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Invited review

Dysfunctional synapse in Alzheimer's disease – A focus on NMDA receptors

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ABSTRACT

Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly. Alterations capable of causing brain circuitry dysfunctions in AD may take several years to develop. Oligomeric amyloid-beta peptide (Aβ) plays a complex role in the molecular events that lead to progressive loss of function and eventually to neurodegeneration in this devastating disease. Moreover, *N*-methyl-D-aspartate (NMDA) receptors (NMDARs) activation has been recently implicated in AD-related synaptic dysfunction. Thus, in this review we focus on glutamatergic neurotransmission impairment and the changes in NMDAR regulation in AD, following the description on the role and location of NMDARs at pre- and post-synaptic sites under physiological conditions. In addition, considering that there is currently no effective ways to cure AD or stop its progression, we further discuss the relevance of NMDARs antagonists to prevent AD symptomatology. This review posits additional information on the role played by Aβ in AD and the importance of targeting the tripartite glutamatergic synapse in early asymptomatic and possible reversible stages of the disease through preventive and/or disease-modifying therapeutic strategies.

This article is part of the Special Issue entitled 'The Synaptic Basis of Neurodegenerative Disorders'.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and the most prevalent neurodegenerative disease in the elderly population, affecting almost 40 million people worldwide. AD progression has been associated with a gradual damage in function and structure in the hippocampus and neocortex, the vulnerable brain areas used for memory and cognition. AD is characterized by synaptic loss, abnormal amyloid-beta peptide (Aβ) processing of Aβ precursor protein (APP) and hyperphosphorylation of tau, a microtubule associated protein. High levels of intracellular Aβ and the accumulation of the secreted form are believed to be central causative factors for AD (reviewed by Ferreira et al., 2010). Tau was shown to interact with APP both *in vitro* and *in vivo* (Barbato et al., 2005) and $A\beta_{1-42}$ aggregates promote *in vitro* tau aggregation in a dose-dependent manner (Rank et al., 2002), suggesting a direct link between senile plaques and neurofibrillary tangles in AD.

AD has been associated with an impairment of cholinergic terminals, which appear largely vulnerable, followed by glutamatergic terminal dysfunction and finally by the lesion of the somewhat more resilient GABAergic terminals (Bell and Claudio, 2006). The fact that glutamate is the principal excitatory neurotransmitter in the brain areas mainly affected in AD is in accordance with the impairment in glutamate neurotransmission that occurs in this disease. Thus, the ionotropic glutamate receptor subtype *N*-methyl-D-aspartate (NMDA) (described in Section 3) has been implicated in memory function and is believed to be involved in AD progression. In fact, recent findings posit that Aβ induces an increase in cytosolic calcium levels that may underlie mitochondrial calcium dyshomeostasis and ultimately damage the neurons, namely by activating NMDA receptors (NMDARs) (reviewed by Ferreira et al., 2010).

2. Synaptic dysfunction in AD

In its most incipient clinical form, early symptoms of AD like confusion and loss of episodic and working memory can be postulated to be due to network disconnections produced by

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oligomeric forms of Aβ (reviewed by Selkoe, 2002). Concordantly, synaptic dysfunction was observed in Tg2576 mice presenting early increased Aβ levels (Calkins et al., 2011; Tamagnini et al., 2012).

Synapses are the fundamental units of information transfer and storage in the brain, composed of pre- and postsynaptic compartments. Synapse transmission, or neurotransmission, consists in the release of neurotransmitters, which in turn bind and activate receptors located at postsynaptic or presynaptic sites. The role of glial cells has been also recognized, giving rise to the concept of a tripartite synapse organization (Fig. 1). In fact, astrocytes may respond to neuronal activity through an elevation of internal Ca^{2+} concentration, which further leads to the release of neurotransmitters able to cause feedback regulation of neuronal activity and synaptic efficacy (Araque et al., 1999). Thus, neurotransmission implicates functional pre- and post-synaptic sites, as well as operational astrocytes.

Functional synapses require active mitochondria, which are mainly involved in the generation of energy (ATP and NAD^{+}), regulation of cell signaling and calcium homeostasis. It was reported that synaptic mitochondria are more susceptible to Ca^{2+} overload than nonsynaptic mitochondria (Brown et al., 2006). Accordingly, Du et al. (2010) identified differences in synaptic *versus* nonsynaptic mitochondrial properties and function of mitochondrial populations isolated from AD transgenic mice brain overexpressing the human mutant form of APP and Aβ (Du et al., 2010). In this study, synaptic mitochondria from young transgenic mice showed an increase in Aβ accumulation, increased mitochondrial permeability transition, a decline in both respiratory function and activity of cytochrome c oxidase, as well as increased mitochondrial oxidative stress. In AD patients, oxidative stress markers were demonstrated to correlate with Mini-Mental Status Examination scores; importantly, oxidative stress was more localized to the synapses, with levels increasing in a disease-dependent manner (Ansari and Scheff, 2010). However, recent findings showed that intrinsic bioenergetic capacities, including respiration, calcium handling, and transmembrane potentials were maintained in presynaptic nerve terminals isolated from different symptomatic AD mouse models (J20, Tg2576, and APP/PS), when compared with age-matched controls (Choi et al., 2012).

2.1. Aβ at presynaptic level and glial cells

Recent studies link the defects in function of presynaptic boutons associated with presynaptic protein dysfunction to the etiology of several neurodevelopment and neurodegenerative diseases, including AD (reviewed by Waites and Garner, 2011). On the other hand, Aβ may exert a physiological function at the presynaptic terminal, as the peptide may be essential for neurotransmitter release (Puzzo et al., 2011). Nevertheless, a brief exposure to a very low concentration of Aβ resulted in impairment of long term potentiation (LTP) produced by presynaptic defects (Russell et al., 2012). Morphological and biochemical synaptic changes associated with aging may contribute to exacerbate the damaging effects of Aβ, particularly at presynaptic level (Quiroz-Baez et al., 2013),

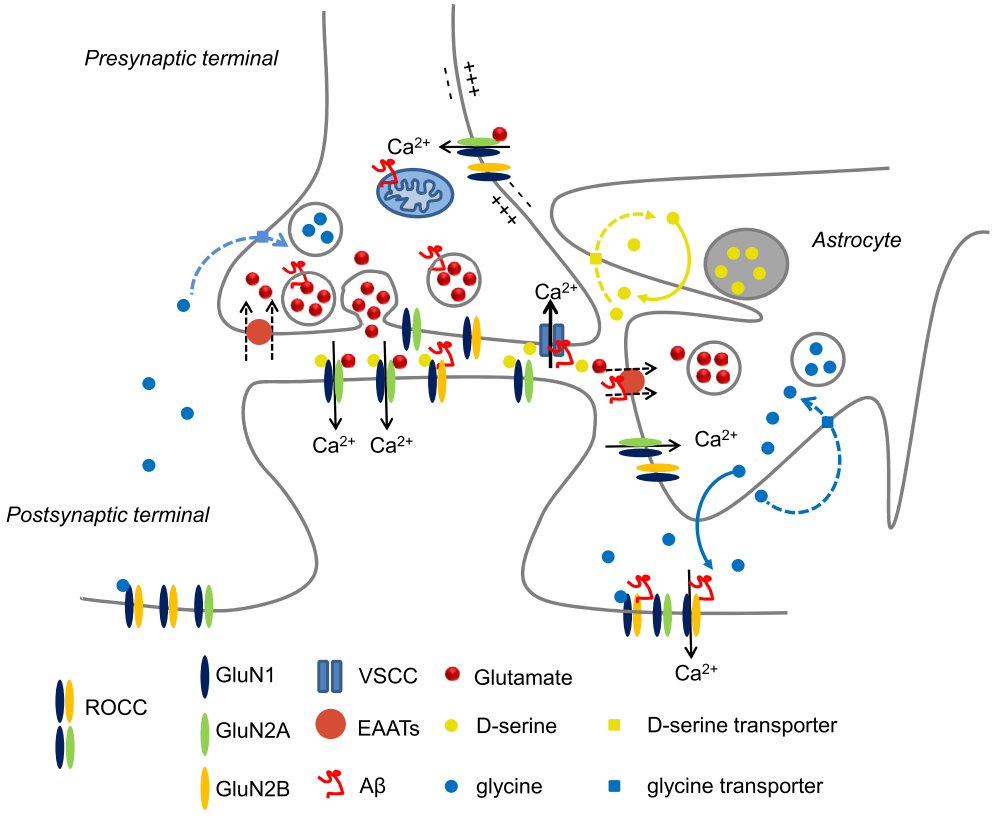

Fig. 1. Tripartite glutamatergic synapse – a target for Aβ. Upon presynaptic neuron stimulation achieved by Ca2+ entry through voltage-sensitive calcium channels or by presynaptic or perisynaptic receptor-operated calcium channels (e.g. namely NMDARs), released glutamate can activate NMDARs localized in the postsynaptic membrane (synaptic stimulation) leading to Ca^{2+} entry through the NMDARs and the propagation of the action potential. Glutamate can then be taken up by surrounding astrocytes through EAAT1/2 or by the presynaptic terminal through EAAT2/5, and then stored into vesicles (reviewed by Corlew et al., 2008), precluding excitotoxicity. In conditions of excessive glutamate release or impairment of clearance, namely due to the presence of Aβ, bulk extracellular glutamate concentration increases, leading to extrasynaptic NMDARs activation. The differential activation (synaptic *versus* extrasynaptic) can also be modulated by glycine released from neurons and/or astrocytes (Muller et al., 2009) or D-serine released by astrocytes (Kang et al., 2013). Note that both glycine and D-serine can also be taken up by the presynaptic terminal or astrocytes by their respective transporters. The figure shows potential intracellular and extracellular targets for Aβ.