Anticholinergic Activity and Alzheimer's Disease

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As members of the Showa University Dementia Study Group (Wade Study Group), we greatly appreciate the opportunities we have to write about the relationship between anticholinergic activity (AA) and neuropsychiatric disorders, and Alzheimer's disease (AD) in particular. In this special issue, we review our previous articles concerning the endogenous hypothesis of AA in AD that we originally proposed and here extend the hypothesis to various neurocognitive disorders such as Lewy body disease (LBD), delirium and neuropsychiatric disorders including depression and schizophrenia.

In this issue, we emphasize the following 3 points with regard to our hypothesis. First, AA not only depresses the acetylcholine (ACh) system through antagonization of ACh receptors, but also accelerates the accumulation of insoluble amyloids in the brain. The resulting dysfunction of the ACh system is not always reversible. Second, downregulation of ACh can also induce AA by way of inflammation. Therefore, the relationships between AA and this dysfunction of the ACh system are bidirectional. Given that downregulation of the ACh system is an essential feature of AD, we consider that endogenous AA accelerates AD pathology. We refer to these bidirectional effects of AA and downregulation of ACh as either the 'hypothesis of endogenous AA in AD', 'the endogenous

AA cascade in AD' or 'progression of AD by its own mechanism'. Although there are AA-inducing factors other than downregulation of ACh (e.g. drugs, febrile illness or mental stress), upregulation of ACh is possible if the ACh system is not depressed or overloaded. Thus, upregulation of the ACh system can inhibit AA even in the presence of other factors (fig. 1). The appearance of AA would then suggest that the ACh system is impaired in some way or that disease other than AD is responsible for the AA.

Third, downregulation of ACh in the central nervous system (CNS) causes upregulation of inflammation in the CNS and other organ systems. It is, therefore, conceivable that AD, a disease of the CNS, and diabetes mellitus, a disease that affects the peripheral nervous system, have some aspects of pathogenesis in common. Moreover, downregulation of the ACh system seems to be responsible for the simultaneous appearance of AA in the CNS and other organ systems. A correlation between AA in both systems can be explained, then, not only by the permeability of AA through the blood-brain barrier, but also by this simultaneous appearance of AA in both systems.

Dr. Tomioka, MD, PhD, Dr. Hachisu, PhD, and Dr. Hori, MD, PhD, conceived the contents of this special issue. We are extremely grateful to all authors for their

Fig. 1. a We speculate that when downregulation of ACh reaches a critical level, the inflammatory system is upregulated and cytokines that have AA appear. **b** Even if downregulation of ACh does not reach a critical level, when another AA-inducing factor is present (e.g. medication, febrile illness or mental stress), the inflamma-

tory system is upregulated, and AA appears. **c** When the ACh system is intact and not depressed or overloaded, upregulation of ACh is possible even if another AA-inducing factor is present (e.g. medication, febrile illness or mental stress). Consequently, the inflammatory system is not upregulated, and AA does not appear.

valuable contributions to this publication: Dr. Hachisu for explaining serum AA as a peripheral biological marker of AA in the CNS; Dr. Yoshiyama, MD, PhD, for discussing the adverse effects of AA in the brain from the viewpoint of neuropathology; Dr. Konishi, PhD, for explaining the endogenous appearance of AA in AD; Dr. Kitajima, MD, PhD, for explaining AA in neurocognitive disorders other than AD that show downregulation of ACh; Dr. Hosoi, PhD, for discussing pharmacotherapy for AD and LBD based on the hypothesis of AA in AD and LBD; Dr. Hori for covering AA in depression; Dr. Tani, MD, PhD, for explaining AA in schizophrenia; Dr. Hosoi for covering plasma cholinesterase activity as another biological marker of AD, and Dr. Hachisu for discussing brain-derived neurotrophic factor in AD. We additionally thank Dr. Tomioka, Dr. Hachisu, Dr. Konishi and Dr. Hori for their careful checking of the papers.

The two main aims of this special issue were to review and refine our hypothesis of the endogenous appearance of AA in AD (article by Dr. Konishi) and to demonstrate the utility of serum AA for evaluating the anticholinergic burden in the CNS (article by Dr. Hachisu). The refined hypothesis was derived from the findings presented in our 3 previous reports [1–3] and the review process we undertook. Therefore, it is a limitation of this special issue that our discussion is derived mainly from reviewing our 2 original articles [4, 5], 3 case reports [6–8] and review articles [1–3] whose findings have not been proven in large-scale studies. We have presented our refined hypothesis in just 1 article [9], and this special issue marks the first publication of our additional suggestions, implications and case presentations supporting our revised hy-

pothesis. Moreover, through this reviewing of our hypothesis, we have extended it to cover other neurocognitive disorders, such as LBD and delirium, and other neuropsychiatric disorders, such as depression and schizophrenia. We have also proposed other biological markers for AD, including plasma cholinesterase and brain-derived neurotrophic factor. In the future, we hope to prove our hypothesis in clinical settings.

As a final note, we designed this special issue so that the articles could be read in any order and we ask the readers' indulgence of some repetition of our endogenous hypothesis of AA in AD at the beginning of certain articles to allow for this. We sincerely hope that this special issue is of value to our readers.

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