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Review

Glutamatergic Dysfunctioning in Alzheimer's Disease and Related Therapeutic Targets

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Abstract. The impairment of glutamatergic neurotransmission plays an important role in the development of Alzheimer's disease (AD). The pathological process, which involves the production of amyloid-β peptides and hyperphosphorylated tau proteins, spreads over well-delineated neuroanatomical circuits. The gradual deterioration of proper synaptic functioning (via GluN2A-containing N-methyl-D-aspartate receptors, NMDARs) and the development of excitotoxicity (via GluN2B-containing NMDARs) in these structures both accompany the disease pathogenesis. Although one of the most important therapeutic targets would be glutamate excitotoxicity, the application of conventional anti-glutamatergic agents could result in further deterioration of synaptic transmission and intolerable side-effects. With regard to NMDAR antagonists with tolerable side-effects, ion channel blockers with low affinity, glycine site agents, and specific antagonists of polyamine site and GluN2B subunit may come into play. However, in the mirror of experimental data, only the application of ion channel blockers with pronounced voltage dependency, low affinity, and rapid unblocking kinetics (e.g., memantine) and specific antagonists of the GluN2B subunit (e.g., ifenprodil and certain kynurenic acid amides) resulted in desirable symptom amelioration. Therefore we propose that these kinds of chemical agents may have therapeutic potential for present and future drug development.

Keywords: Alzheimer's disease, glutamate excitotoxicity, kynurenic acid amides, memantine, neurodegeneration, neuroprotection, therapy

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, the main clinical feature of which is dementia [1, 2]. Indeed, AD is the most common type among dementia syndromes [3] and is responsible for 60–80% of the cases [4], leading to a considerable socioeconomic burden. Although clinical diagnosis can be determined during the disease course in most cases, currently autopsy is necessary for a definite diagnosis. The main pathological hallmark of AD is the presence of neurofibrillary tangles (NFTs) and senile plaques in specific brain areas [5]. With regard to the involvement of dysfunctional neurotransmission in disease pathogenesis, certain cholinergic and glutamatergic systems are the most affected [6, 7].

The aim of this short review is to highlight aspects of glutamatergic dysfunction in AD and to discuss some possibilities of pharmaceutical interventions by targeting the glutamatergic system.

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ALTERATIONS IN GLUTAMATERGIC SIGNALING IN ALZHEIMER'S DISEASE: PATHOLOGICAL BASIS

With regard to the sensitivity and specificity for the diagnosis of AD, the Braak staging system [5] gives the best accuracy (79%) among the neuropathological criteria systems [8]. This system classifies AD into stages mainly by the temporal evolution of NFTs (composed of intracellular aggregates of hyperphosphorylated tau protein), but it also takes into account the loci of extracellular amyloid-β (Aβ) deposits in the brain. The system distinguishes between the following stages: transentorhinal/entorhinal (stage I, II), limbic (stage III, IV), and neocortical (stage V, VI). This classification shows a good correlation with the severity of dementia [9], though originally the pathological stages were established by Braak irrespective of the clinical stage of the dementia. Certain neuropathological investigations have special significance in the assessment of early stages of AD [10]. The most important ones include the assessment of NFTs in the neurons of the second layer of the entorhinal cortex in the slices of the inferior temporal lobe. The entorhinal cortex receives converging polysynaptic glutamatergic inputs from the multimodal association cortices and limbic areas including the hippocampal formation, while it projects into the hippocampal formation and back to the association cortices [11–13]. One of the main efferent glutamatergic projections of the entorhinal cortex is the perforant pathway, which predominantly originates from the second layer and serves as the main excitatory input of the hippocampal formation. The fourth layer of the entorhinal cortex in turn receives excitatory input from the hippocampal formation. A significant decrease was observed in the neuronal number of the fourth and especially the second layers of the entorhinal cortex in clinically very mild AD [14]. Another study likewise demonstrated a considerable decrease in neuronal number and volume of the entorhinal cortex (especially the second layer) and those of the cornu ammonis (CA)1 region of the hippocampus in preclinical AD cases [15]. It is important to mention that the presence of NFTs can also be observed in these early stages in the CA1-subiculum part of the hippocampal formation and in the perirhinal cortex, inferior temporal gyrus, amygdala, posterior part of the parahippocampal gyrus, the cholinergic basal forebrain and in the dorsal raphe nuclei, but in a lesser extent compared to the second layer of the entorhinal cortex [16]. In the next stages, almost all the limbic structures, notably the hippocampal formation (consisting of the dentate gyrus, the hippocampus proper, and the subiculum) and the amygdala become considerably damaged [17] in addition to the more expressed involvement of the previously described brain structures. As partially mentioned above, the main glutamatergic input of the hippocampal formation comes from the second (toward the dentate gyrus) and the third (toward the subiculum and CA1 sector of the hippocampus proper) layers of the entorhinal cortex via the perforant and temporo-alvear pathways [18]. Scheff et al. [19] hypothesized that synaptic loss in the outer molecular layer (OML) of the dentate gyrus would be responsible for the transition from mild cognitive impairment to early AD. Total synaptic counts in the OML had a significant negative correlation with NFT density in the entorhinal cortex. Although there was a negative correlation between the individual's Braak score and total synaptic number in the OML, this association was not significant and furthermore, this study did not find significant correlation of Braak staging with the scores of any of the applied psychometric tests. However, a high positive correlation of total synaptic number in the OML with the values of tests of cognitive functions such as the Mini-Mental State Examination and delayed memory recall (one of the most sensitive measures of hippocampal function) was demonstrated, which suggests that synaptic loss would be one of the strongest predictive factors for cognitive decline. As a part of the trisynaptic circuit, the information is transmitted further from the dentate gyrus via intrahippocampal association pathways (via mossy fibers toward the CA3 sector of the hippocampus, and then via Schaffer collaterals toward the CA1 sector) [20]. The synaptic loss can also be observed in the CA1 sector of the hippocampus in mild AD cases [21]. The pyramidal cells of the CA1 sector predominantly innervate the subiculum, which projects to the pre/parasubiculum (parts of the subicular complex which also receives neocortical inputs likewise the entorhinal cortex), the amygdala, the fourth layer of the entorhinal cortex, the anterior and midline thalamic and mammillary nuclei (via the fornix) [22]. Regarding further parts of the Papez circuit, the information processes from the mammillary nuclei to the anterior thalamic nuclei (via the mammilothalamic tract) and further to the cingulated gyrus (via the anterior thalamic radiation) and to the presubiculum (via the cingulum), which projects to the fourth layer of the entorhinal cortex [23]. The pre/parasubiculum also send minor projections to the dentate gyrus [24]. It is important to mention that parts of the hippocampal formation in the two hemispheres

are strongly interconnected via commissural fibers. The amygdaloid complex, which consists of distinct nuclei, receives inputs from multiple brain regions via several kinds of transmitter systems, including glutamatergic pathways [25]. The major sources of sensory and polymodal information to the amygdala are certain parts of the cerebral cortex, including the association and prefrontal cortices [26]. The amygdala also forms reciprocal and strong connections with areas related to long-term declarative memory system, including the perirhinal and entorhinal cortices and the hippocampal formation [27]. Furthermore, the amygdaloid complex has widespread projections to certain cortical, subcortical, and brainstem structures [25]. The key feature of advanced stages of AD (stage V-VI) is the occurrence of severe destruction of neocortical association areas [28, 29]. Although NFT pathology only becomes expressed in advanced stages of AD in neocortical areas, the alteration in the level of some molecular markers of synaptic dysfunctioning can be observed even in early stages of AD. Accordingly, vesicular glutamate transporter (VGLUT)1 expression is found to be decreased in the prefrontal, parietal and occipital and inferior temporal cortices, while it was unaltered in the lateral temporal cortex [30–32]. With regard to the murine models of AD, a significant reduction of VGLUT1 was observed in both the frontal cortex and the hippocampus [33, 34]. The expression of VGLUT2 and synaptophysin was altered only in the prefrontal cortex in human AD cases [30]. Loss of VGLUT1 and VGLUT2 in the prefrontal cortex correlated with cognitive status even at early phases of cognitive decline [30]. Although the typical spreading of neuropathological alterations over the above-mentioned glutamatergic structures with strong connections (Fig. 1) can be well observed in most cases, limbic-predominant and hippocampal-sparing subtypes of AD cases were also reported [35].

ALTERATIONS IN GLUTAMATERGIC SIGNALING IN ALZHEIMER'S DISEASE: MOLECULAR BASIS

The main culprits responsible for the disconnection of the previously delineated glutamatergic networks would be the Aβ peptide and the tau protein [36]. $A\beta_{1\text{-}42}$ aggregates are capable of inducing tau hyperphosphorylation [36] and promote *in vitro* tau aggregation in a dose-dependent manner [37]. In addition to NFTs, soluble tau also would have neurotoxic properties [38]. Aβ can influence glutamatergic neurotransmission in several ways. Although under physiological concentrations, endogenous Aβ is necessary for proper neurotransmitter release [39], in excess it weakens synaptic transmission affecting the synaptic vesicle pools [40]. Accordingly, Aβ is co-localized in glutamatergic boutons immunoreactive for VGLUT1 and VGLUT2 in postmortem AD brains [41]. Furthermore, soluble Aβ oligomers induce the disruption of dendritic spines, resulting in severe neuropil damage [42]. The degeneration of synapses and dendritic spines is one of the earliest feature of AD [43]. Glutamatergic synapses contain α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and N-methyl-D-aspartate receptors (NMDARs) localized on dendritic spines. The basal synaptic transmission is mainly mediated by AMPARs. However, in view of receptor dysfunction in AD, the NMDAR would be the major site of Aβ action, and in turn, NMDAR activation enhances Aβ production [44]. A conventional NMDAR is composed of two glycine or D-serine-binding GluN1 and 2 glutamate-binding GluN2 (A-D) subunits, forming a heterotetramer. The GluN1 subunits form the ion channel, while the GluN2 subunits have more of a regulatory and refining role. It has been shown that the GluN2B subunit-containing NMDARs predominate at the extrasynaptic site [45], which preferential localization becomes more predominant by the phosphorylation at Tyr1336 [46]. Oligomeric Aβ promotes Fyn kinase activation via binding to the post-synaptic prion protein (PrP^C), resulting in the increased phosphorylation of the GluN2B subunits at Tyr1472 [47]. This activation induces altered NMDAR localization with destabilization of dendritic spines and the loss of surface NMDARs. It is important to mention that several other receptors are regulated by PrP^C, including metabotropic glutamate receptor (mGluR) 1 and 5 [48]. The available data suggest that the activation of NMDARs at the synaptic site promotes neuronal survival, while activation at the extrasynaptic site mediates neurotoxic effects [49]. However, some recent findings suggest that the simultaneous activation of synaptic NMDARs are also necessary for the initiation of cell death program [50]. So in brief, the inactivation of glutamatergic synaptic transmission and the activation of that at the extrasynaptic sites would both accompany the pathomechanism of AD. Oligomeric Aβ impairs long-term potentiation (LTP; a form of synaptic strengthening following brief, high frequency stimulation [51]) and enhances long-term depression (LTD; a form of synaptic weakening following low frequency stimulation

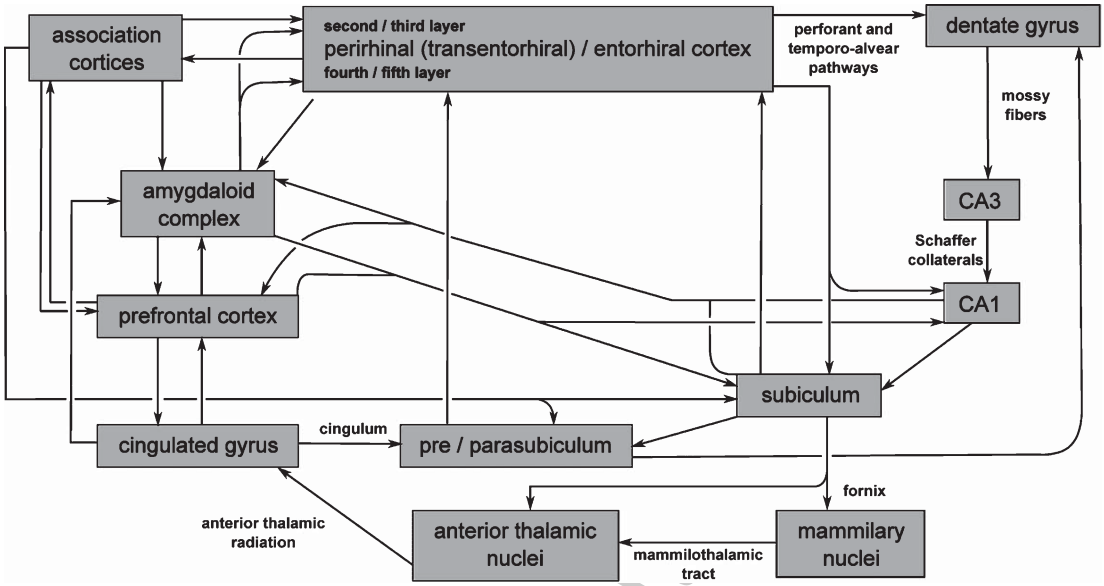

Fig. 1. The schematic depiction of the predominant connections between the affected glutamatergic brain areas in Alzheimer's disease. (CA, cornu ammonis).

or synaptic inactivity [52]) and the depotentiation of LTP, thereby causing synaptic dysfunctioning [53, 54]. Oligomeric Aβ-induced internalization of synaptic AMPARs and NMDARs [55, 56] and non-apoptotic caspase activation [57] both accompany LTD enhancement. Although several forms of synaptic plasticity depend on NMDAR-driven calcium flux [58], some recent data indicate that Aβ-mediated synaptic AMPAR depression requires NMDAR activation in a metabotropic manner, i.e., without ion flow via the NMDAR [59]. NMDARs also have an important role in spontaneous glutamate release-induced depression of evoked neurotransmission, thereby influencing synaptic efficacy as well [60]. In addition to the demonstrated alteration of glutamatergic neurotransmission via postsynaptic and extrasynaptic NMDARs in AD, recent experimental data provide increasing evidence of the involvement of presynaptic NMDARs in the enhancement of timing-dependent LTD, resulting in impaired memory functions, which phenomenon may have implications in the development of cognitive decrement in AD [61–63]. With regard to caspase-3 activation, the increased activity of the pyramidal neurons of the entorhinal cortex, the subiculum, and the CA1-3 sector of the hippocampus was found in early stages of AD [64]. The second layer of the entorhinal cortex showed the highest activity. Aβ accumulation activates NMDARs at early stages of AD [65], and *in vitro* studies suggest that this activation might be mediated by GluN2B-containing NMDARs [66]. It has been also demonstrated that NMDARs are connected to neuronal nitric oxide synthase by a scaffolding protein PSD-95 (postsynaptic density protein of molecular weight 95 kDa), which binds to the GluN2B subunit of the NMDAR [67]. Thus, PSD-95 would have an important role in the evocation of downstream excitotoxic events mediated by GluN2B subunit-containing NMDARs via the production of nitric oxide in an excessive amount [68]. Recent data indicate that the activation of NMDARs by $A\beta_{1\text{-}42}$ may be secondary to its binding to postsynaptic anchoring proteins such as PSD-95 [42]. Extrasynatptic NMDAR activation triggers the increased production of Aβ due to the shift of amyloid β-protein precursor (AβPP) production from AβPP695 to Kunitz protease inhibitory domain-containing isoforms with higher amyloidogenic potential [69]. This kind of positive feedback leads to the formation of a vicious circle [70]. GluN2B-mediated neurotransmission also seems to be involved in tau-induced neurotoxicity [71]. Tau phosphorylation causes tau mislocalization and subsequent synaptic impairment as phosphorylated tau can accumulate in dendritic spines, where it may affect the synaptic trafficking and/or anchoring of glutamate receptors [72]. The interaction of tau with fyn targets fyn to dendritic spines, where it can exert the above-mentioned phosphorylation of GluN2B subunit of NMDAR, thereby enhancing the excitotoxic process [73]. In addition to its neuronal effects, Aβ also downregulates glutamate uptake capacity of astrocytes and thereby induces a

dysfunctional extracellular glutamate clearance [74]. Besides the elevated levels of glutamate in the extracellular space, the presence of an energy impairment, as a consequence of mitochondrial dysfunction and oxidative stress, would be another causative factor in glutamate excitotoxicity, which leads to a partial membrane depolarization resulting in relief of the Mg^{2+} blockade of the NMDAR channel and calcium overload [75].

THERAPEUTIC APPROACHES TARGETING THE GLUTAMATERGIC NEUROTRANSMISSION SYSTEM WITH A SPECIAL VIEW OF NMDA RECEPTORS IN ALZHEIMER'S DISEASE: PITFALLS AND POSSIBILITIES

The application of agents that completely block NMDAR activity has limited usefulness due to severe clinical side-effects such as hallucinations, agitation, memory impairment, catatonia, nausea, vomiting, a peripheral sensory disturbance, and sympathomimetic effects such as increased blood pressure [76, 77]. In order to achieve neuroprotection by targeting the NMDARs in AD, the best therapeutic strategy could be the normalization of synaptic GluN1/GluN2A activity and the abolishment of excitotoxicity mediated by extrasynaptic GluN1/GluN2B subunits. In view of NMDAR antagonists with tolerable side-effects, ion channel blockers with lower affinity, glycine site agents as well as specific antagonists of the polyamine site or the GluN2B subunit may come into play (Fig. 2) [78]. Memantine (3,5-dimethyladamantan-1-amine) is a low affinity open channel blocker, which preferentially antagonizes excessively activated NMDARs without affecting physiological NMDAR activity [79]. Accordingly, this substance has recently been demonstrated to selectively target mainly GluN2B-containing extrasynaptic NMDARs [80], i.e., it is three times more potent in the inhibition of calcium influx via GluN1/GluN2B than via GluN1/GluN2A subunit-containing NMDARs [81]. Furthermore, memantine concentration-dependently inhibited the expression of Kunitz protease inhibitory domain-containing AβPP isoforms as well as neuronal production and release of Aβ [69, 82]. Accordingly, memantine is a widely applied medicament in the treatment of moderate-advanced stages of AD with beneficial effects as regards language, memory, praxis, and communication dysfunction as well as the activities of daily living [83]. Although memantine has some potential side-effects such as somnolence, weight gain, confusion, hypertension, nervous system disorders, and falling [84], to date this is the only commercially available NMDAR antagonist in the treatment of AD. In summary, the good effect/side-effect profile would be explained by its pronounced voltage dependency, low affinity, and rapid unblocking kinetics, properties which make the restoration of the desired signal-to-noise ratio in glutamatergic neurotransmission available [85].

Kynurenic acid (KYNA; produced by kynurenine aminotransferases, KATs), a side-product of the main pathway of the tryptophan metabolism, can influence glutamatergic neurotransmission at several levels [86], and exerted neuroprotective effects in several paradigms [86–90]. On the one hand, KYNA can exert wide-spectrum endogenous antagonism of ionotropic excitatory amino acid receptors [91], mainly targeting the strychnine-insensitive glycine-binding site on the GluN1 subunit of the NMDA receptor [92]. This action requires relatively high (~10–20 μM) concentrations of KYNA under physiological conditions [93]; the basal extracellular concentration of KYNA in rats (15–23 nM) [94, 95] is far below the required level to directly interfere with glutamate receptor functions. Accordingly, only excessive elevation of the KYNA level could be accompanied by adverse effects in rats, such as reduced exploratory activity, ataxia, stereotypy, sleeping, and respiratory depression, while there was only a slight effect on the learning ability [96]. However, human postmortem analyses revealed elevated levels of KYNA in the striatum and hippocampus of AD patients [97], alteration of which is suggested to accompany to the cognitive dysfunction in AD rather than to exert a compensatory protective role. Accordingly, the achievement of lowering brain KYNA levels by knocking out one of its producing enzyme (KAT II) resulted in the improvement of cognitive functions in mice [98]. With regard to the mechanisms of influencing glutamatergic transmission, on the other hand, KYNA non-competitively blocks the alpha7-nicotinic acetylcholine receptors [99], thereby inhibiting glutamate release at the presynatptic site [100]. This blockade can be effective at high nanomolar concentrations (IC_{50} = ~7 μM), and can also influence hippocampus-dependent cognitive functions [101]. In addition to the multiplex receptor antagonism, recent studies showed that KYNA is capable of facilitating AMPA receptor responses in nanomolar concentrations [102, 103]. The significance of this phenomenon is not really known yet.

The selective inhibition of GluN2B subunit-containing NMDARs could be another successful

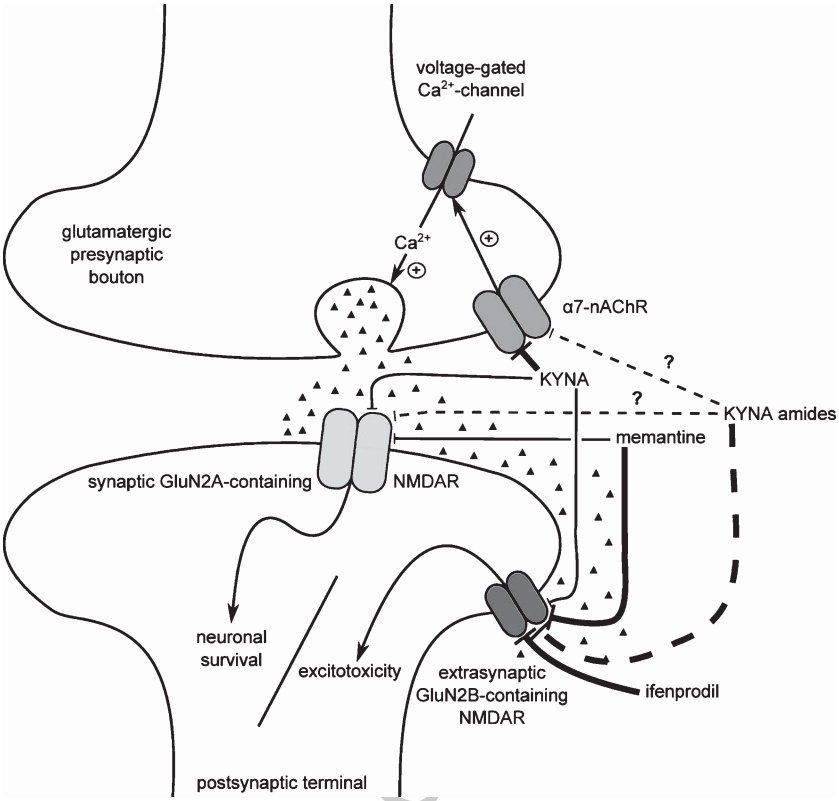

Fig. 2. Some possibilities of influencing glutamatergic dysfunctioning in Alzheimer's disease. (α7-nAChR, alpha7-nicotinic acetylcholine receptors; KYNA, kynurenic acid; NMDAR, N-methyl-D-aspartate receptor; ▲, glutamate, the thickness of the lines represents the extent of inhibition, while dashed lines refers to possible mechanism of action).

strategy in the amelioration of neurodegenerative processes [104]. Ifenprodil (α-(4-hydroxyphenyl)-β-methyl-4-benzyl-1-piperidineethanol) is a synthetic negative allosteric modulator of such of receptors, with relatively high affinity (IC_{50} = ~150 nM) [105]. Ifenprodil binding seems to interact with polyamine binding in a negative allosteric manner, i.e., it can inhibit the potentiation of NMDAR currents evoked by certain polyamines [106, 107]. It has a considerably good side-effect profile: only mouth dryness, nausea, headache, and palpitations were observed. Accordingly, several derivatives, including Ro 25-6981 ([R-(R*,S*)]-α-(4-hydroxyphenyl)-β-methyl-4-benzyl-1-piperidinepropanol), have been synthesized with the aim of presenting lead compounds in pharmaceutical development in the field of neurodegenerative disorders [104]. With regard to AD, Aβ-induced endoplasmic reticulum and oxidative stress was prevented by ifenprodil [108]. Furthermore, this substance and Ro 25-6981 also prevented the Aβ-mediated inhibition of LTP in rodent hippocampal slices [109–112]. Indeed, Ro 25-6981 abolished LTD enhancement and learning impairment in rats as well [113]. Evotect's EVT 101, another GluN2B antagonist which has been shown to penetrate into the human brain, was well tolerated in a double-blind, 4-week phase Ib study (http://www.evotec.com).

A possible pharmaceutical modification of KYNA is amidation at the carboxyl moiety [114, 115]. The resulting KYNA amides may be of special interest since they have been shown to preferentially act on GluN2B subunit-containing extrasynaptic NMDARs [116]. This feature may also offer the opportunity to establish an extracellular concentration that is capable of inhibiting the tonic extrasynaptic NMDAR currents without impairing synaptic glutamatergic neurotransmission. Accordingly, one of the KYNA amide compounds synthesized by our group, N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride exerted protective effects both in the four-vessel occlusion model of cerebral ischemia (rats; [117]) and in the N171-82Q transgenic mouse model of HD [118].

Finally, in addition to directly influencing NMDARs, it is important to mention that there are some indirect regulators of NMDAR functioning, targeting of which can be used as alternative therapeutic approaches in the amelioration of glutamatergic dysfunction in AD. These targets include some metabotropic glutamatergic receptors [119] and certain adenosine receptors [120, 121].

CONCLUSION

Although more and more details are being revealed regarding the pathomechanism of AD, the recent therapeutic strategies are restricted only to few pharmaceutical agents. The glutamatergic system is presumed to be the major altered neurotransmitter system in AD; therefore, there is a great need for the development of pharmakons targeting this system with acceptable side-effect profile. From this respect, ion channel blockers with lower affinity as well as GluN2B subunit specific antagonists might be the most promising candidates for future AD therapy. Although the present short review focused on the possibilities of therapeutic amelioration via targeting the glutamatergic neurotransmission system with special attention to NMDARs, it should be noted that achieving neuroprotection in AD—especially in terms of 'synaptoprotection'—is a complex issue, with pharmacological targets and approaches we could not detail here, but have already been comprehensively discussed by others [122, 123].

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