Expert Opinion on Therapeutic Targets (Editorial)

Tropisetron: A promising drug to prevent Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder. Despite this, there are no drugs for preventing the onset of AD. Preclinical studies suggest that interaction between amyloid-β peptides (Aβ) and the α7 nicotinic acetylcholine receptor (α7 nAChR) plays a key role in AD pathology, and that α7 nAChR agonists could act as potential therapeutic drugs for AD. A recent study demonstrated that tropisetron, a potent α7 nAChR agonist and serotonin 5-HT_3 receptor antagonist, also bound to the ectodomain of amyloid precursor protein (APP). Furthermore, tropisetron promoted greater improvements in memory than current AD therapeutic drugs, such as memantine and donepezil. Positron emission tomography studies detected Aβ deposition and inflammation in the brains of subjects with amnestic mild cognitive impairment (MCI) before the onset of AD. Given the role of α7 nAChR in Aβ deposition and inflammation, tropisetron represents an attractive potential therapeutic drug to delay or prevent MCI and AD. Additionally since this drug is used internationally to treat chemotherapy-induced emesis, its safety record is already known.

Key words: Alzheimer's disease; α7 Nicotinic receptor; β-Amyloid; Encenicline, 5-HT_3 receptor; Inflammation; Mild cognitive impairment; Tropisetron

1. Introduction

The World Alzheimer Report 2013 (1) estimated that between 2010 and 2050, the worldwide numbers of older people needing care will nearly treble, from 101 to 277 million. Nearly half of these older people are likely to be living with and experiencing the effects of dementia. Furthermore, costs will increase in line with the number of older people suffering dementia. The World Alzheimer Report predicted a near doubling in worldwide societal costs from US$604 billion in 2010 to US$1,117 billion, by 2030 (1).

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder, and AD is the most common cause of dementia. It is a slowly progressing disease characterized by three stages – an early preclinical stage with no symptoms, a middle stage with mild cognitive impairment (MCI) and a final stage with dementia (**Figure 1**). Currently, there are no therapeutic agents for preventing the onset of MCI or AD. A decade of disappointing clinical trials testing agents aimed at modifying AD disease in patients, suggest that effective treatment should be targeted at earlier stages of the disease, that is, even before overt symptoms arise (2).

2. Role of Aβ - α7 nAChR interaction in AD pathology

Although the precise mechanisms underlying AD pathology are currently unknown, the accumulation and aggregation of amyloid-β (Aβ) peptides in brain regions, such as the hippocampus and cerebral cortex, are believed to be an early event in the pathogenesis of this disease. Another prominent feature of AD pathology is the loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChRs) throughout the brain (**Figure 1**) (3, 4). However, the mechanisms linking Aβ to the loss of cholinergic neurons and nAChRs remain to be fully elucidated. The α7 subtype of nAChRs, a major subtype of nAChRs in the brain, is a functional homopentameric receptor since ACh-gated ion channels open when five identical α7-subunits assemble together (4). The α7 nAChRs are located presynaptically, including on

cholinergic projection pathways from the basal forebrain, where they are active in the Ca^{2+}-dependent release of neurotransmitters. Additionally, α7 nAChRs are localized postsynaptically on γ-aminobutyric acid-ergic inhibitory interneurons, particularly in the hippocampus and cerebral cortex (4). Accumulating evidence suggests that the α7 nAChR is integral to the pathogenesis of AD, and therefore that α7 nAChR agonists could be potential therapeutic drugs for MCI and AD (3, 4). Despite the presence of high amounts of amyloid precursor protein (APP) and Aβ deposits in the brain, deleting α7 nAChR subunits in the mouse model of AD protects against dysfunction of synaptic integrity (pathology and plasticity) and cognitive function (5). Furthermore, chronic administration of nicotine prevented Aβ-induced reductions of α7 nAChR in an animal model of AD (6). Although the mechanism underlying the neuroprotective effect of nicotine is unclear, it is likely that nicotine protects cells against Aβ toxicity by upregulation of α7 nAChR (6). Subsequently, S 24795, a partial agonist at α7 nAChR, was found to reduce $Aβ_{42}$ - α7 nAChR interaction and $Aβ_{42}$-induced τ phosphorylation (7). Taken together, disrupting the Aβ - α7 nAChR interaction may represent a novel approach to reducing Aβ-mediated functional deficits, neurodegeneration, and possibly the neuropathological features of AD.

3. Tropisetron

Tropisetron (Navoban®), a 5-hydroxytryptamine $(5\text{-HT})_3$ receptor antagonist, is widely used to treat chemotherapy-induced emesis outside of the United States (U.S.). In addition to its 5-HT_3 receptor antagonism properties, tropisetron is also a partial agonist at the α7 nAChR. Tropisetron (5-20 mg/day) is reportedly effective in the treatment of auditory sensory gating P50 deficits, cognitive impairment, and negative symptoms in patients with schizophrenia (8-11), indicating that tropisetron would be a potential therapeutic drug for schizophrenia (3, 12).

Using a clinical compound library, Spilman et al. (13) recently identified tropisetron as

an agent that consistently increased soluble amyloid precursor protein α (sAPPα), which acts as a trophic factor (**Figure 2**). A subsequent assay showed that tropisetron consistently increased the sAPPα/$A\beta_{1-42}$ ratio, suggestive of a beneficial effect in ameliorating the AD phenotype. *In vivo* studies using J20 mice (an animal model of AD), showed that tropisetron (0.5 mg/kg/day) improved the sAPPα/Aβ ratio, along with spatial and working memory in mice, and that tropisetron was effective both during the symptomatic, pre-plaque phase (5-6 months) and in the late plaque phase (14 months). As well as possessing 5-HT_3 receptor antagonism and α7 nAChR partial agonism properties, tropisetron also binds to the ectodomain of APP, with a sub-micromolar affinity (13). Interestingly, direct comparisons of tropisetron with current AD therapeutic drugs such as, memantine and donepezil, revealed that tropisetron induced greater improvements in memory and the sAPPα/$A\beta_{1-42}$ ratio (13). Furthermore, it is reported that tropisetron protects against Aβ-induced neurotoxicity *in vivo*, through both 5-HT_3 receptor-dependent and independent pathways (14).

4. Role of α7 nAChR in inflammation

Positron emission tomography (PET) studies using [^{11}C]PIB (Pittsburgh Compound-B) and [^{11}C](*R*)-PK11195 (an antagonist at the mitochondrial 18 kDa translocator protein) demonstrated that Aβ deposition and microglial activation could be detected in the brain of patients with amnestic MCI (15, 16). Longitudinal studies suggested that MCI subjects with high PIB retention are much more likely to convert to AD than subjects with low PIB retention (16), indicating that Aβ - PET may play a prognostic role in the clinical evaluation of MCI. Most significantly, longitudinal studies showed that cognitively normal subjects with elevated PIB were at much higher risk for longitudinal cognitive decline and the emergence of clinically significant cognitive impairment, relative to PIB negative, age- and education-matched subjects (16). In addition, the AD Neuroimaging Initiative research suggests that AD begins with Aβ accumulation and inflammation in the brain, which ultimately leads to

synaptic dysfunction, neurogeneration, and cognitive or functional decline, although inflammation is not always detrimental in the AD pathological process (**Figure 1 and 2**)(16).

In 2003, Wang et al. (17) reported on the key role of α7 nAChR in the inflammatory process. They found that the anti-inflammatory action of vagal stimulation worked in wild-type, but not α7 nAChR knock-out mice (17). This led to the proposal of a "cholinergic anti-inflammatory pathway" (18). Preclinical models have provided a plethora of evidence supporting a beneficial effect for activation or mimicry of the "cholinergic anti-inflammatory pathway" in a number of disorders (e.g., inflammatory bowel disease, postoperative and endotoxin-induced ileus) (18). Interestingly, a report showed that tropisetron can attenuate serum levels of the pro-inflammatory cytokine, interleukin-6 (IL-6), in rats after cecal ligation and puncture (19), indicating a potent anti-inflammatory effect for tropisetron. It is also known that 5-HT_3 receptor antagonists, including tropisetron, conferred anti-inflammatory properties. Considering the crucial role of α7 nAChR on Aβ deposition and inflammation in the brain, tropisetron may act to prevent or delay the onset of Alzheimer's disease from the state of MCI (**Figure 1 and Figure 2**).

5. Encenicline (EVP-6124)

EnVivo Pharmaceuticals Inc. (now Forum Pharmaceuticals, Inc.) reported results for a Phase 2b trial of encenicline hydrochloride (EVP-6124; 0.3, 1 or 2 mg, 23-weeks), another α7 nAChR partial agonist, in patients (n=409) with mild to moderate AD (20). Encenicline (2 mg) showed statistically significant effects on a number of cognitive and clinical endpoints, including the primary endpoint of AD Assessment Scale-Cognitive Subscale (ADAS-Cog) status. The drug was safe and well tolerated, showing predominantly mild treatment-emergent adverse effects (1 mg = 48.5%, 2 mg = 53%). Next, the company initiated COGNITIV AD, a Phase 3 clinical trial program, using encenicline in mild to moderate AD. The program consists of two randomized, double-blind, placebo-controlled trials, enrolling approximately

1,600 patients at sites in the U.S. and other countries worldwide (20).

6. Conclusion

As mentioned above, tropisetron interacts with both the 5-HT_3 receptor and α7 nAChR, as well as interfacing directly with APP, targets that are all associated with early AD pathology (**Figure 2**). This makes tropisetron an attractive potential therapeutic drug to delay or prevent MCI and AD, particularly since current medications do not affect the underlying disease process. Further clinical studies are needed to fully evaluate the efficacy of tropisetron in AD prevention.

Expert Opinion

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a worldwide prevalence estimated to quadruple over the next 50 years. It is a slowly progressing disease, characterized by three stages; an early preclinical stage with no symptoms, a middle stage with mild cognitive impairment (MCI) and a final stage with dementia. However, no effective treatment is available to slow down or stop the onset of MCI or AD.

A prominent feature of AD pathology is the loss of cholinergic neurons and nicotinic acetylcholine receptors (nAChRs) throughout the brain (**Figure 1**). Given the role of the amyloid-β (Aβ**)** - α7 nAChR interaction in AD pathology, both Aβ and α7 nAChR are valid therapeutic targets for AD. A number of PET studies demonstrated the presence of Aβ depositions in the brain, some 10 to 20 years before dementia or even MCI is diagnosed (**Figure 1**). A recent preclinical study showed that in addition to interaction with both the 5-HT_3 receptor and α7 nAChR, tropisetron interacts directly with APP, targets that are all associated with early AD pathology (13). Interestingly, direct comparisons of tropisetron with current AD therapeutic drugs (e.g., memantine and donepezil), revealed greater improvement in memory and sAPPα/$Aβ_{1-42}$ ratios with tropisetron (13). In addition, tropisetron showed excellent oral bioavailability, brain penetration, cognitive effects and biomarker effects at currently used human equivalent doses (13).

Taken together, current evidence highlights tropisetron as a promising therapeutic drug to delay or prevent MCI and mild to moderate AD, especially since it already has worldwide approval for clinical use in a different disorder (**Figure 1 and Figure 2**). Future studies using a combination of tropisetron and other drugs, such as β-site APP cleaving enzyme (BACE1) inhibitors will be interesting.

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Declaration of Interest

Dr. Hashimoto holds a patent for the use of tropisetron in neuropsychiatric diseases, including schizophrenia and Alzheimer’s disease. In addition, Dr. Hashimoto has served as a scientific consultant to Astellas, Dainippon-Sumitomo and Taisho, and he has also received research support from Abbvie, Dainippon-Sumitomo, Otsuka, and Taisho.

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Figure legends:

Figure 1. The life course in healthy aging, MCI subjects and AD patients

As people grow older, healthy subjects develop age-related memory loss. Subjects with mild cognitive impairment (MCI) develop a greater degree of memory problems relative to age-matched healthy subjects, although they do not experience the personality changes or other problems characteristic of AD. Studies using PET showed that amyloid-β (Aβ) deposition and inflammation are present in the brains of MCI subjects. AD patients suffer severe memory loss, Aβ deposition, inflammation and loss of cholinergic neurons and α7 nAChRs. The deposition of Aβ in the brain starts before MCI, and increases with age. Therefore, tropisetron could potentially prevent the onset of AD if administered during or before the onset of MCI.

Figure 2. Schematic diagram of the proteolytic events and cleave products associated with APP and possible mechanistic action of tropisetron in the prevention of AD

Amyloid precursor protein (APP) is metabolized by a membrane-associated protease, α-secretase, and this cleavage releases the extracellular amino-terminal ectodomain of APP (APPSα), which displays trophic properties. The alternative cleavage pathway involves two sequential cleavages by β- and γ-secretase and gives rise to a series of amyloid-β (Aβ). Accumulating evidence suggests that interaction between Aβ peptides and α7 nAChRs is integral to the pathology of AD. The interaction between Aβ peptides and α7 nAChRs might induce Aβ deposition and inflammation in the brain, resulting in the loss of cholinergic neurons and α7 nAChR. These neurotoxic events may promote cognitive decline, followed by MCI, and

ultimately lead to AD. In combination with an α7 nAChR agonist and serotonin 5-HT_3 receptor antagonist, tropisetron, binds to APP, with a sub-micromolar affinity. The interaction of tropisetron with 5-HT_3 receptors also plays a role in the anti-inflammatory and neuroprotective effect against Aβ-induced neurotoxicity. Taken together, tropisetron could act as a potential therapeutic drug for AD, if be administered during the period of MCI or early stages of AD.

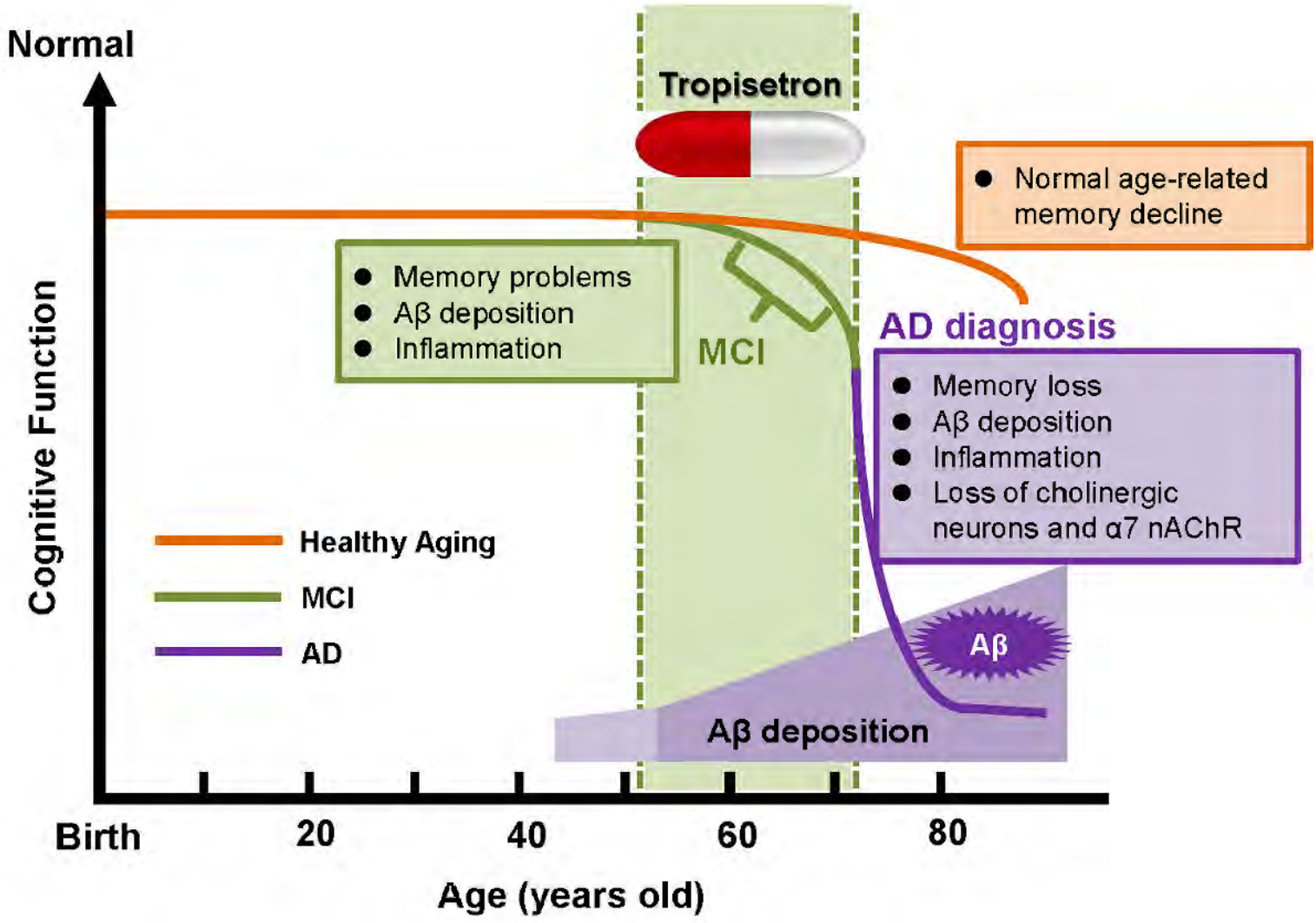
Normal
Tropisetron
Normal age-related memory decline
Memory problems
Aβ deposition
Inflammation
MCI
AD diagnosis
Memory loss
Aβ deposition
Inflammation
Loss of cholinergic neurons and α7 nAChR
Cognitive Function
Healthy Aging
MCI
AD
Aβ
Aβ deposition
Birth
20
40
60
80
Age (years old)

Figure 1

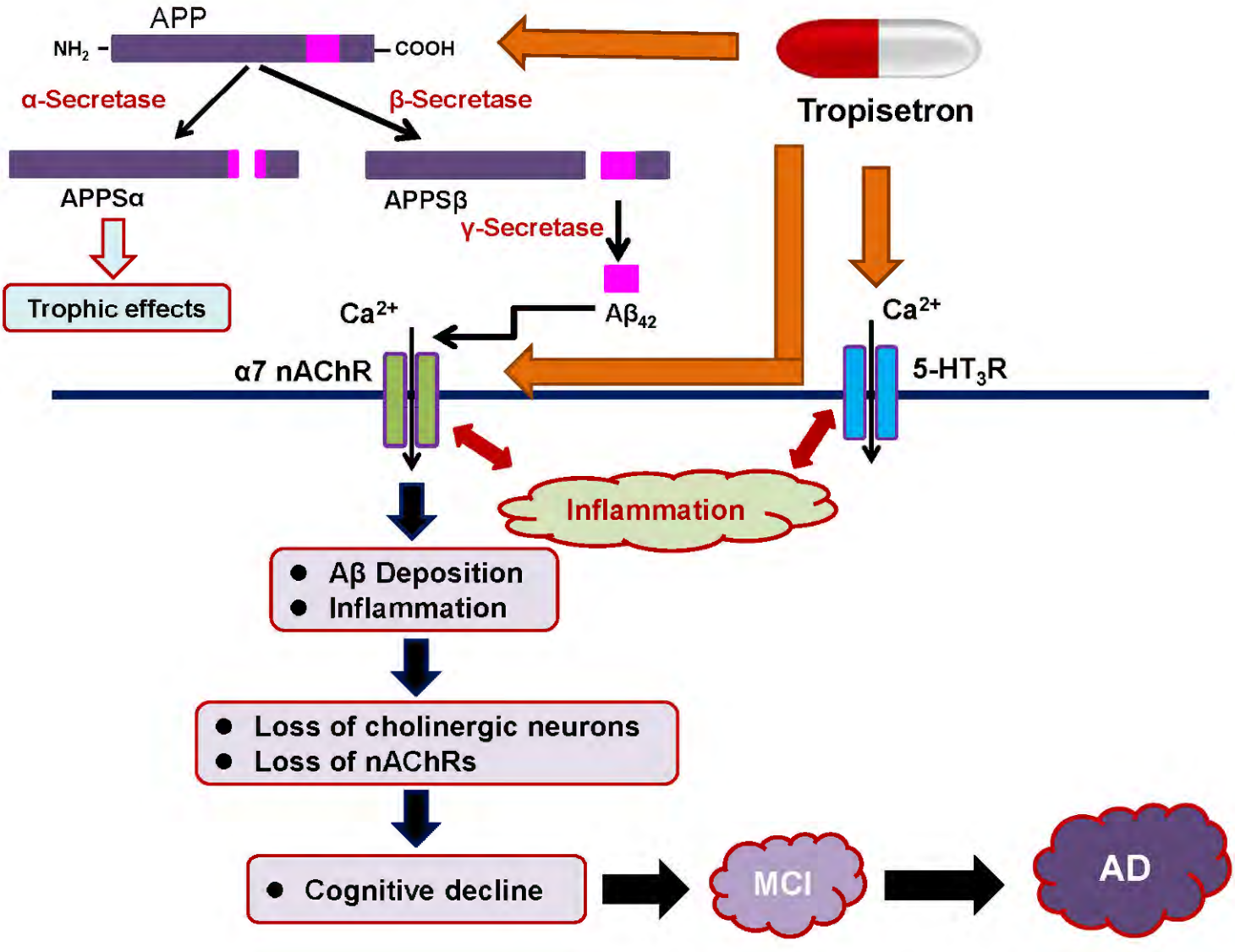
APP
NH2
COOH
α-Secretase
β-Secretase
Tropisetron
APPSα
APPSβ
γ-Secretase
Trophic effects
Ca2+
Aβ42
Ca2+
α7 nAChR
5-HT3R
Inflammation
Aβ Deposition
Inflammation
Loss of cholinergic neurons
Loss of nAChRs
Cognitive decline
MCI
AD

Figure 2