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International Journal of Current Research
Vol. 10, Issue, 08, pp.72965-72969, August, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

USE OF SERUM ANTICHOLINERGIC ACTIVITY TO DETERMINE THE OPTIMAL DOSE OF ANTIPSYCHOTIC MEDICATION FOR PATIENTS WITH SCHIZOPHRENIA

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ARTICLE INFO

Article History:
Received 25th May, 2018
Received in revised form
30th June, 2018
Accepted 27th July, 2018
Published online 31st August, 2018

Key Words:

Acetylcholine (ACh), Anticholinergic Activity (AA), Endogenous Anticholinergic Activity, Serum Anticholinergic Activity (SAA), Schizophrenia.

ABSTRACT

In this article, we revise our previous hypothesis of the endogenous appearance of anticholinergic activity (AA) in schizophrenia and expand our commentary on the relationship between AA and schizophrenia. We speculate that the inflammatory system is upregulated in Alzheimer's disease (AD) when the acetylcholine (ACh) downregulation reaches a critical level and then hyperactive inflammation generates cytokines with AA. We also speculated that the same mechanism might be active in schizophrenia; that is, downregulation of ACh or overloading of this system might already exist at even the preclinical stage (in those with a high-risk mental state) and when mental stress is added, the compensatory mechanism might fail, so AA might appear and psychotic symptoms develop. Recently, we reported the significant negative relationship between serum anticholinergic activity (SAA) and extrapyramidal symptom severity in patients with schizophrenia. These results support the theory of hyperactive ACh in schizophrenia. Accordingly, we re-hypothesize that there is a compensatory increase in the activity of the cholinergic system even in the prepsychotic phase. We also re-speculate that there might be an imbalance in not only the dopaminergic system, but also the cholinergic system in schizophrenia. Therefore, substantial levels of AA or antipsychotics with considerable AA might be needed in schizophrenia. Prescription of antipsychotics with AA might correct the imbalance in both dopamine and ACh and possibly achieve remission in patients with schizophrenia. Based on these speculations, we propose the use of SAA as a biological marker for evaluating the optimal dose of antipsychotics for patients with schizophrenia and suggest that, when the quantities of prescribed antipsychotics can be adjusted to achieve an SAA of slightly over 10 nM, the clinical symptoms (extrapyramidal motor symptoms and cognitive dysfunctions) might be minimized.

Citation: ***Kimiko Konishi, Masayuki Tani, Norihisa Akashi, Michiho Sodenaga, Mitsugu Hachisu and Koji Hori.*** **2018.** "Use of serum anticholinergic activity to determine the optimal dose of antipsychotic medication for patients with schizophrenia", *International Journal of Current Research*, 10, (08), 72965-72969.

INTRODUCTION

Anticholinergic activity (AA) involves substances with the ability to bind to the muscarinic acetylcholine receptor (Tune and Coyle, 1980). The main source of AA is prescribed medication (Tune *et al*., 1992), although physical illness (Flacker *et al*., 1999) and mental stress (corticoids) (Plascheke *et al*., 2010) also cause AA.

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DOI: https://doi.org/10.24941/ijcr.32004.08.2018

We previously commented that AA was also caused by the downregulation of acetylcholine (ACh) (Hori *et al*., 2012) and proposed a hypothesis of the endogenous appearance of AA in Alzheimer's disease (AD) (Hori *et al*., 2013, Hori *et al*., 2014a, Hori *et al*., 2014b, Konishi *et al*, 2015). We have also considered that AA might be linked to other neurocognitive disorders such as Lewy body disease and delirium (Kitajima *et al*., 2015) and neuropsychiatric diseases such as mood disorder (Hori *et al et al*, 2015b) and schizophrenia (Tani *et al*, 2015). Recently, we reported the relationship between serum anticholinergic activity (SAA) and the severity of cognitive dysfunction and extra pyramidal symptoms in patients with schizophrenia (Akashi *et al*, 2014).

Based on these results, in this article, we revise our hypothesis of the endogenous appearance of AA in schizophrenia (Tani *et al*, 2015), newly speculate on other diseases affected by AA, and propose the usefulness of SAA as a peripheral biological marker for determining the optimal doses of antipsychotics for patients with schizophrenia.

Hypothesis of endogenous anticholinergic activity in Alzheimer's disease: ACh regulates not only cognitive function, but also the inflammatory system (Pavlov *et al*, 2006, Mabley *et al*., 2009). Therefore, we previously speculated that, because AD is characterized by the downregulation of ACh (Rosi *et al*., 2009), the inflammatory system would be upregulated in AD. Namely, we speculated that the ACh reduction downregulates the anti-inflammatory pathway, which allows upregulation of the inflammatory pathway (the cholinergic anti-inflammatory pathway) (Pavlov *et al*, 2006, Mabley *et al*., 2009). Hyperactive inflammation would subsequently generate cytokines with AA, such as C-reactive protein (Nazarov, *et al*., 2007) and, when the level of ACh reaches a critical level (i.e., moderately severe disease), AA would be endogenously generated. Based on these suppositions, we proposed the hypothesis of the endogenous appearance of AA in AD (Hori *et al*., 2013, Hori *et al*., 2014a, Hori *et al*., 2014b, Konishi *et al*, 2015).

Anticholinergic activity in other neurocognitive and psychiatric disorders: Because, as mentioned above, other factors besides ACh downregulation cause AA, such as medication (Tune *et al*., 1992), physical illness (Flacker *et al*., 1999), and mental stress (Plascheke *et al*., 2010), AA could also be caused by a combination of these factors, even when the ACh level does not reach a critical level (i.e., at mild cognitive impairment or mild disease stages) (Konishi *et al*, 2013). Indeed, we treated a 74-year-old woman with positive SAA, even though her cognitive decline was not sufficient to endogenously elicit AA. In this instance, we speculated that the SAA positivity was induced by the addition of mental stress to preexisting ACh downregulation (Konishi *et al*, 2013, Hori *et al* 2015a). We consider mental stress and other factors capable of inducing SAA, to be 'AA inserts'. From this case, we speculated that AA is found in not only neurocognitive disorders such as delirium (Kitajima *et al*, 2014, Kitajima *et al*., 2015) and hallucination in Lewy body disease (Kitajima *et al*, 2014, Kitajima *et al*., 2015), but also neuropsychiatric disorders such as mood disorder (Hori *et al*., 2015b) based on the dual actions of ACh downregulation coupled with the effects of another AA insert (Hori *et al*., 2015a). Indeed, we reported a 55-year-old patient with depression whose AA disappeared after prescription of donepezil, indicating a possible relationship between AA and mood disorder (Hori *et al*., 2015b).

Anticholinergic activity in schizophrenia: Previously, we also speculated that this hypothesis would apply to schizophrenia (Tani *et al*., 2015). Indeed, antibodies against astrocytic muscarinic-1 and muscarinic-2 receptors are present in the serum of patients with paranoid-type schizophrenia and downregulation of ACh is indicated in schizophrenia even in the prodromal phase (Borda *et al*, 2004). We speculated that, based on the downregulation of ACh, which is compensated by other mechanisms in the prodromal phase, the addition of mental stress would lead to failure of the compensatory mechanism and the appearance of psychotic symptoms. We also speculated that the prodromal phase in schizophrenia might correspond to the mild stage in AD and the acute phase to the moderate stage concerning AA (Tani *et al*., 2015). In fact, Raedler *et al*. (2007) 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.
In contrast, Tandon *et al*. (1999) commented that AA can be associated with ACh hyperactivity. They also hypothesized, after administering the centrally acting acetylcholinesterase inhibitor physostigmine to normal volunteers, that hyperactivity is associated with negative symptoms; the negative symptoms were selectively ameliorated by treatment with clozapine and olanzapine, two agents with AA, suggesting that muscarinic hyperactivity may be involved in the negative symptoms (Tandon *et al*., 1999). According to this hypothesis, in the acute phase of schizophrenia, because 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 the psychosis.

After treatment with antipsychotic agents, the dopaminergic hyperactivity is improved by blocking dopamine type 2 receptors, but the cholinergic hyperactivity may still be present. Therefore, clinically, negative symptoms might represent a normal dopaminergic-hypercholinergic state, so-called postpsychotic depression (Mineur *et al*., 2013, Gibbons *et al*, 2009). 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 (Gibbons *et al*, 2009). Yeomans (1995) suggested, in terms of antimuscarinic psychosis, that an increased cholinergic cell (Ch5) tone with genetically increased tegmental cholinergic cells (Ch5 and Ch6) or fewer Ch5 autoreceptors of schizophrenia might induce Ch5 overactivation and that this overactivation would boost 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.

We have previously reported the relationship between SAA and clinical symptoms including cognitive function and extrapyramidal symptoms (Akashi *et al*., 2015). The SAA was measured in 15 chronically medicated patients with schizophrenia and 10 healthy controls. We also measured extrapyramidal motor symptoms, psychiatric symptoms, and cognitive function. There was a significant negative association between SAA and severity of extrapyramidal motor symptoms in patients with schizophrenia ($p = 0.043$) (Fig. 1) and a trend for a positive association between SAA and thought disorder ($p = 0.072$). In terms of the association between SAA and severity of extrapyramidal motor symptoms in schizophrenia, our result was compatible with that of Tune and Coyle (1980). We found no significant association between SAA and other psychiatric symptoms or cognitive functions. Thus, we considered that AA might improve extrapyramidal motor symptoms but exacerbate thought disorders (Akashi *et al*., 2015).

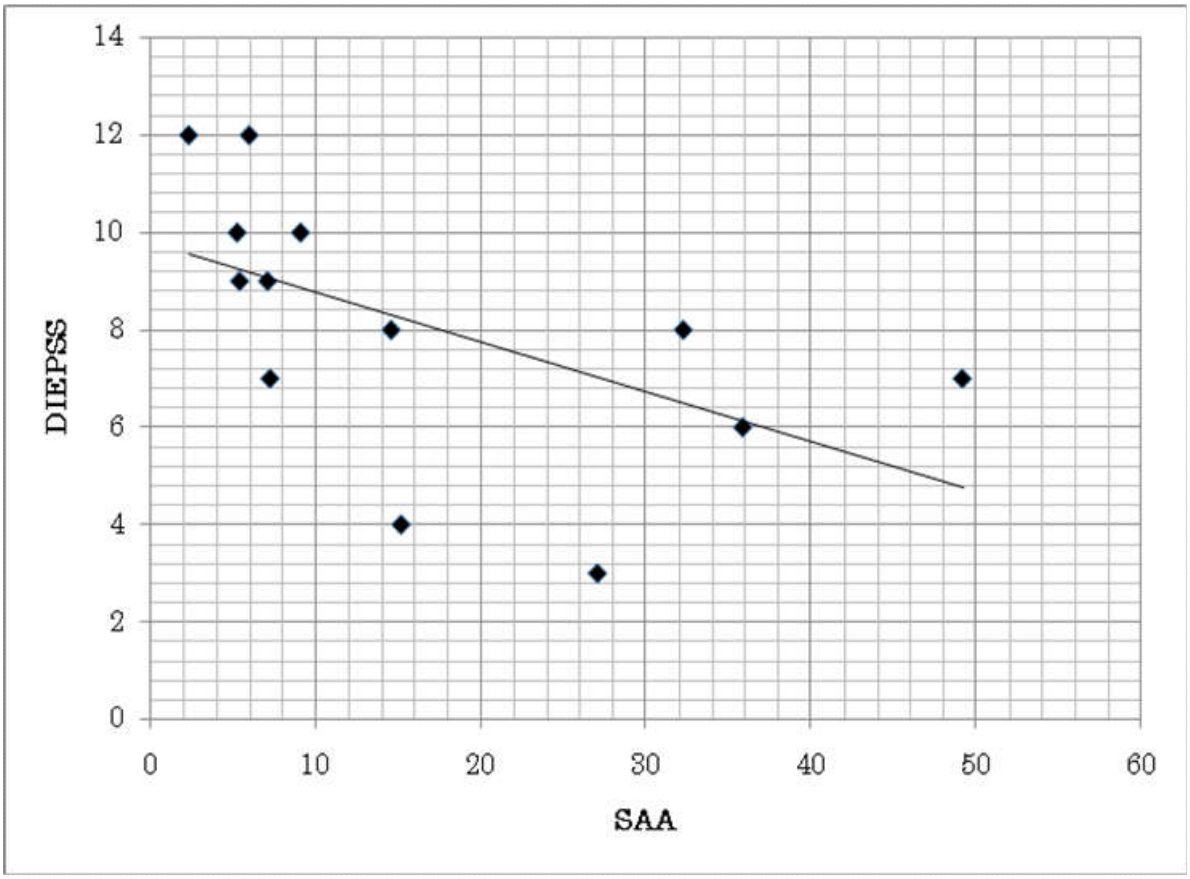

Fig. 1. There is a significant negative association between SAA and extrapyramidal motor symptoms in patients with schizophrenia (p = 0.043). DIEPSS, drug-induced extrapyramidal symptoms scale (Inada, 2009). SAA, serum anticholinergic activity. This figure is reproduced from Akashi *et al*., 2015 with permission from Showa University, Tokyo, Japan

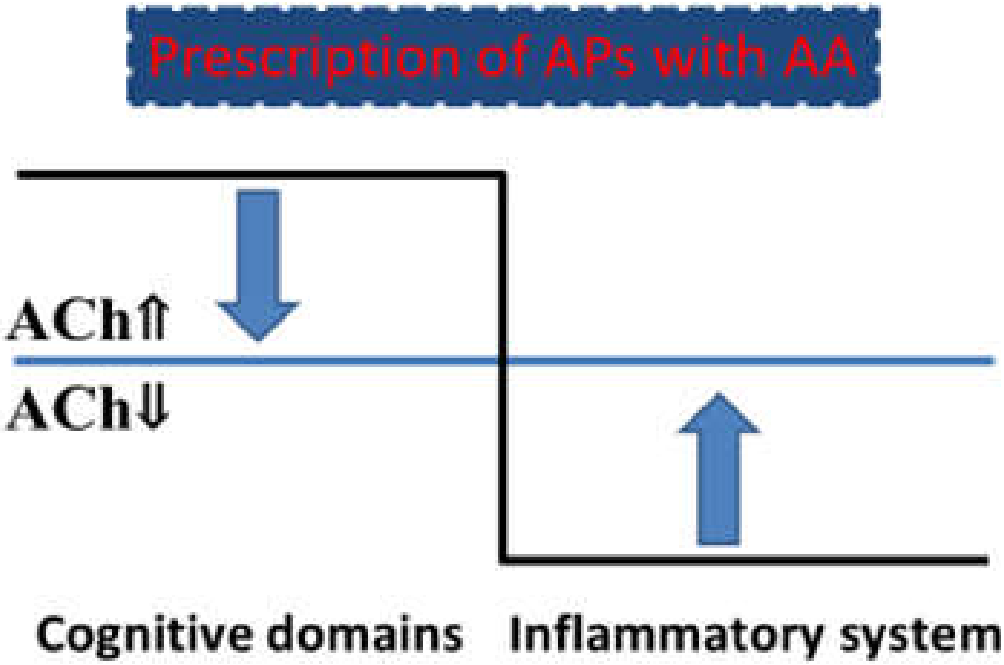

Fig. 2. A hypothesized imbalance in ACh in schizophrenia. There may be ACh hyperactivity in cognitive domains but ACh hypoactivity in the inflammatory system. Therefore, substantial levels of AA or antipsychotics with considerable AA might be needed in schizophrenia. If antipsychotics with AA are prescribed, ACh is downregulated in cognitive domains and ACh is upregulated in the inflammatory system, which may trigger remission in patients with schizophrenia. AA, anticholinergic activity; ACh, acetylcholine; AP, antipsychotics

These results did not support the theory of ACh downregulation in schizophrenia but the theory of ACh hyperactivity. Thus we believe that down regulation of ACh might be found in the inflammatory system in schizophrenia, but there might be ACh hyperactivation in cognitive domains. Indeed, ACh hyperactivation is suggested to induce cognitive dysfunction in cognitive domains (Sarter *et al*., 1998). It is also reported that 6-hydroxydopamine lesions decrease neocortical muscarinic receptor availability and this induces hyperactivation of the cortical cholinergic system (Knol *et al*, 1998). Based on these considerations, we speculate here that there might be an imbalance in schizophrenia in not only the dopaminergic system, but also the cholinergic system. That is, there might be ACh hyperactivity in cognitive domains but ACh hypoactivity in the inflammatory system. Therefore, substantial levels of AA or antipsychotics with considerable AA might be needed to treat schizophrenia. Prescription of antipsychotics with AA might downregulate ACh in cognitive domains and upregulate ACh in the inflammatory system, which might cause remission in patients with schizophrenia (Fig. 2).

Serum anticholinergic activity as a favorable biological marker for evaluating the optimal dose of antipsychotics in schizophrenia: We have previously discussed the usefulness of SAA in reducing the anticholinergic burden in the central nervous system (Hori *et al*., 2014b). Therefore, here, we now discuss the particulars of SAA for this purpose. We believe that optimal doses of antipsychotic medicines can be quantitatively determined using SAA. As mentioned, there is a significant negative association between SAA and extrapyramidal motor symptoms and a trend for a positive association between SAA and thought disorder in patients with schizophrenia. Moreover, as shown in Fig. 2, there might be a sudden amelioration of extrapyramidal motor symptoms when the SAA exceeds 10 nM, although these results should be investigated in large patient sample. Of course, cognitive functions deteriorate when SAA (indicative of AA) is increased (Hori *et al*., 2011).

Therefore, we speculate that, when the quantities of prescribed antipsychotics can be adjusted to achieve a SAA of slightly over 10 nM, the clinical symptoms (extrapyramidal motor symptoms and cognitive dysfunctions) might be minimized. If this is not the case, we at least confirmed that extrapyramidal symptom severity is negatively correlated with the SAA level (Fig. 1) and that there is a tendency for a positive association between cognitive dysfunction severity and SAA (Akashi *et al*., 2015). Therefore, we believe that we should adjust the SAA value to be as near as possible to the cross point of these two lines. To date, we have not been able to obtain further data on SAA because radiation management at the company that has been measuring SAA (LIS Medience, Uto, Kumamoto, Japan) prevents this. We are currently trying to measure SAA ourselves to help to verify our revised hypothesis.

Conflicts of Interest: Koji Hori has 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., and Mitsubishi Tanabe Pharma Co. Mitsugu Hachisu has received lecture fees from Meiji Seika Pharma Co. Ltd. and Mitsubishi Tanabe Pharma Co. These companies had no role in the preparation or decision to publish this article.

Disclosure Statement: Koji Hori has received funding from Eisai Co. Ltd., Daiichi Sankyo Inc., Ono Pharmaceutical Co. Ltd., and Ito Memorial Fund. Mitsugu Hachisu has received funding from Astellas Pharma Inc., Meiji Seika Pharma Co. Ltd., Dainippon Sumitomo Pharm Co. Ltd., Eli Lilly Japan KK, and Shionogi & Co. Ltd. However, the sponsors had no role in the preparation or decision to publish this article.

Author Contributions

Masayuki Tani and Koji Hori mainly draft the manuscript and the group's study of AA and SAA. Kimiko Konishi, Mitsugu Hachisu, Norihisa Akashi, and Michiho Sodenaga critically revised the manuscript", which meets authorship criteria. Kimiko Konishi, Mitsugu Hachisu, Masayuki Tani, and Norihisa Akashi also wrote the previous articles on AA that are mentioned in this manuscript. Kimiko Konishi is now trying to measure SAA again at St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan. Michiho Sodenaga supports the concept of anticholinergic activity and will contribute to research into AA and schizophrenia, mainly via recruitment of patients to future studies of AA and schizophrenia.

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