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Short Communication Open Access

Anti-Dementia Agents are Partially Symptomatic Treatment and Partially Disease Modifying Treatment

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Short Commentary

Antidementia agents, i.e., cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor (NMDA-R) antagonist are now considered to be symptomatic treatment. However, 4 ChEIs and 1 NMDA-R antagonist are proven to have neuroprotecting actions against amyloid pathology [1-4]. Amyloid has thought to have deteriorating actions to neurons especially cholinergic neurons (neurons those use acetylcholine (ACh) as neurotransmitter). However, reported that downregulation of ACh accelerated accumulation of amyloid, i.e., there were interactions between downregulation of ACh and accumulation of amyloid [5]. If so, downregulation of ACh (or hyperactivation of NMDA receptor) might be included in amyloidgenic process. Accordingly, antidementia agents might have not only symptomatic treatment property but also disease modifying treatment property. Moreover, there is needed the hypothesis that connects downregulation of ACh and accelerated accumulation of amyloid. In this article, we introduce our articles those showed endogenous hypothesis of anticholinergic activity (AA) in Alzheimer's disease (AD) and we speculate the disease modifying property in antidementia agents.

We reported that the relationships between AA using serum anticholinergic activity (SAA) and clinical symptoms in AD [6,7]. Among 76 AD patients, 26 positive for SAA [SAA (+)] group had been prescribed a significantly higher number of psychotropic medications, had been diagnosed with a significantly more severe stage of AD, had exhibited significantly lower cognitive functions, and had displayed significantly more severe behavior symptoms such as delusions, hallucinations, and diurnal rhythm disturbances. Logistic regression analysis revealed that there were significant correlations between SAA and the presence of delusion and diurnal rhythm disturbances. As for cognitive dysfunction, immediate memory and recall were significantly lower in the SAA (+) group than those in the SAA (−) group. These results were almost the same those of other reports. However, we showed a new finding in these two articles. The first new finding was the endogenous appearance of AA in AD. We determined that AA was caused by psychotropic medications and led to behavioral symptoms. Moreover, we reasoned that because we generally prescribe psychotropic medicines for the clinical psychiatric symptoms of agitation and psychosis in AD, cyclic relationships might exist among these three factors. We named this vicious cycle, the "vicious cycle of AA in AD (VCAA)". Because we generally prescribe psychotropic medicines for the clinical psychiatric symptoms of agitation and psychosis in AD, endogenous AA may be observed [6,7].

Moreover, we speculated the reasons for the endogenous appearance of AA in AD and acceleration of AD pathology [8-10] by way of review of articles those with key words; inflammations, downregulations of ACh and AA because AA appears by way of inflammation with endogenous manners. Because ACh controls activity of inflammation in both central nervous system (CNS) and in peripheral tissues and AD is characterized by that cholinergic system is downregulated, inflammatory processes in both CNS and peripheral tissues might be caused by the downregulation of ACh and NMDA receptor expression is also upregulated by the downregulation of ACh which leads to hyperactivity of the inflammatory system. Cytokines that have AA might appear as a result of the inflammation. Therefore, we previously hypothesized that both AA in CNS (CAA) and peripheral tissue (serum anticholinergic activity; SAA) might appear endogenously in the moderate stage of AD; the "endogenous anticholinergic hypothesis in AD" [8-10].

On the base of these speculations, because amyloid appears even in normal aged people and even in mild stage in AD [10], we also speculated that there might be at least three amyloid patterns in AD; normal pattern (N pattern) which might be needed for normal aging, pathological pattern not related with downregulation of ACh (P1 pattern) and pathological pattern related with downregulation of ACh (P2 pattern) (Figure 1) [8]. In AD during mild cognitive impairment (MCI) and mild stage by P1 amyloid cognitive decline is slow and at moderate stage by P1 and P2 amyloid cognitive decline is rapid (Figure 1). 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. Two AD pharmacotherapeutic options exist: prevention and treatment. ChEIs maintain normal ACh levels, prevents rapid neuron degeneration and delays the appearance of P2 pattern amyloid. This therefore delays the rapid progression of AD (Figure 2). NMDA receptor (NMDA-R) antagonists are then efficacious for decreasing the speed of AD progression during the moderate stage (Figure 3).

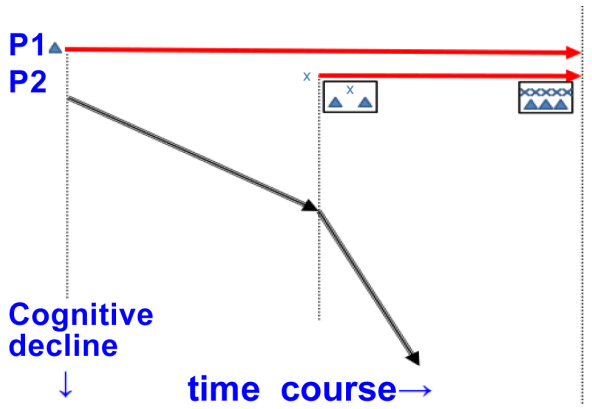

Figure 1: The normal patter amyloid (N pattern amyloid) represents a physiological pattern, which is related to normal aging. The P1 pattern amyloid (pathological pattern amyloid not related with downregulation of ACh) represents a pathological pattern unrelated to ACh downregulation and typically observed in MCI or mild AD. The P2 (pathological pattern amyloid related with downregulation of ACh) pattern also represents a pathological pattern, and represents that which we postulate is related to the ACh downregulation observed in moderate AD. In the brain P1 pattern and P2 pattern amyloids appear. This figure is from the article by Hori et al. [8] and partially exchanged.

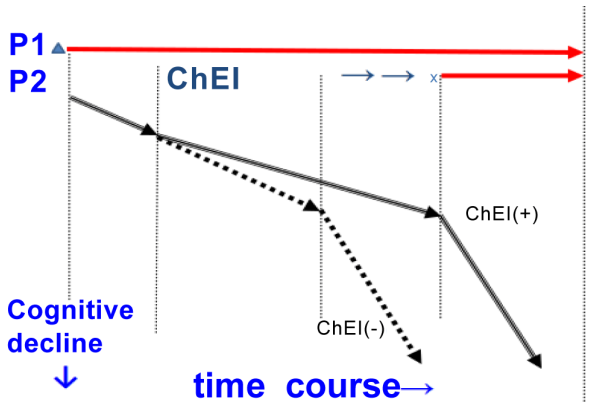

Figure 2: ChEIs maintain normal ACh levels, prevents rapid neuron degeneration and delays the appearance of P2 pattern amyloid. This therefore delays the rapid progression of AD.

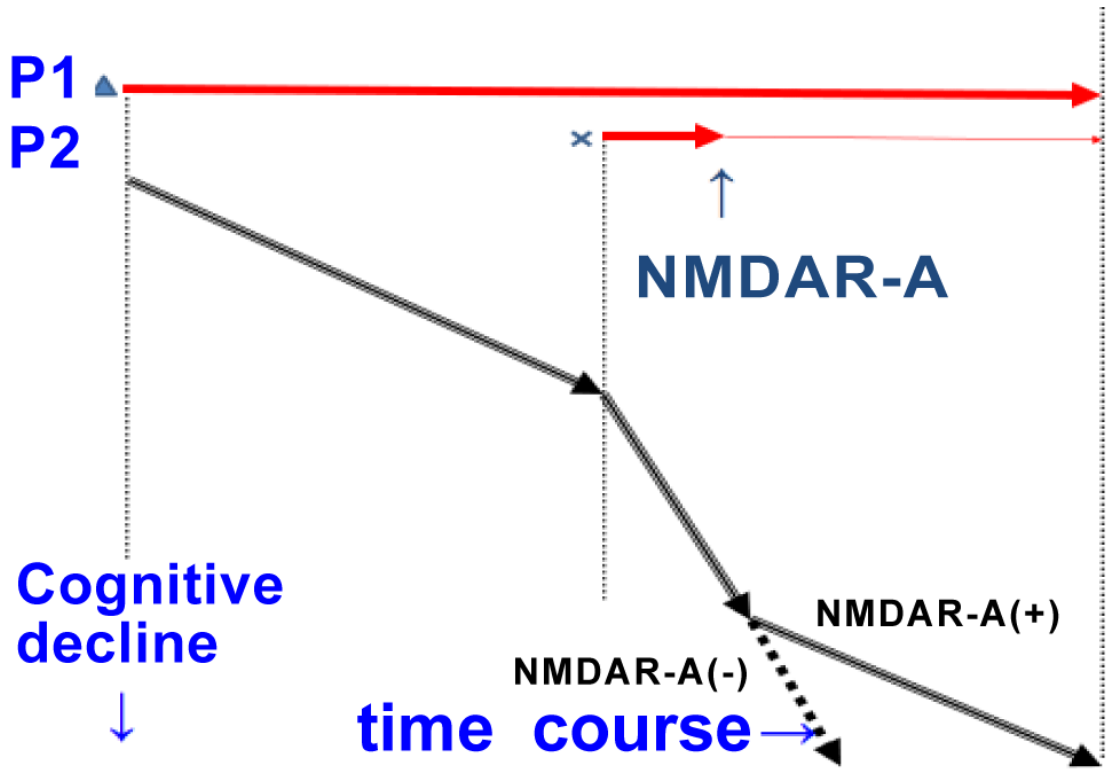

Figure 3: NMDAR-A is efficacious for decreasing the speed of AD progression during the moderate stage.

On the basis of the above considerations, we also speculated that antidementia agents, i.e., cholinesterase inhibitors (ChEIs) and NMDA-R antagonist are partially symptomatic treatment (for P1 pattern amyloid) and partially disease modifying treatment (for P2 pattern amyloid).

We can explain other two facts from this speculation. 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.

Moreover, this speculation also explains why ChEIs can't prevent the conversion from MCI to mild dementia. We consider that we should investigate the mechanism underlying P1 pattern amyloid and amyloidogenesis. At present, there is no preventive therapy against the P1 pattern [10].

Although we consider that we should prove our hypothesis, AA may be a final common pathway in the amyloid-producing process, and may represent an interface between inflammation (downregulation of ACh) and the amyloid-producing process [10].

Finally, we consider that if a treatment goes well, progress of AD is slow. In this case, hyperactivation of inflammatory system is prevented and P2 pattern amyloid could not appear. On the contrary P1 pattern amyloid appear continuously.

Therefore, not the rapid decline but the slow decline of cognitive function could occur even at moderate stage (Figure 4). From this point we should find the new pharmacological treatments for preventing hyperactivation of inflammatory system in order not to accelerate the speed of decline of cognitive function of AD.

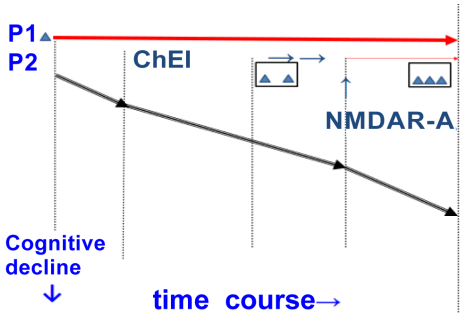

Figure 4: If a treatment goes well, progress of AD is slow. In this case, hyperactivation of inflammatory system is prevented and P2 pattern amyloid could not appear. On the contrary P1 pattern amyloid appear continuously. Therefore, not the rapid decline but the slow decline of cognitive function could occur even at moderate stage. In the brain P1 pattern amyloids appear. ACh: acetylcholine, AD: Alzheimer's disease, ChEI: cholinesterase inhibitor, MCI: mild cognitive impairment, NMDAR-A: N-methyl-D-aspartate receptor antagonist. Red arrows show the three patterns of amyloid. : P1 pattern amyloid, ×: P2 pattern amyloid.

There may be a possibility that these hypothesis are over speculations. However, we constitute these hypotheses step by step. As showing first, we evaluating relationships between AA (or SAA) and clinical symptoms in AD. Based on these results, we speculated the endogenous hypothesis in AD. Then we reviewed the articles and speculated the reasons for endogenous appearance of AA in AD, i.e., endogenous AA cascade in AD. As third step, we speculated three amyliodgenic patterns. Therefore, this hypothesis is not overspeculated. Moreover, there is needed the hypothesis that connects downregulation of ACh and accelerated accumulation of amyloid in order to elucidate AD pathology.

Conflicts 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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