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International Journal of Current Research
Vol. 9, Issue, 12, pp.63090-63095, December, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

REVIEW ARTICLE

DIFFERENTIATIONS OF SELECTION FOR CHOLINESTERASE INHIBITORS TO TREAT ALZHEIMER'S DISEASE BASED ON THE CLINICAL AND BIOLOGICAL ASPECTS

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ARTICLE INFO

Article History:
Received 15th September, 2017
Received in revised form
12th October, 2017
Accepted 19th November, 2017
Published online 31st December, 2017

Key words:
Acetylcholine (ACh), Alzheimer's disease (AD), Brain derived neurotrophic factor (BDNF), Butylycholinesterase, Cholineacetyltransferase (ChAT), Cholinesterase inhibitor (ChEI), Mild cognitive impairment (MCI), Plasma cholinesterase activity.

ABSTRACT

There is no convention or rule to select one of three cholinesterase inhibitors, i.e., donepezil (D), galantamine (G) and rivastigmine (R) for Alzheimer's disease (AD). Therefore, in this article we will give our considerations regarding the differentiations of prescription among these three medicines based on the clinical symptoms and biological markers.In clinical points of view, prescription D is good for AD patients at mild cognitive impairment. At mild stage, when prominence of apathy, R should be prescribed and for those showing depression, anxiety, delusion, hallucination and aggressiveness, G should be prescribed. In biological points of view, with plasm brain derived neurotrophic factor (BDNF) contents and plasma cholinesterase (p-ChE) activity, we speculate that there might be critical values in both plasma BDNF contents and p-ChE activity in ADsymptoms. Therefore, we also speculate that G should be prescribedat patients with low plasma BDNF orR with high p-ChE.

Citation: Koji Hori, Misa Hosoi, Kimiko Konishi, Michiho Sodenaga, Hiroi Tomioka and Mitsugu Hachisu, 2017. "Differentiations of selection for cholinesterase inhibitors to treat alzheimer's disease based on the clinical and biological aspects", *International Journal of Current Research*, 9, (12), 63090-63095.

INTRODUCTION

In Japan, 3 cholinesterase inhibitors (ChEIs), donepezil (D), galantamine (G) and rivastigmine (R) are available for treatment of Alzheimer's disease (AD). ChEIs are not allowed to be prescribed combined with each other in a rule of Japanese medical insuarance, therefore we have to select one of these inhibitors depending on a symptom of AD. As D has been available since 1999 and other two ChEIs (G and R) have been available since 2011, D has long been prescribed and used to most AD in Japan. One important issue is that the three ChEIs, D, G or R is selected without rationalized treatment based on objective parameters to the symptoms. R and G are unique in its pharmacological nature inhibiting butyrylcholinesterase (BuChE) (Furukawa-Hibi *et al*., 2011) and allosterically potentiating nicotinic ACh receptors (nAChR) addition to inhibiting acetylcholinesterase (AChE) activity, respectively (Geerts *et al*., 2002). Therefore, we should consider these characteristics in case of selection of ChEIs. In this article, we propose the differentiation of selection of ChEIsto treat AD based on the clinical symptoms and biological markers taking into the difference of these three ChEI characteristics.

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Putative changes in central nervous system in Alzheimer's disease at MCI and mild stage and differentiation of selection of cholinesterase inhibitors between at MCI stage and mild stage

The degeneration of cholinergic neurons have been observed in AD pathology (Whitehouse *et al*., 2011). In this pathology, the activity of choline acetyltransferase (ChAT; an enzyme that synthesizes ACh) is thought to be downregulated in the mild to moderate stages of AD (Ferreira-Vieira *et al*., 2016), however,

the activity of ChAT were reported to be upregulated in patients with MCI or early AD (deKosky *et al*., 2002). The upregulation of ChAT activity is explained as a compensation to keepACh activity remains normal. This compensatory reaction to the onset of AD may be attributable to hyperactivity of presynaptic cholinergic neurons. If this compensatory mechanism workswell, the activity of cholinergic system might be intact, rather than deteriorated. We speculate that when clinical symptoms appear, ever if the cholinergic neuronal system is burdened, the whole activity of AChis still intact, i.e., the cholinergic neuron is relative reserve and not degenerated. In fact, cholinergic neuron is reported to be reserved (Gilmor *et al*., 1999). In this context, we also speculate that when at MCI stage, symptoms occur at limited two situation. Onesituation is when patients with AD at the MCI stage relax, at which time the ACh level might be lower than normal. In this situation, these patients might show apathy (e.g., when they watch television, they fall asleep). The other situation is when they are more stressed than usual. In this situation, their cholinergic system might not be able to be up regulated any further because ChAT is already activated and does not permit further upregulation (Hori *et al*., 2016). Therefore, we speculate that when clinical symptoms occur, neuronal whole activity is intact (i.e. not degenerated). From these speculations, we hypothesize that in the MCI stage, AD pathology burdens the brain in AD patients, whileChAT activity is upregulated (deKosky *et al*., 2002), and consequently ACh levels are normal. Moreover, we also propose that in mild-stage AD, ACh gradually decreases because hyperactivity of presynaptic neurons may take a turn to early and rapid neuronal degeneration, consequently downregulating ChAT activity. Therefore, in the mild stage downregulation of ACh occurs and amyloid pathology increases. In the moderate stage, as we mentioned, because downregulation of ACh reaches a critical level, AA appears endogenously (Fig. 1a–b) (Hachisu *et al*., 2015).

Moreover, the activity of nAChR is also reported to be downregulated (Ogawa *et al*., 2006). Therefore, at mild stage in AD, not only downregulation of ACh but also downregulation of nAChR occur. Alternatively, we speculate that at MCI stage, the activities of nAChR might in normal levels because we consider that at MCI stage cholinergic neurons are reserved and amyloid pathology is not so prominent (Konishi *et al*., 2015). Moreover, BuChE exists in amyloid (Darvesh *et al*., 2012, Mizukami *et al*., 2016). Therefore, at MCI activity of BuChE might not be high and rather there might be possibly hyperactive of AChE, because of upregulation of ChAT. However, in mild stage the activity of BuChE might be high and that of AChE is relative low. Therefore, it is better to treat MCI with D rather than G and R. On the contrary, at mild stage in AD, nervous cells are degenerated and amyloid proliferate, then the activity of nAChR might be deteriorated and BuChE might be hyperactivated. Therefore, at mild stage in AD, G or R should be prescribed rather than D. The concepts of the selection of prescriptions are presence of compensatory mechanism (upregulation of ChAT) of ACh activityin MCI stage and not to hyperactivateChAT activity in order to sustain the compensatory mechanism adequately as long as possible. However, in mild stage changes of the concept to select the prescriptions should be done and the deterioration of compensatory mechanisms (upregulation of nAChR and ACh) occur in mild stage of AD. Therefore the concept of selection of medicines isin order to cover the downregulations ofnAChR and AChsystems.

Differentiation of selection for cholinesterase inhibitors based on clinical symptoms

As mentioned above, R is unique in its pharmacological character to inhibit not only AChE but also BuChE and G is so because G has not only an action of AChEI and allosteric potentiating capacity to nAChR (Furukawa-Hibi *et al*., 2011, Geerts *et al*., 2002). Therefore, we consider the characteristics of BuChE and nAChR in order to select ChELs at mild stage. In normal brain, AChE, which exists on neuronal cells is main enzyme to degrade ACh. In the AD brain, glia cells and amyloids proliferate and neuronal cells shrink, therefore AChE decrease and the main enzyme that degrade AChchages toBuChEthat exists on the glia cells and amyloids (Darvesh *et al*., 2012, Mizukami *et al*., 2016). Therefore, when AD progresses, the activities of AChEs decrease and BuChEs increase (Perry *et al*., 1978, Darveshh *et al*., 2003). Accordingly the ratio of BuChEs/AChEs increases. As mentioned above at MCI stage, even when AD pathology is burdened, nervous cells are almost normal. Therefore, main enzyme which catalysesACh is still AChE. However, at mild stage in AD, when nervous cells decrease and glia cells and amyloids increase, main enzymes those catalyseACh are changes to mainly BuChEnot AChE (Perry *et al*., 1978, Darveshh *et al*., 2003). In fact Perry *et al*. reported thatAChEs decrease with liner fashion and BuChEs increase with sigmoid fashion by the progression of AD (Perry *et al*., 1978). Moreover, BuChE is considered to accelerate an accumulation of amyloids, i.e., BuChE is considered to accelerate AD pathology (Darveshh *et al*., 2012). Therefore, when at mild stage, R which inhibits actions on both AChE and BuChEis suitable than D. Moreover, we consider that treatment of R is suitable to relativelyyounger patient with AD pathology. In relative older patients cognitive dysfunctions by both AD pathology and aging (Barnes *et al*., 2015). On the contrary, in relatively younger patient only AD pathology causes cognitive dysfunctions. Therefore, AD pathology is thought to be more pronounced in relatively younger patient than older patient when the same cognitive disturbances exist. We had better to consider that R should be prescribed for relatively younger patients with AD. Needless to say, at mild stage, downregulation of ACh is more severe than that at MCI stage. Moreover, downregulation of ACh is related with apathic symptom (Rea *et al*., 2015). Therefore, we should also prescribe R when the apathy is prominent. In fact, wehave experienced at the relatively younger AD patient with apathy who have been prescribed D. When we changed the prescription to R from D, his clinical symptoms mainly apathy were ameliorated after the change to R from D (Horiuchi *et al*., 2014). Therefore, when the symptoms of apathy is prominent in relative younger patients with AD, Rshould beprescribed.

As for nAChR, this receptors exist not only on the post-synaptic neurons but also on the synaptic terminal of ACh, serotonin, noradrenaline and gamma amino butyric acids and potentiate release of these transmitters (Picciotto *et al*., 2000). These neurons are related with depressive symptoms and anxiety (Stahl *et al*., 2000). Moreover, we also commented that aging and AD pathology cause depression andanxiety to connect with symptoms of delusion, hallucination and aggressiveness (Hori *et al*., 2012; Hosoi *et al*., 2017).

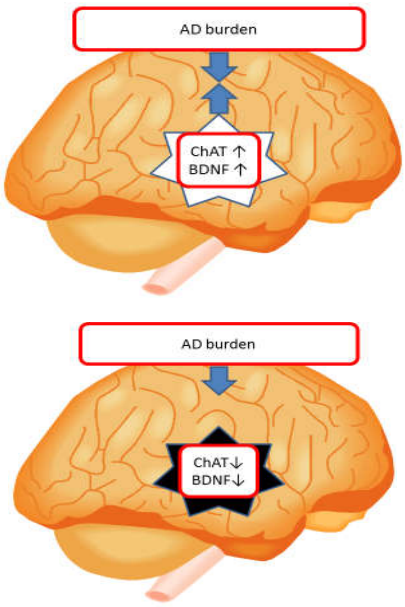

Figure 1.
(A) MCI stage: AD pathology causes a burden in the brains of patients with AD; however, ChAT activity BDNF are upregulated and ACh is maintained at a normal level. (B) Mild stage: ACh gradually decreases because hyperactivity of presynaptic neurons may cause early and rapid neuronal degeneration with a consequent downregulation of ChAT activity and BDNF.Figures are reproduced from Hachisu et al. [8], with permission of Karger, Basel, Switzerland. Abbreviations: ACh, acetylcholine; AD, Alzheimer's disease; ChAT, choline acetyltransferase; BDNF: brain-derived neurotrophic factor, MCI, mild cognitive impairment

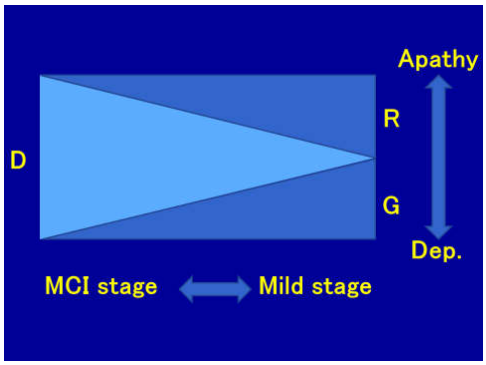

Figure 2. In clinical points of view, we should prescribe D patients with AD at MCI. At mild stage in AD, we should do R those with prominent apathy and G with depressive symptoms (depression, anxiety, delusion, hallucination and aggressiveness). AD: Alzheimer's disease, Dep: depressive symptoms, D: donepezil, G: galantamine, MCI: mild cognitive impairment, R: rivastigmine.

Table 1. We speculate that there are critical points (critical value) in both p-BDNF and p-ChE. We should separate AD patients into four groups, i.e., (1) high p-BDNF and high p-ChE group, (2) high p-BDNF and low p-ChE group, (3) low p-BDNF and high p-ChE group, (4) low p-BDNF and low p-ChE group. We should prescribe R patients with high p-BDNF and high p-ChE, D patients with high p-BDNF and low p-ChE group, G or R patients with low p-BDNF and high p-ChE group, and G patients with low p-BDNF and low p-ChE group. D: donepezil, G: galantamine, p-BDNF: plasma brain-derived neurotrophic factor, p-ChE: plasma cholinesterase activity, R: rivastigmine

	p-ChE ↑	p-ChE ↓
p-BDNF ↑	R	D
p-BDNF ↓	R or G	G

Therefore, G is better to be prescribed to the patients with AD showing delusion, hallucination and aggressiveness. We also have experienced that an AD patient whose delusion, hallucination and aggressiveness were ameliorate by the prescription of G (Hori *et al*., 2012). We summarize that at MCI stage, compensatory mechanisms work and degeneration of nervous cells doesn't occur. Accordingly downregulations of ACh and nAChR don't occur. Therefore, main enzyme that degenerate ACh is AChE. We should prescribe D for MCI patients in order for compensatory mechanisms to work as long as possible. At mild stage, downregulations of ACh and nAChR occur because the degenerations of central nervous cells occur mainly those with cholinergic neurons with the deteriorations of compensatory reactions. Therefore, according to the symptoms those are related with downregulation of ACh or nAChR. We propose that patients whose symptoms prominent apathy should be prescribed R. On the contrary, the symptomsprominent depression, anxiety, delusion, hallucination and aggressiveness, G should be prescribed. Moreover, patients at MCI stage, D should be prescribed (Fig.2).

Biological markers as for differentiation of selection of cholinesterase inhibitors

In this chapter, wediscuss biological markers as for differentiation of selection of ChEIs. As we discuss below, we recommend toprescribe G, when theplasma brain-derived neurotrophic factor (p-BDNF) is lowand prescribe R, whenthe plasma cholinesterase (p-ChE) activity is high (Hosoi *et al*., 2015). BDNF is now considered to play a role to restore not only the depression but also to accelerate the synaptic plasticity of neurons in the hippocampus and BDNF accelerates the synaptic plasticity of neurons in the hippocampus, inducing a learning and memory and this phenomena are interpreted well known a long-term potentiation in the hippocampus (Hellweg and Jockers-Scherübl 1994, Heldt *et al*., 2007). The main symptoms of AD are deficit of memory and cognition and pathologically neurodegeneration; therefore, the loss of BDNF is easily assumed. There are many reports that BDNF at the mRNA (Garzon *et al*., 2002) and protein (Hock *et al*., 1998, Michalski and Fahnestock, 2003, Bendix *et al*., 2014) levels are decreased in the hippocampus and the cortex of the AD brain. Therefore, it is considered that production of BDNF is upregulated byACh.In fact, there are report that serum BDNF is increased by the treatment of ChEIs (Savaskan *et al*, 2000, Durany *et al*., 2000). We also speculate that among ChEIs, G is most favorable for upregulation of BDNF because activities of5-HT, NA and GABA neurons might beupregulated bypresynspticnAChR stimulation (Picciotto *et al*., 2000). In contrast, there are reports that the BDNF and activation of the receptor tropomyosin-related receptor kinase B (TrkB) are not reduced in AD symptoms (Lampón *et al*., 2012, Oropesa *et al*., 2014). We speculate that at MCI stage there might be a hyperactivity of BDNF because of a high activity of choline acetyltransferase (ChAT) in this stage, compensating AD pathologyin MCI (Hachisu *et al*., 2015). In MCI, BDNF and ChAT activities were hyperactivated because of a compensatory mechanism of AD pathology when there might not be prominent neuronal loss. In contrast, at a stage of mild AD, BDNF and ChAT activities go down. From these speculations, we recommend a prescription of ChEIthat if the p-BDNF is under the normal level, prescribe Gand is higher than the normal level, prescribe D.

The p-ChE is known as a nonspecific cholinesterase enzyme that hydrolyses many different choline-based esters (Oropesa *et al*., 2014). Therefore, p-ChE is not the AChEbut BuCh. When we prescribe R, p-ChE activity should be evaluated. Until now it is considered that high p-ChE activity is related tolow grade inflammation (Lampón *et al*., 2012), to reduce p-ChE activity is important to recover cognitive function of AD(Nakamura *et al*., 2014).Certainly, as a hyperactivity of p-ChEinduces low grade inflammation, that causes diabetes mellitus, hyperlipidemia (Inácio et al., 2006, Chaves *et al*., 2013) or psychiatric disorders (Haring *et al*., 2015). On the other hand, downregulation of p-ChE is related with anemia (Rice, 1977), liver dysfunction (Temel *et al*., 2015) and frail (Hubbard *et al*., 2008), which we speculate this might be related to downregulation of detoxication and antioxidant (Haghnazari *et al*., 2016). Therefore, it is important to keep p-ChE at an appropriate range of activity. Both higher and lower p-ChE activities might affected to cognition, and behavioral symptoms in various psychotic disorders and also psychiatric symptoms. We consider the regulation of p-ChE activity can be work well on AD. The former example is reported by Bando and Nakamura (Bando and Nakamura, 2016). They reported that 40% reduction of p-ChE activity was related with the reduction of behavioral symptoms in AD. The later example was reported by Cerejeira *et al*. (Cerejeira *et al*., 2011). They reported that low level of p-ChE in before operation was related with the occurrence of delirium in postoperative phase. We consider that we should select R or D from the p-ChE activity in the patients (Hosoi *et al*., 2017). Therefore it is important to keep p-ChE between at appropriate normal range.

- From these considerations above, we emphasize that there are critical points (critical value) in both p-BDNFconcentration and p-ChE activity. We should separate AD patients into four groups, i.e., (1) high p-BDNF and high p-ChE group, (2) high p-BDNF and low p-ChE group, (3) low p-BDNF and high p-ChE group, (4) low p-BDNF and low p-ChE group. Prescribe R is good to patients with high p-BDNF and high p-ChE, prescribe D is patients with high p-BDNF and low p-ChE group, prescribe G or R is patients with low p-BDNF and high p-ChE group, and prescribe G is patients with low p-BDNF and low p-ChE group (Table1).As for in patients with high p-BDNF and low p-ChE group, there might be a possibility that agent with not only inhibition of AChE and BuChE but also potentiation of nAChRmight beimportant.
- There is no data about the BDNF and AD. However, as for p-ChE we will report the results between the p-ChE and AD. In this report we will also comment the critical point (critical value) of p-ChEactivity for differentiation of selection of R or D.

Summary

In this article, wediscussed the differentiation for choiceof ChEIs based on the characteristics of BuChE and nAChR activities in AD in view of clinical symptoms and biological markers.In clinical points of view, we should prescribe D patients with AD at MCI. At mild stage in AD, when the apathy is prominent we recommend to prescribeR anddepression, anxiety, delusion, hallucination and aggressiveness are observed, G should be prescribed. In biological points of view, with p-BDNF concentration and p-ChE activity, R should be prescribed to patients with high p-BDNF and high p-ChE, D should be prescribed to patients with high p-BDNF and low p-ChE group, G or R should be prescribed to patients with low p-BDNF and high p-ChE group, and G should be prescribed to patients with low p-BDNF and low p-ChE group. From these points of views, agents those have AChEI, BuChEI and the ability that potentiates nAChR, also might be needed in future.

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.and Otsuka Pharmaceutical KK, and Mitsubishi Tanabe Pharma Co.MitsuguHachisu received lecture fees from 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 thismanuscript.

Disclosure Statement

Koji Hori received funding form Ito Memorial Fund and MitsuguHachisu 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, these funds were no related with role in study design, data collection and analysis including our before presented articles, decision to publish, or preparation of this manuscript.

Author Contributions

Koji Hori coordinated the study about the inflammatory markers in neuropsychiatric disorders and mainly wrote this article.Misa Hosoi conducted the study about the relationships between the p-ChE and AD. All member other than Misa Hosoi and Koji Hori also contribute to this manuscript as that Kimiko Konishi and MitsuguHachisu measure serum anticholinergic activity as the biological marker of inflammation and gave idea and advice about writing this article, that MichihoSodenagaand HiroiTomiokaprovided an ideas on writing this article, and gave idea about treatment option against inflammation and anticholinergic activity in psychiatric disorders. All checked the manuscript.

Acknowledgments

Dr. Chiaki Hashimoto (St. Mariana University School of Medicine, Department of Neuropsychiatry, Kawasaki, Japan), Dr. Ouga Sasaki (St. Mariana University School of Medicine, Department of Neuropsychiatry, Kawasaki, Japan), Dr. ItsukuSuziki (Kawasaki Municipal Tama Hospital, Department of Neuropsychiatry, Kawasaki, Japan)are other member in study group of geropsychiatry in St. Mariana University School of Medicine and all checked the manuscript.

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