Neuro–
degenerative
Diseases

Anticholinergic Activity and Schizophrenia

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Abstract

In this article, we review the downregulation of acetylcholinergic activity in schizophrenia and discuss the similarity and difference between Alzheimer's disease (AD) and schizophrenia in terms of acetylcholine (ACh) and anticholinergic activity (AA); then, we propose the use of cognition-enhancing therapy for schizophrenia. As ACh regulates an inflammatory system, when the cholinergic system is downregulated to a critical level, the inflammatory system is activated. We consider the possibility that AA appears endogenously in AD and accelerates AD pathology. This hypothesis can also be applied to schizophrenia. In fact, even before the onset of the disorder, in the prodromal phase of schizophrenia, cognitive dysfunction exists, and antibodies against astrocyte muscarinic-1 and muscarinic-2 receptors are present in the serum of patients with the paranoid type of schizophrenia. Then we noted that the prodromal phase in schizophre-

nia might correspond to the mild stage in AD and the acute phase to moderate stage concerning AA. We also think that we should enhance cognition in schizophrenia even in the prodromal phase because as mentioned above, downregulation of ACh is prominent in schizophrenia even in the prodromal phase.

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Introduction

We previously introduced the 'endogenous anticholinergic hypothesis of Alzheimer's disease' (AD) [1–3]. We commented that downregulation of acetylcholine (ACh) has been implicated in AD [4] and that ACh also regulates the inflammatory system. The downregulation of the cholinergic system substantially enhances the expression of N-methyl-D-aspartate receptor which leads to the activation of the inflammatory system. Among the cytokines caused by inflammation, those having anticholinergic activity (AA) appear and accelerate AD pathology [1–3, 5] (fig. 1; Hori et al. [1]). We consider that AA

Fig. 1. We speculate that ACh degradation not only causes cognitive dysfunction and behavioral and psychological symptoms of dementia (BPSD), but also induces inflammation in the central and peripheral nervous systems. This, in turn, induces central and peripheral AA through cytokine pathways. Moreover, AA causes an increase in amyloid that further decreases ACh. This is referred to as the 'endogenous AA cascade'. NMDA = N-methyl-D-aspartate; SAA = serum anticholinergic activity. This figure is reproduced from an article by Hori et al. [1]. The procedure was permitted by the Japanese Society of Neuropsychopharmacology (Tokyo, Japan).
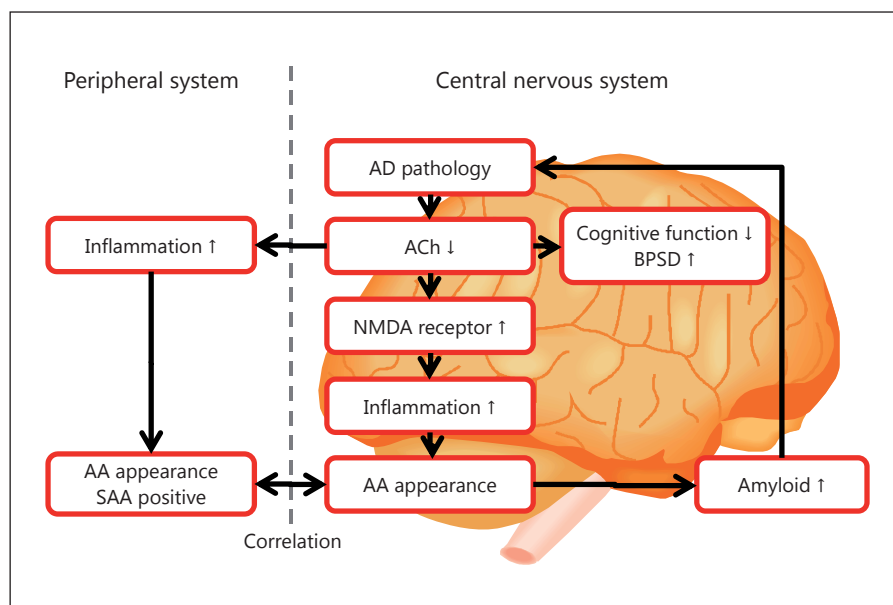
might fill gaps between the cholinergic downregulation and pathological changes in AD, and between inflammation and AD. However, activation of inflammation is observed not only in AD, but also various neuropsychiatric disorders such as schizophrenia. Schizophrenia is a severe chronic mental illness that affects about 1% of the population. The core symptoms of schizophrenia are composed of positive symptoms (such as delusions, hallucinations and disorganized thinking), negative symptoms (such as apathy, anhedonia and social withdrawal) and cognitive dysfunction. Despite numerous studies over the past century, the etiology and pathophysiology of schizophrenia remain obscure, and available treatments are only modestly effective [6]. Over the past decades, neuropsychopharmalogical studies have focused on the roles of neurotransmitter systems in schizophrenia and led to the hypothesis of the pathophysiology of schizophrenia. The deterioration of neurotransmitters in schizophrenia is mainly associated with the dopamine system but also with the glutamate, γ-aminobutyric acid, serotonin, norepinephrine and ACh systems [7]. Recently, many studies indicated that the cholinergic system plays an important role in the pathogenesis of schizophrenia in the fields of genetics, neuropharmacology, neurobiology, brain imaging and neurophysiology. In this review, we discuss the disturbance of the cholinergic system in schizophrenia and the influence of AA on the pathogenesis of schizophrenia.

The Cholinergic System in Schizophrenia and the Anticholinergic Hypothesis of Schizophrenia

Even before the onset of this disorder, at the prodromal phase of schizophrenia, cognitive dysfunction exists [8]. It is related to cholinergic dysfunctions such as executive dysfunction, dysfunction of attention and memory deficit [9–13]. In fact, 15% of drug-naïve patients show extrapyramidal signs, indicating that dopamine-acetylcholine imbalance may be behind the early phase of schizophrenia [14]. These reports suggest that downregulation of ACh almost reaching the critical level activates the inflammatory system. The impairments of the cholinergic systems in schizophrenia after onset have been thoroughly investigated; some researchers indicated that cholinergic, especially muscarinic, systems play an important role in the pathogenesis of schizophrenia [15, 16]. Postmortem studies have observed a decrease in the levels of muscarinic receptors in large areas of the brain in schizophrenia, and these findings have been well replicated [17, 18]. For example, Deng et al. [19] found a decreased density of muscarinic receptors M_1, M_2, M_4 and M_5 in the superior temporal gyrus in schizophrenia that is reported to be involved in the pathology of schizophrenia and suggested that abnormal cholinergic projection from the basal forebrain to the superior temporal gyrus may cause a downregulation of muscarinic receptors in schizophrenia. On the other hand, muscarinic receptors in the dorsal

striatum, hippocampus and prefrontal cortex that are projected from brainstem cholinergic neurons are also decreased [20]. Neuroimaging studies using [^{123}I]quinuclidinyl benzylate SPECT revealed that muscarinic receptor availability was less in the caudate, putamen, thalamus, frontal cortex, temporal cortex and occipital cortex [21]. These studies suggest that muscarinic receptor reduction in schizophrenia may be disease specific as it is not apparent in bipolar disorder or major depression [15]. Because the cholinergic dysfunction plays an important role in positive symptoms, negative symptoms, cognitive impairments, autonomic functions and motor functions in patients with schizophrenia, based on these reports, Raedler et al. [21] proposed the 'muscarinic hypothesis of schizophrenia'. They described that downregulation of muscarinic cholinergic neurotransmission contributes to the clinical symptoms of schizophrenia – not only cognitive dysfunctions, but also psychotic symptoms – and that hyperactivity of the dopaminergic system is secondary to the downregulation of muscarinic cholinergic neurotransmitters.

From these reports we will speculate that downregulation of muscarinic receptors in schizophrenia might cause AA. We also speculate as follows: the downregulation of ACh neuronal system in the prodromal phase of schizophrenia adds 'small inserts' of AA (i.e. medications [22], physical illnesses [23], mental stresses [24]) by mainly small mental stress and provokes the onset of schizophrenia. In fact, immunological study revealed that antibodies against astrocyte M_1 and M_2 muscarinic cholinergic receptors are detected in the serum of patients with the paranoid type of schizophrenia, and this suggested that the paranoid or negative symptoms and the acuity stage of the schizophrenia could be influenced by the muscarinic ACh receptor-specific antibody [21]. Therefore, there is a possibility that there is antibody binding to muscarinic receptors in the serum of schizophrenia patients and that this causes cognitive dysfunctions similar to AD which deteriorates due to AA [9, 11]. Moreover, when a downregulation of ACh reaches an almost critical level, the cholinergic receptors, mainly muscarinic receptors, in case of schizophrenia are widely disrupted, and various symptoms of pathophysiology in schizophrenia appear. Therefore, even a small dose of an exogenous AA insert causes endogenous AA. In sum, the onset of schizophrenia might be related with AA inserts on the basis of the downregulation of ACh. The cholinergic system impairments of schizophrenia had been widely studied in various fields, and the cholinergic hypoactivity hypothesis is gradually accepted as a part of the pathophysiology of schizophrenia (fig. 2a, b).

The Prodromal Stage in Schizophrenia Might Correspond to the Mild Stage in AD and Its Acute Phase to the Moderate Stage of AD

As previously described, we suggest that AA might cause the onset of schizophrenia on the basis of downregulation of ACh neuronal system (fig. 2a, b). We previously reported that if the cholinergic system is intact, the ACh system does not emerge because the upregulation of the cholinergic system inhibits the appearance of AA by suppressing the inflammatory processes [2]. Even if AA appears after the prescription of medicines or due to inflammation in the peripheral tissues in the healthy state, the intact central cholinergic system can be activated and can compensate for any inflammation, although peripheral AA promotes inflammation in the peripheral system. Therefore, in the healthy state, inflammation in the central nervous system and lowering of central AA do not occur (fig. 3a, b). On the contrary, if the cholinergic system is deteriorated, AA emerges because it is difficult to upregulate the cholinergic system and suppress the inflammatory processes. Therefore, if ACh is deteriorated (or burdened) in AD by physical or mental inserts, such as prescribed medicine, inflammation in the peripheral tissues or mental stress causing AA, the clinical symptoms of delusion, hallucination, diurnal rhythm disturbance, memory disturbance and worsened executive function appear. Because the ACh system in patients with schizophrenia might also be deteriorated, physical or mental inserts might cause AA, and the appearing clinical symptoms lead to the onset of schizophrenia (fig. 3c, d). Our speculation about the process of progression of schizophrenia is also similar to that of AD. In case of AD, ACh is gradually downregulated and when the downregulation of ACh is sufficiently substantial to express the N-methyl-D-aspartate receptor, the inflammatory system is activated. AA appears through hyperactivity of inflammation, and we accordingly proposed the 'endogenous anticholinergic hypothesis in AD' [1–3] (fig. 1; Hori et al. [1]). Of course, AA causes various clinical symptoms as we previously described. We also speculate that the prodromal phase in schizophrenia might be similar to the mild stage of AD and that the acute phase of schizophrenia might correspond to the moderate stage of AD. Therefore, even in the prodromal phase, patients with schizophrenia show various behavioral symptoms [25], which are similarly observed in AD. As the pathology of schizophrenia is different from that of AD, there is a difference in the appearance of symptoms between schizophrenia and AD.

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Fig. 2. a, **b** In schizophrenia, the cholinergic system is burdened secondary to pathology of schizophrenia (S pathology). At the prodromal stage, the cholinergic system is already deteriorated. Therefore, if there is only the 'weak AA insert', the cholinergic system is not upregulated; in this scenario, AA appears, and the acute phase occurs. ChAT = Choline acetyltransferase.
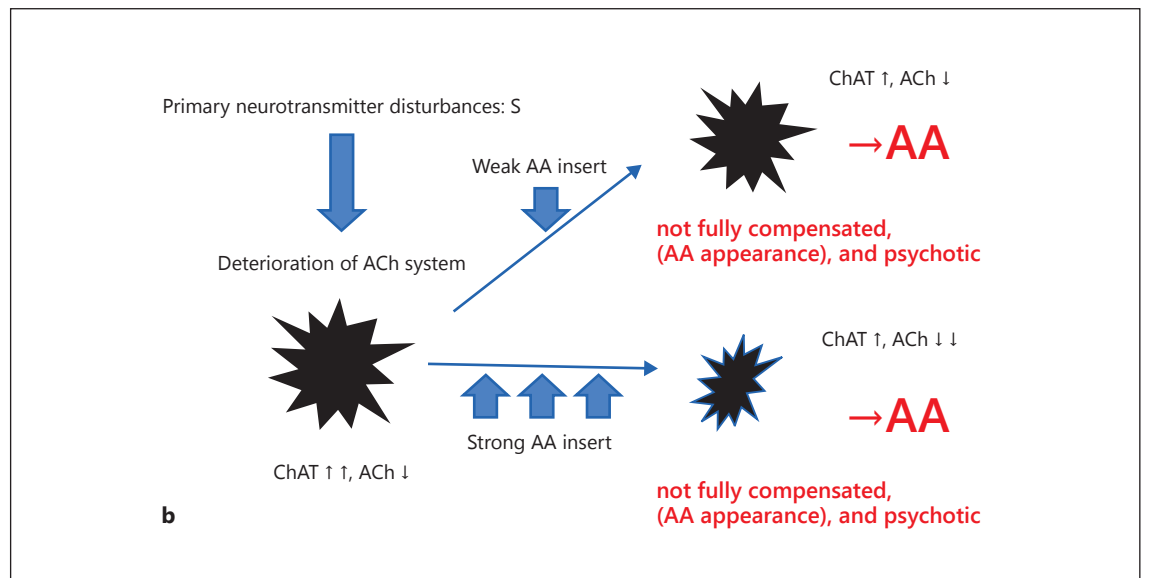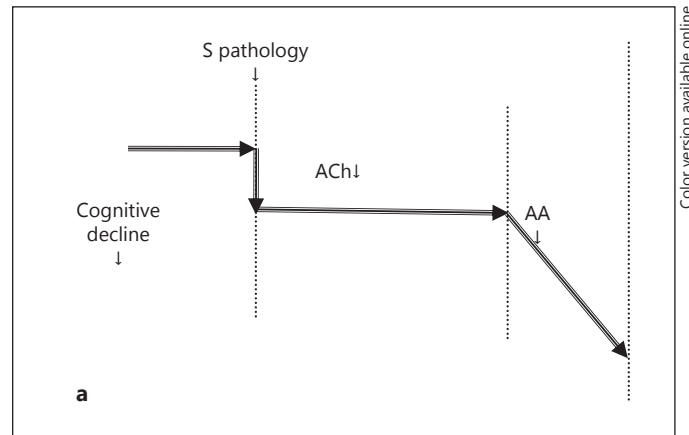
We also speculate that in depression, the same mechanisms might work although hyperactivity of ACh causes a depressive state [26]. In the depressive state, hyperactivity of ACh occurs as the compensatory mechanism of the depressive state or anxiety [27]. However, hyperactivity of ACh causes early and rapid degeneration and consequent downregulation of ChAT activity. In fact, it is pointed out that there is downregulation of ACh in depression or bipolar disorder [28]. Therefore, the ACh system in depression might be burdened. However, we speculate that deterioration of ACh in depression might not be as severe as that in schizophrenia and muscarinic receptors might not be so deteriorated. Therefore, the depressive and manic phase is upset without therapy. As previously mentioned, we speculate that if the cholinergic system is intact, AA and hyperactivated inflammation do not emerge because the upregulation of the cholinergic system inhibits the appearance of AA by suppressing the inflammatory processes (fig. 3a–d). Therefore, even if once AA appears and causes a manic state, the not so deteriorated ACh system might compensate for AA and the hyperactivated inflammatory system, and soon these states might be upset. Moreover, we should enhance cognition in schizophrenia even in the prodromal phase, because, as we described before, downregulation of ACh is prominent in schizophrenia even in the prodromal phase. Nonpharmacological cognition-enhancing therapy is better mainly to employ as therapy. Then, we should check whether cholinesterase inhibitors can be used in schizophrenia [29]. In fact, according to White and Cummings [30], the psychiatric symptoms are commonly observed both in schizophrenia and AD. This might suggest
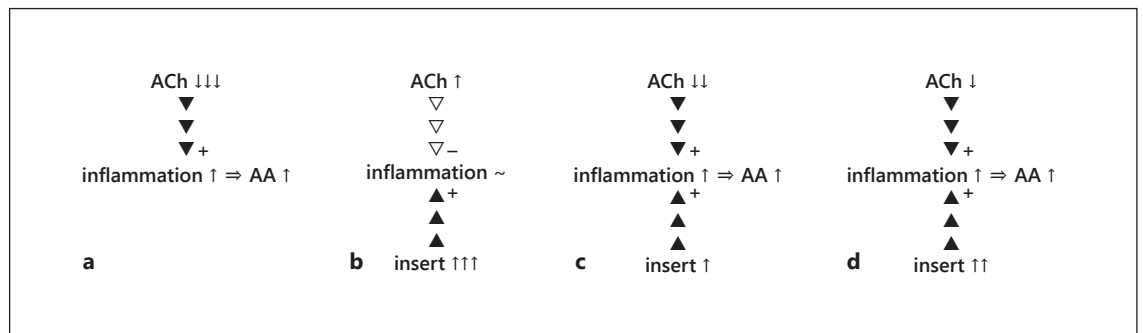

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Schizophrenia

ACh ↓↓↓   ACh ↑   ACh ↓↓   ACh ↓

▼   ▽   ▼   ▼

   ▽

▼ +   ▽ −   ▼ +   ▼ +

inflammation ↑ ⇒ AA ↑   inflammation ~   inflammation ↑ ⇒ AA ↑   inflammation ↑ ⇒ AA ↑

   ▲ +   ▲ +   ▲ +

   ▲   ▲   ▲

   ▲   ▲   ▲

a   **b** insert ↑↑↑   **c** insert ↑   **d** insert ↑↑

Fig. 3. a Substantial level of downregulation of ACh causes hyperactivity of inflammation and AA endogenously. **b** Even if an insert appears (for example, by prescription medication or due to inflammation in the peripheral tissues), the intact central cholinergic system can be activated and can compensate for any peripheral inflammation, although peripheral AA promotes inflammation. Therefore, in this healthy state, inflammation in the central nervous system and central anticholinergic activity cannot occur. **c** Downregulation of ACh reaches not substantial level; however, it is relatively severe. Therefore, AA is induced by relatively mild inserts based on the relatively severe deterioration of ACh that causes hyperactivity of the inflammatory system. **d** Downregulation of ACh reaches not a substantial level, and its severity is relatively mild. Therefore, AA is induced by relatively severe inserts based on the relatively mild deterioration of ACh that causes hyperactivity of the inflammatory system.

that an unknown neurochemical alteration involving the dopaminergic and/or cholinergic axis underlies the two mental disorders. Based on the hypothesis that hallucination and delusion belong to a cholinergic deficiency syndrome, Lemstra et al. [31] advocated that cholinomimetics should be prescribed for these symptoms. Based on the above, we conclude that there might be an imbalance between the monoaminergic (dopaminergic) system and the cholinergic system that causes hallucination and delusion in AD as well as schizophrenia. Indeed, a cholinesterase inhibitor is used to protect against psychotic symptoms in both AD [32] and schizophrenia [33].

Limitation of the Anticholinergic Hypothesis of Schizophrenia

It should be noted that there are at least 2 limitations to our hypothesis with a reduction of ACh activity and AA appearing in schizophrenia.

One is that the appearance of AA is based on a hyperactivity of ACh proposed by Tandon et al. [6, 16], which is different from our hypothesis. According to their hypothesis, the appearance of AA is a compensation to ACh hyperactivity. They suppose that ACh hyperactivity shows negative symptoms from experimental results administering a centrally acting acetylcholinesterase inhibitor, physostigmine, to normal volunteers; negative symptoms were selectively ameliorated by clozapine and olanzapine having AA, and this suggests that muscarinic

hyperactivity may be implicated in negative symptoms. According to this hypothesis, in the acute phase of schizophrenia, as the activity of the mesolimbic and mesocortical dopamine systems is increased, there is a compensatory increase in the activity of the cholinergic system in the prepsychotic phase. Subsequently, hyperactivity of the cholinergic system interacts with the dopaminergic system, and the dopaminergic hyperactivity exacerbates psychosis. After treatment with antipsychotic agents, the dopaminergic hyperactivity is improved by blocking D_2 receptors, but the cholinergic hyperactivity may still exist, though it gradually improves the activity; therefore it might be a normal dopaminergic-hypercholinergic state as clinically it appeared for negative symptoms, the so-called postpsychotic depression [6, 16]. The chronic cholinergic hyperactivity might lead to cholinergic downregulation of the muscarinic receptors and result in a decreased density of muscarinic receptors in the brain [16]. Yeomans [34] suggested, in terms of antimuscarinic psychosis, that an increased cholinergic cell (Ch5) tone with genetically increasing tegmental cholinergic cells (Ch5 and Ch6) or fewer Ch5 autoreceptor of schizophrenia might induce Ch5 overactivation, and this overactivation boosts cascades of A10 dopaminergic cell activation, thalamic activation and pontine reticular formation activation. In this way, not cholinergic downregulation but cholinergic hyperactivity is thought to play a critical role in the pathophysiology of schizophrenia, but the role of AA is still obscure. For schizophrenia, AA might be useful for measuring peripheral anticholinergicity, but not as a

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diagnostic biomarker predicting the degree of progression of schizophrenia. In view of the cholinergic hyperactivity hypothesis of schizophrenia, the cholinergic hyperactivity might be present in the early prodromal phase of schizophrenia and possibly induce compensatory endogenous AA that exacerbates cholinergic hyperactivity. Severe mental stress and inflammation preceding the acute phase would emphasize this process. AA might already exist before the treatment with neuroleptics.

The other is that antipsychotics used to treat schizophrenia have AA. Therefore, antipsychotics might exacerbate positive symptoms, negative symptoms, cognitive impairments, autonomic dysfunction and motor functions in patients with schizophrenia. We should reinvestigate the role of antipsychotics in view of AA in schizophrenia.

Conclusion

We noted that, based on the downregulation of ACh, AA appeared in schizophrenia and contributes to clinical symptoms. We have shown that exacerbation of symptoms in schizophrenia is similarly explained by our previous hypothesis of the 'appearance of endogenous AA in AD'. We consider that this hypothesis that AA appears in schizophrenia is really valid, though we have no data. Therefore, we have to measure the serum AA also in schizophrenia with medicine-naïve patients and have to approach identification of substances which have AA. Moreover, we have to demonstrate the clinical roles of AA in schizophrenia studying the pharmacokinetic and pharmacodynamic characteristics of the AA substances.

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