disease" [9,10] and refer to this acceleration of AD as "Alzheimer's disease progresses by the mechanism of its own" [9,10].

We also report a case of a 76-year-old man with moderate AD whose SAA was positive when his memory disturbance, disorientation, apathy, and aphasia deteriorated. However, his SAA resolved after 3 months' treatment with the antidementia

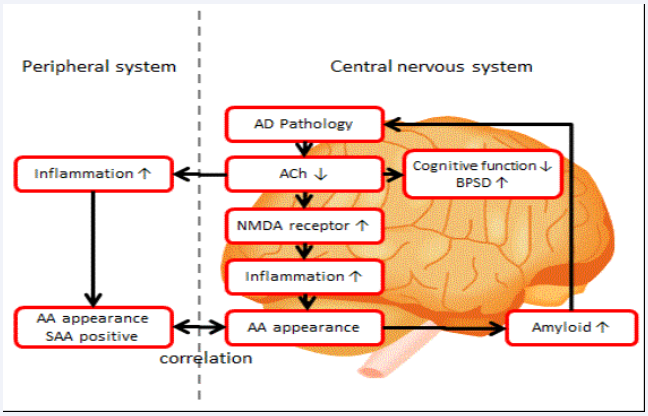

Figure 1 We speculate that the decrease in acetylcholine levels causes both cognitive dysfunction and the behavioral/psychological symptoms of dementia (BPSD). This facilitates the inflammatory processes in the central nervous system and peripheral tissues which increase anticholinergic activity (AA) via cytokine activation. AA in turn promotes the buildup of amyloid, which further downregulates the cholinergic system. We call this vicious cycle an "endogenous AA cascade."

AA: anticholinergic activity. ACh: acetylcholine. AD: Alzheimer's disease. BPSD: behavioral and psychological symptoms of dementia. NMDA: N-methyl-D-aspartate. SAA: serum anticholinergic activity. This figure is from the article by Hori et al. [9].

NMDA receptor antagonist, memantine. At the same time, his apathy and aphasia resolved [34].

The roles of acetylcholine and anticholinergic activity in Alzheimer's disease

We have speculated on the roles of ACh downregulation and AA in AD. We considered that ACh downregulation was related to both cognitive disturbance and the acceleration of the inflammatory system in AD; furthermore, AA resulted in the behavioral and psychological symptoms and appeared endogenously to accelerate AD in cooperation with ACh downregulation. ACh is known to inhibit inflammation in both the central nervous system and peripheral tissue [32,33], and its downregulation causes a hyper inflammatory state. Peripheral medication and tissue inflammation raise the anticholinergic burden in the peripheral tissue (i.e., SAA), and the intact ACh system compensates with central and peripheral hyper activation of the inflammatory system; central disturbances such as mental stress increase the ACh burden in the central nervous system alone, and the intact ACh system compensates similarly [10]. Therefore, ACh down regulation may extend the pathological processes in the central nervous system to the peripheral tissue, and vice versa. Alternatively, the ACh system may act as a buffer against extreme responses to these stressors. From this perspective, AD may be best considered as a systemic illness with both central nervous system and peripheral tissue involvement [9]. In fact, diabetes mellitus often intervenes with AD [35].

AA may be caused by prescription medication and inflammation, including illness, mental stress, and Ach down regulation. Therefore, AA may be a final common pathway in the amyloid-producing process, and may represent an interface between inflammation and the amyloiid-producing process. Consequently, various factors may accelerate AD by AA caused by inflammatory hyperactivity based on ACh down regulation [10]. We have already reported a patient with AD and mild cognitive impairment (MCI) who's AA was positive, perhaps as a result of his AD pathology interacting with mental stress and medication [36].

Two patterns of acceleration in Alzheimer's disease

We previously proposed the "endogenous anticholinergic hypothesis in Alzheimer disease" [8-10] to explain that AA appears endogenously in AD and accelerates AD pathology. According to this hypothesis, we can explain that the progression of dementia is relative slow at the MCI (mild) stage, but that it is relatively rapid at the moderate stage of AD. Moreover, delirium occurs readily in AD and physical illness, iatrogenic overdose, polypharmacy, and mental stress accelerate the progression of AD can be explained by this model.

In this review, we speculate that two patterns of AD acceleration exist (Figure 2). In the first pattern, when the level of ACh reaches a critical level, endogenous AA triggers a rapid cognitive decline at a moderate stage in AD (T1 point). The second pattern begins without ACh downregulation reaching a critical level (T2 point). Thus, in the second pattern, hyperactivity of the inflammatory system and AA follow minimal ACh downregulation due to exogenous factors (i.e., medications, illness, and mental stress), i.e., delirium. In general, when exogenous inserts are dissolved, cognitive function returns to the previous level. However, when the duration of AA exposure increases, cognitive function fails to return to baseline levels. We speculate that Lewy body pathology could contribute to hyperactivity of the inflammatory system and that Lewy body pathology is also related with AA [37]. In Figure 2, we suggest that we could quantitatively define a "moderate stage" when SAA was positive. When AA appears, ACh downregulation is accelerated and NMDA receptor hyperactivity occurs. At this time, we should therefore prescribe NMDA receptor antagonists. It is also crucial to avoid iatrogenic overdose and polypharmacy

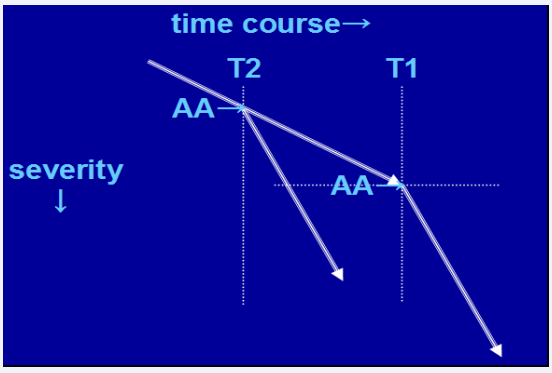

Figure 2 In the first pattern, when the level of ACh reaches a critical level, endogenous AA triggers a rapid cognitive decline at a moderate stage in AD (T1 point). The second pattern begins without ACh downregulation reaching a critical level (T2 point). Thus, in the second pattern, hyperactivity of the inflammatory system and AA follow minimal ACh downregulation due to exogenous factors (i.e., medications, illness, and mental stress), i.e., delirium. We speculate that Lewy body pathology may also be a factor related to AA. AA: anticholinergic activity, ACh: acetylcholine, AD: Alzheimer's disease.

in patients with AD, and to ensure that they are free from physical illness and mental stress to limit the rapid deterioration [10]. At the moderate stage, AA appears endogenously and accelerates AD pathology and disease progression, and it is particularly important to avoid these intrinsic and extrinsic contributors to AA.

Three amyloidogenic patters in Alzheimer's disease

Three amyloidogenic patterns appear in AD (Figure 3). The first pattern is physiological (N pattern), which is related with the normal aging process. We speculated that the N pattern of amyloidosis may be necessary for normal presenile or senile brain maturation. The second pattern is pathological (P1 pattern) and is unrelated to the ACh downregulation observed in MCI or mild AD. The third pattern is also pathological (P2 pattern) and is related to the ACh downregulation observed in moderate AD. While the N pattern may begin during normal aging, the P1 pattern probably begins when the clinical symptoms of mild AD occurs and is likely to be misdiagnosed as normal aging due to its shallow decline. However, the P2 pattern is clearly prominent and readily diagnosed as AD at the moderate stage when AD presents with clinical symptoms such as memory disturbance, disorientation, aphasia, delusions, hallucinations, and diurnal rhythm disturbance. At the moderate stage, the decline rate is also more rapid than those with MCI or mild disease.

We considered that the "moderate stage" could be quantitatively defined as SAA positivity, (i.e., the P2 pattern begins). Alternatively, when AA was superimposed on the substantially deteriorated cognitive deterioration at the end of the mild stage, it transitioned to the moderate stage, i.e., when deterioration of the ACh system reached a critical level and the inflammatory system was disinhibited.

Based on this, ACh upregulation and NMDA receptor downregulation may relate to both the symptoms in AD and the amyloid-producing process of the P2 pattern. Therefore, cholinesterase inhibitors (ChEIs) and NMDA receptor antagonists would also represent disease modifying agents for the P2 pattern. In fact, ChEIs and memantine were proven to protect neuronal death caused by amyloid toxicity [38-41]. Two AD pharmacotherapeutic options exist: prevention and treatment. ChEIs maintain normal ACh levels and prevent hyperactivation of choline acetyltransferase (ChAT), an enzyme that produces ACh and causes rapid neuron degeneration. This therefore prevents the rapid progression of AD. NMDA receptor antagonists are then efficacious for decreasing the speed of AD progression during the moderate stage [8].

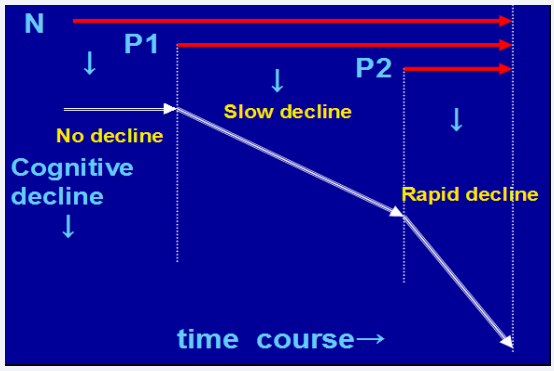

Figure 3 The N pattern represents a physiological pattern, which is related to normal aging. The P1 pattern represents a pathological pattern unrelated to ACh downregulation and typically observed in MCI or mild AD. The P2 pattern also represents a pathological pattern, and represents that which we postulate is related to the ACh downregulation observed in moderate AD. ACh: acetylcholine, AD: Alzheimer's disease, MCI: mild cognitive impairment. Red arrows show the three patterns of amyloid.

Moreover, this speculation may explain a limitation of the "amyloid vaccine" for AD. As previously mentioned, three amyloidogenic patterns may exist. If the N pattern amyloid is necessary for normal brain maturation, then P1 (and/or P2) amyloid patterns should be abolished. Therefore, we should investigate the mechanism underlying P1 pattern amyloid and amyloidogenesis. At present, there is no preventive therapy against the P1 pattern.

The limitations of the endogenous appearance of anticholinergic activity in Alzheimer's disease hypothesis

There are two main limitations of our primary hypothesis. One is that amyloid develops 10–20 years prior to symptomatic disease [42], and is unrelated to the present clinical symptoms. In this respect, indissoluble amyloid itself is not toxic and we considered that there was a problem in the production of amyloid. We speculate that when the process producing indissoluble amyloid reaches a threshold, a potent oligomer developes and AD progresses [43]. In addition, the appearance of physical amyloid may be defined as the disease prodrome.

All examinations that have sought to discover an effective anti-inflammatory agent for AD have yielded negative results. We consider that such agents may be useful in the prevention or slowing down of rapid progression of AD at the moderate stage. Alternatively, downregulation of ACh and AA are adapted only with P2 pattern amyloidgenesis.

CONCLUSION

In this review, we primarily summarized our previous reports, and added further speculation about the endogenous appearance of AA in AD. We remain convinced of the role of endogenous AA in AD. At present, we are seeking to confirm this assertion using SAA in a longitudinal study.

CONFLICT OF INTEREST

Koji Hori received lecture fees from Eisai Co., Ltd.; Pfizer Japan Inc.; Novartis Pharma K.K.; Daiichi Sankyo Inc.; Ono Pharmaceutical Co., Ltd.; Janssen Pharmaceutical K.K.; Yoshitomi Yakuhin Co.; and Mitsubishi Tanabe Pharma Co. Mitsugu Hachisu received funding from Astellas Pharma Inc.; Meiji Seika Pharma Co., Ltd.; Dainippon Sumitomo Pharm Co., Ltd.; Eli Lilly Japan K.K.; and Shionogi & Co., Ltd.. He also received lecture fees from Meiji Seika Pharma Co., Ltd. and Mitsubishi Tanabe Pharma Co.

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