

Role of Cholinergic System in Neuropsychiatric Disorders

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Abbreviations AA: anticholinergic activity; ACh: Acetylcholine; AD: Alzheimer's disease; ChAT: Cholinacetyl transferase; HPA axis: Hypothalamic-pituitary-adrenal axis; LBD: Lewy body disease

Opinion

Needless to say acetylcholine (ACh) is related with cognitive function [1]. However, ACh also suppresses inflammatory system [2], therefore, downregulation of ACh not only causes cognitive dysfunction, but also accelerates inflammatory system. This hyperactivity of inflammatory system is related with various neuropsychiatric disorders including Alzheimer's disease (AD) [3] and depression [4].

Moreover, we also speculate this hyperactivity of inflammatory system also induces anticholinergic activity (AA) and this AA accelerates amyloid pathology [5]. Based on this speculation, we propose "the hypothesis of endogenous appearance of AA in AD" [6]. That is, when the downregulation of ACh reaches critical level, AA appears endogenously by way of hyperactivation of inflammatory system and accelerates amyloid pathology [5,6]. Because the factors those cause AA and now reported three other than downregulation of ACh, i.e., medication [7], physical illness [8] and mental stress [9]. Therefore, it is natural that when based on the small amount of deterioration of ACh other AA insert is added, AA also appears [10]. In fact, we showed the patient with AD at MCI level whose serum anticholinergic activity might be positive caused by both small amount of down regulation of ACh and mental stress [11]. Moreover, overburden of cholinergic system might also attribute to the appearance of AA because ACh is no more upregulated in order to compensate for AA insert (upregulation of ACh). Therefore there might be a possibility of the appearance of AA in other disease than AD. We also speculate there might be a possibility of the endogenous appearance of AA in depression and Lewy body disease (LBD). Increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and the small amount of downregulation of ACh. It is plausible to conclude that in depression and LBD AA might appear endogenously [12,13]. In depression, the cholinergic system is burdened secondarily to the underlying depressive pathology. During remission, activity of cholinacetyl transferase (ChAT), an enzyme that produces ACh, might be sufficiently upregulated to compensate for the cholinergic burden caused by depressive pathology. However, at the pathological state (depressive state), more upregulation of ACh is not impossible because the ChAT activity is already upregulate. Therefore, in depression there might be a possibility of endogenous appearance of AA [14]. In delirium, we also speculate there might be a possibility of the

appearance of AA in delirium. In delirium, increased activity of the HPA axis by exogenous factor, i.e., physical illness, medication or mental stress and the small amount of downregulation of ACh caused by aging or AD, AA also appears.

From these considerations we speculate that at least in AD, LBD and depression, the progression of disease might be related with AA at least late stage. Alternatively at late phase of AD, LBD and depression, main pathology might be amyloid pathology. We propose the concept of "anticholinergic spectrum disorders" [13]. In this context, we commented that when the ACh deterioration is small, a larger AA insert of HPA axis dysfunction is necessary for the appearance of AA. However, when the ACh deterioration is large, a small AA insert of HPA axis dysfunction is sufficient for the appearance of AA. Of course, when the ACh deterioration is at a critical level, AA appears without HPA axis dysfunction. However, if ACh is not deteriorated or overloaded, the intact ACh system can be upregulated and compensate for any other AA inserts. We speculate that in this "anticholinergic spectrum disorders", at least AD, LBD, delirium and depression might be included.

In this article, we commented that the critical role of ACh in disease progression of neuropsychiatric diseases.

Conflict of Interest

Koji Hori received lecture fees from Eisai Co. Ltd., Pfizer Japan Inc., Novartis Pharma KK, Daiichi Sankyo Inc., Ono Pharmaceutical Co. Ltd., Janssen Pharmaceutical KK, Yoshitomi Yakuhin Co. Meiji Seika Pharma Co. Ltd., However, the sponsors had no role in study design, data collection and analysis including our before presented articles, decision to publish, or preparation of this manuscript.

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Author Contributions

Koji Hori coordinates the study regarding to this article and wrote the manuscript.

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