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# Metabotropic glutamate receptors: the potential for therapeutic applications in Alzheimer's disease

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A dysfunction of glutamate signaling is implicated at several levels in the pathogenesis of Alzheimer's disease. Currently, metabotropic glutamate receptors, which have a wide distribution in the central nervous system and activate a multitude of cell signaling pathways, are pursued as targets for therapeutic intervention in Alzheimer's disease. Research is still limited, but results underscore the relevance of ongoing studies. Here we discuss the latest updates regarding metabotropic glutamate receptors and their role in Alzheimer's disease, as well as promising metabotropic glutamate receptor ligands that have been investigated in preclinical models of Alzheimer's disease.

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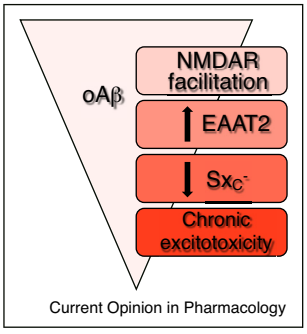
## Introduction

Alzheimer's disease (AD) is an incurable dementing illness affecting about 33 million people worldwide (WHO, 2015), with numbers estimated to double every 20 years. The failure in treating AD is because, in 95% of the cases, the disease cannot be related to any particular gene or event (the so-called sporadic AD). Age is the main risk factor for sporadic AD, with a variety of minor genetic and life-style-related risk modifiers contributing to the overall disease risk [1]. Major advances in disease understanding started in the 80s, with the isolation of β-amyloid (Aβ) from the extracellular senile plaques of the AD brain and the identification of tau as the main component of intracellular neurofibrillary tangles of the AD brain (reviewed in [2••]). To date, the neuropathological evidence of senile plaques and neurofibrillary tangles is necessary for the diagnosis of proved AD, whereas biomarkers of Aβ brain deposition (e.g. PET amyloid imaging) and tau pathology (e.g. elevated CSF tau) enhance the specificity of lifetime diagnosis of AD [3]. Although many aspects of AD pathogenesis remain enigmatic, heritable forms of AD (3–5% of all cases) point to Aβ accumulation as one critical event [2••]. In familiar AD, mutations of genes coding for the amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) exalt Aβ production, particularly of the long form of the peptide (Aβ1-42), which is prone to aggregate into the senile plaques through intermediate pathogenic steps (i.e. oligomeric and fibrillary aggregates) [2••]. A counter-example exists of a rare genetic mutation that reduces the risk of developing AD by altering the coding sequence of Aβ and reducing Aβ production [4]. Aβ derives from the proteolysis of APP (a cell transmembrane protein) via cleavage by β-secretase 1 (BACE) and the γ-secretase protein complex, which includes a presenilin as catalytic unit [5] (the so-called *amyloidogenic pathway*). An alternative APP cleavage by α-secretase (the *non-amyloidogenic pathway*) precludes the formation of Aβ and produces, instead, a soluble extracellular APP fragment (sAPPα), endowed with many putative beneficial functions [5]. Aβ produced within the amyloidogenic pathway is not necessarily harmful [6], ranging from a soluble functional monomeric state [7•] to a toxic build-up of neurotoxic oligomeric species [8]. Soluble Aβ oligomers are thought to drive AD progression trough tau, which is required for microtubule disassembly, impaired synaptic activity and ectopic cell cycle re-entry of adult neurons [9].

While Aβ and tau lead AD pathology, other players intervene in the disease progression by reducing neuronal resilience to stressors and shaping the regional selectivity of neuronal loss [10]. Among these, glutamate figures primarily. Nearly all excitatory neurons of the central nervous system (CNS) are glutamatergic and at least half of the nerve endings release glutamate. Glutamate receptors are found in both neuronal and glial cells, and comprise ionotropic glutamate (iGlu) receptors (including NMDA, AMPA and kainate receptors) and metabotropic glutamate (mGlu) receptors. Owing to a high $Ca^{2+}$ permeability and a topographical distribution that correlates with tangles and plaques [11], NMDA receptors have been seen as pre-eminent mediators of damage to glutamatergic-innervated neurons in AD [12]. Aβ impairs the

**Figure 1**




Overactivation of the glutamatergic system in Alzheimer's disease. Aβ oligomers (oAβ) render neurons more sensitive to excitotoxicity via a facilitation of NMDA receptor (NMDAR) currents. The increase of extracellular glutamate via a downregulation of EAAT2 and an upregulation of the system $x_c^-$ contributes to the overall chronic excitotoxicity.

ability of glycogen synthase kinase-3 (GSK-3) inhibitors or silencers to suppress NMDA currents [13], and increases extracellular glutamate via the up-regulation of the microglia cysteine/glutamate antiporter system, $x_c^-$ [14], and the down-regulation of the astrocyte glutamate transporter, EAAT2 [15] (Figure 1). Evidence obtained in transgenic mouse models of AD (i.e. mice carrying mutations of FAD-linked genes) also supports a role for a decreased glutamate uptake capacity [16•] and an increased glutamate release [17] in the AD brain. The use of the NMDA channel blocker, memantine, for the symptomatic treatment of AD, though of limited therapeutic value, has renewed interest in how glutamate intervenes in AD pathogenesis. Here, we will focus on mGlu receptors and their potential usefulness as targets for drug intervention in AD.

## mGlu receptors: brain distribution and signaling

mGlu receptors are G protein-coupled receptors (GPCRs) that, following activation, regulate both G protein-dependent and independent signaling pathways [18]. Eight mGlu receptor subtypes have been identified (from mGlu1 to mGlu8) and classified into three subgroups (from I to III) according to sequence homology, cell signaling activation and agonist selectivity. Group I mGlu receptors (mGlu1 and mGlu5) are functionally linked to polyphosphoinositide (PI) hydrolysis, and negatively coupled with $K^+$ channels [19]. Both group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7 and mGlu8) negatively regulate adenylate cyclase, but can activate mitogen-activated protein (MAP) kinase and PI-3-kinase pathways [20,21].

Group I mGlu receptors are widely expressed throughout the brain and are mostly postsynaptic, with a perisynaptic location surrounding iGlu receptors [22]. Both group II and group III mGlu receptors are mostly located at presynaptic elements, acting to inhibit glutamate and GABA release [23]. Among group II and group III receptors, mGlu3 and mGlu7 are the most widely expressed ones [24,25], whereas mGlu2, mGlu4 and mGlu8 receptors are expressed in restricted brain areas [26–28] and mGlu6 is present in the retina [29].

Coming to the native cellular location, all mGlu receptor subtypes are present in neurons; mGlu3 and mGlu5 receptors are also found in astrocytes, whereas mGlu2, mGlu3, and mGlu5 receptors are expressed in microglial cells [30]. In some cases, two different mGlu receptors are co-expressed in the same neurons (e.g. mGlu1 and mGlu5 in striatal neurons) [31] and even co-localized (e.g. mGlu7 and mGlu8 at the presynaptic terminal of GABAergic interneurons) [32], suggesting the existence of functional heteromers and/or receptor heterodimers. Accordingly, mGlu receptor dimerization is required for activation by glutamate [33]. While native mGlu receptors were first described as homodimers [34], at least in recombinant cells, intragroup heterodimers can form within each mGlu receptor group. Moreover, group II and group III mGlu receptor subtypes may associate with each other into functional intergroup heterodimers, but not with mGlu1 or mGlu5 receptors [35]. Noteworthy, the existence of mGlu2-4 heterodimers in native neurons has been demonstrated recently [36•]. mGlu receptors can also form heteromeric complexes with other GPCRs, including serotonin 5-HT2A, dopamine D2, μ-opioid and adenosine receptors, enabling a direct allosteric interaction between subunits of two different GPCRs and the potential for biased signaling (i.e. the activation of some but not all the signaling pathways linked to a receptor) (reviewed in [37]). Hence, the molecular complexity of mGlu receptors appears, at once, a challenge for pharmacological modulation and an opportunity for therapeutic intervention in a variety of CNS disorders.

Currently, a number of ligands to allosteric sites of mGlu receptors are available, which can modulate glutamate response in positive (positive allosteric modulators, PAMs) negative (negative allosteric modulators, NAMs) or neutral ways (neutral allosteric ligands (NALs)). Allosteric ligands (ALs) are highly subtype-selective (as opposed to orthosteric ligands), and could exhibit functional diversity (i.e. they could trigger a biased signaling) [37]. Some of these ALs have been investigated in preclinical models of AD.

## Group I mGlu receptors in AD

The best correlate of cognitive impairment in AD patients is the loss of synapses [38]. Similarly, synaptic dysfunction coincides with the onset of memory deficits in mouse models of AD in the absence of frank neuronal loss [39]. Group I mGlu receptors are involved in different forms of experience-dependent synaptic plasticity,