● PERSPECTIVE

Cholinergic receptor, nicotinic, alpha 7 as a target molecule of Arctic mutant amyloid β

Alzheimer's disease (AD) is a progressive cognitive disorder that develops predominantly in elderly patients and is characterized by cognitive impairments affecting memory, learning, and attention (Selkoe, 2002). As the prevalence of AD is increasing concurrently with an increase in the aging demographic of society, the elucidation of its cause and underlying developmental mechanisms, as well as the development of preventive and therapeutic methods are eagerly awaited. Pathological features of AD include the appearance of senile plaques and neurofibrillary tangles throughout the cerebral cortex. Senile plaques appear to precede neurofibrillary tangles and are considered to be closely involved in the pathogenesis of AD. It is believed that the major constituent of senile plaques is amyloid β protein (Aβ), which then self-aggregates, forming the senile plaques (Mattson, 2004).

Point mutations associated with familial AD (FAD) are frequently observed at amino acid residues 22 and 23, which are present in the Aβ internal turn structure. Among them, the Aβ E22G mutation (termed the Arctic mutation) was originally characterized as being associated with a purely cognitive phenotype typical of AD, with Arctic Aβ accumulating in the brain parenchyma (Nilsberth et al., 2001). In the initial study of its mechanism, research focused on the aggregation pattern of Aβ. It was first reported that Arctic Aβ tends to form protofibrils, which are intermediate forms of Aβ aggregates (Nilsberth et al., 2001). However, the detailed molecular mechanisms such as the target molecules involved in signal transduction remained unknown.

The nicotinic acetylcholine receptor (Cholinergic receptor, nicotinic, alpha 7 (CHRNA7)) is known as a candidate gene target in schizophrenia. It is a cholinergic receptor that regulates the homeostasis of intracellular calcium ions in neurons (Bertrand et al., 1993; Séguéla et al., 1993). It has been shown that the activation of CHRNA7 is neuroprotective (Qi et al., 2007; Liu et al., 2012). Furthermore, one study showed that Aβ42 binds to CHRNA7 as a ligand (Wang et al., 2000). Further, it has also been previously reported that knockout of CHRNA7 in an AD pathological model mouse, in which deposition of Aβ occurs, can prevent learning and memory impairment (Dziewczapolski et al., 2009). These data indicate that CHRNA7 plays an important role in AD pathology.

We have previously sought to elucidate the mechanism of FAD onset by clarifying the binding between Arctic Aβ and CHRNA7 and the subsequent effect on the physiological functions of CHRNA7 (Ju et al., 2014). We confirmed that Aβ40 does not bind to CHRNA7, whereas Arctic Aβ40

specifically binds to CHRNA7 with high affinity. In addition, it was confirmed that aggregation of Arctic Aβ40 was enhanced in the presence of CHRNA7. We overexpressed CHRNA7 in CHO-K1 cells in order to examine the influence of Arctic Aβ40 on calcium ion permeability. Indeed, Arctic Aβ40 suppresses the function of CHRNA7, inhibiting elevation of intracellular calcium ion, and subsequent activation of extracellular-signal-regulated kinase (ERK 1/2) induced by nicotine. These results suggest that Arctic mutant Aβ40 aggregates converge on CHRNA7 receptors and inhibit their functions (Ju et al., 2014). Recently, we conducted a follow-up study, focusing on the neuroprotective effect of CHRNA7 (Ju et al., 2017). We specifically investigated whether Arctic Aβ40 affects the neuroprotective function of CHRNA7. We confirmed the neuroprotective function of CHRNA7 against oxidative stress using SH-SY5Y cells; when Arctic Aβ was added to SH-SY5Y cells overexpressing CHRNA7, the neuroprotective effect mediated by CHRNA7 was suppressed. Furthermore, in order to investigate the influence on downstream signals, the activity of the signaling pathway relating to the neuroprotective function
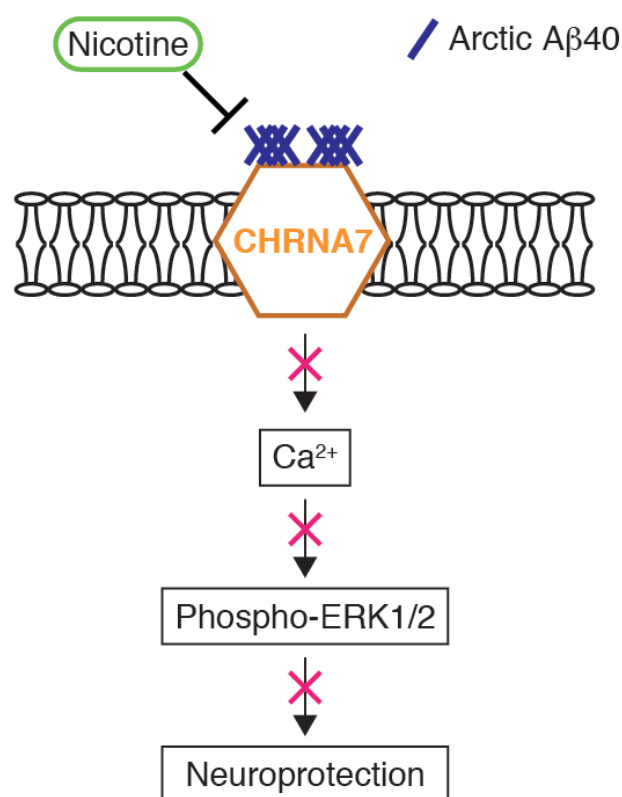

Figure 1 Schematic representation of the influence of Arctic Aβ40 on the physiological functions of CHRNA7.
CHRNA7: Cholinergic receptor, nicotinic, alpha 7; Aβ: amyloid β protein; ERK1/2: extracellular-signal-regulated kinase.

of CHRNA7 was investigated. Only ERK1/2 was activated by nicotine, and this activation was suppressed by adding Arctic Aβ40. Finally, we demonstrated that activation of ERK1/2 is involved in the neuroprotective action of CHRNA7 against oxidative stress by administering a selective inhibitor (PD98059) of MAPK/ERK kinase (MEK). These results suggest that Arctic mutant Aβ40 aggregates converge on CHRNA7 and inhibit their neuroprotective functions (Ju et al., 2017) (**Figure 1**).

Taken together, our studies demonstrate new findings on the interaction between Arctic Aβ40 and CHRNA7 in AD, and the influence of Arctic Aβ40 on the function of CHRNA7 from a neurochemical and mechanistic point of view (Ju et al., 2014, 2017). We anticipate that these finding will help to elucidate the molecular mechanisms underlying AD pathology, as well as be useful in the search for substances that inhibit the binding of Arctic Aβ and CHRNA7, ultimately contributing to the prevention and treatment of AD. Another function of CHRNA7 in neurons is in the molecular mechanisms of memory. Activation of CHRNA7 is involved in long-term potentiation in glutamatergic synapses (Mansvelder and McGehee, 2000). Therefore, it will be important to investigate the influence of Arctic Aβ on the biological function of CHRNA7, focusing the molecular mechanisms of memory, and clarifying the underlying mechanisms of AD.

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Accepted: 2018-05-31

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