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Review

Metabotropic glutamate receptors and neurodegenerative diseases

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ABSTRACT

Glutamate is the most important excitatory neurotransmitter of the mammalian central nervous system (CNS), playing an important role in memory, synaptic plasticity and neuronal development. However, glutamate overstimulation is also implicated in neuronal cell death. There are two major types of glutamate receptors: ionotropic and metabotropic. Thus far, eight metabotropic glutamate receptors (mGluRs) subtypes have been characterized and are divided into three subgroups based on sequence homology and cell signaling activation. mGluRs activate a wide variety of cell signaling pathways by G protein-coupled pathways or via G protein-independent cell signaling activation. Moreover, these receptors exhibit widespread distribution in the CNS and are implicated in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). This review aims to discuss the latest updates concerning mGluRs and their role in neurodegenerative diseases. mGluRs agonists and antagonists as well as positive and negative allosteric modulators have been tested in several animal models of neurodegenerative diseases. Furthermore, mGluR knockout mouse models have been crossed to mouse models of AD and HD, providing important data about mGluRs role in neurodegenerative disease progression. Thus, mGluRs constitute potential therapeutic targets for the development of therapies to treat neurodegenerative diseases.

Contents

Abbreviations: AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid; Aβ, amyloid β peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; BDNF, brain derived neurotrophic factor; BF, basal forebrain; CGA, chromogranin A; CNS, central nervous system; DAG, diacylghycerol; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; GIRK, inward rectifying K^+ channels; GP, globus pallidum; GPe, globus pallidum externa; GPCR, G protein-coupled receptors; HD, Huntington's disease; htt, huntingtin; $InsP_3$, inositol-1,4,5-triphosphate; L-DOPA, 3,4-dihydroxyphenylalanine; L-AP4, L-2-amino-4-phosphonobutyric acid; L-SOP, O-Phospho-L-serine; LTD, long-term depression; LTP, long-term potentiation; LID, L-DOPA-induced dyskinesia; MAPK, mitogen activated protein kinases; mGluR, metabotropic glutamate receptor; NAM, negative allosteric modulator; MPEP, 2-Methyl-6-(phenylethynyl)pyridine; MSN, medium-sized spiny neurons; MTEP, 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine; mTOR, *mammalian target of rapamycin*; NGF, nerve growth factor; NMDA, N-Methyl-D-Aspartate; PAM, positive allosteric modulator; PD, Parkinson's disease; PDK1, phosphoinositide-dependent kinase; PIKE, PI3K enhancer; PI3K, phosphoinositide 3-kinase; PLCβ1, phospholipase Cβ1; PKC, protein kinase C; PLA_2, phospholipase A_2; PLD, phospholipase D; PPG, (R,S)-4-phosphonophenylglycine; PrPc, cellular prion protein; Pyk2, SNc substantia nigra pars compacta; SNr, substantia nigra pars reticulata; Src, -dependent activation of proline-rich tyrosine kinase 2; STN, subthalamic nucleus; STEP, striatal-enriched protein tyrosine phosphatase; TGFβ, transforming growth factor β.

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1. Introduction

Glutamate is the most important excitatory neurotransmitter of the mammalian central nervous system (CNS), playing an important role in memory, synaptic plasticity and neuronal development. However, glutamate overstimulation is also implicated in neurodegeneration [1,2]. There are two major types of glutamate receptors: ionotropic and metabotropic. Ionotropic glutamate receptors, including N-Methyl-D-Aspartate (NMDA), α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) and kainate receptors, are ligand-gated ion channels that promote rapid excitatory neurotransmission [3]. Metabotropic glutamate receptors (mGluRs) are family C G protein-coupled receptors (GPCRs) that, following stimulation, promote Gα-βγ uncoupling, leading to Gα-mediated increases in intracellular second messenger levels, βγ regulation of ion channels, as well as stimulation of G protein-independent pathways [4–7]. mGluRs form constitutive dimers composed of two subunits cross-linked by a disulphide bridge and dimer formation is crucial for mGluRs function [8]. Thus far, eight mGluR subtypes have been identified and characterized and are divided into three subgroups based on sequence homology and cell signaling activation [5,6,9]. mGluR1 and mGluR5 are part of Group I mGluRs and couple to $G\alpha_{q/11}$, promoting the release of Ca^{2+} from intracellular stores (Fig. 1) [10,11]. mGluR2 and mGluR3 belong to Group II and mGluR4, mGluR6, mGluR7 and mGluR8 are part of Group III mGluRs [6]. Both Group II and Group III mGluRs negatively regulate adenylyl cyclase via $G\alpha_i$ and are mostly localized presynaptically, acting as autoreceptors to inhibit glutamate or gamma-aminobutyric acid (GABA) release (Fig. 1) [12]. Group I mGluRs are mostly located at postsynaptic elements in a perisynaptic zone surrounding the ionotropic receptors, where they function to modulate neuronal excitability [13–16].

2. Brain distribution of mGluRs

Group I mGluRs are extensively expressed throughout the brain. High levels of mGluR1 are found in neurons of the cerebellar cortex, olfactory bulb, lateral septum, globus pallidus, entopeduncular nucleus, ventral pallidum, magnocellular preoptic nucleus and thalamic nuclei [17–19]. mGluR5 expression is mostly observed in the telencephalon, especially in the cerebral cortex, hippocampus, subiculum, olfactory bulb, striatum, nucleus accumbens and lateral septal nucleus [13,20,21]. Moreover, mGluR5 is also strongly expressed in the superficial dorsal horn of the spinal cord [22–24]. mGluR2 is only expressed in restricted brain substrates, including the cerebellar cortex and olfactory bulb [25,26]. On the other hand, mGluR3 is expressed extensively throughout the CNS, especially in the olfactory tubercle, cerebral cortex, dentate gyrus, lateral septal nucleus, striatum, nucleus accumbens, amygdaloid nuclei, substantia nigra pars reticulata and cerebellar cortex [27–31]. mGluR7 is the Group III mGluR that is most extensively expressed throughout the brain, whereas mGluR6 is mainly restricted to the retina [32,33]. mGluR4 and mGluR8 are also expressed only in restricted brain areas. mGluR4 is most intense in the cerebellum and is also found in certain areas of the olfactory bulb, cerebral cortex, hippocampus, lateral septum, septofimbrial nucleus, striatum, thalamic nuclei, lateral mammillary nucleus, pontine nuclei and dorsal horn [29,34–38]. mGluR8 expression is observed in the olfactory bulb, certain regions of the cerebral cortex, pontine nuclei and lateral reticular nucleus of the medulla oblongata [39–41].

mGluRs are mainly expressed in neuronal cells, although mGluR3 and mGluR5 are also vastly expressed in glial cells throughout the brain [26–30,36,42–45]. Notably, mGluR3 and mGluR5 expression was shown to be up-regulated in reactive astrocytes [46–48]. In a small proportion (10%) of cultured astrocytes obtained from the spinal cord, mGluR1 receptors have been detected [49]. Moreover, although one study has reported mGluR4 expression in primary cultured cortical astrocytes [50], others have not [44,51]. It has also been shown that cultured microglia express mGluR2, mGluR3, mGluR4, mGluR5, mGluR6 and mGluR8 [44,52–54]. To investigate differences in cell type gene expression in the cortex, Zhang et al., 2014 have purified neurons, astrocytes, microglia, and various maturation states of oligodendrocytes from mouse cortex and used RNA-Seq to generate a high-resolution transcriptome database [55]. Results obtained from this gene wide analysis indicate that mGluR1 and mGluR2 are mainly expressed in neurons, whereas mGluR6 is expressed to the same extent in neurons, astrocytes, oligodendrocytes and microglia. mGluR4, mGluR7 and mGluR8 are more expressed in neurons, but are also expressed in oligodendrocyte precursor cells and newly formed oligodendrocytes. Interestingly, this study indicates that mGluR3 is almost exclusively expressed in astrocytes and that mGluR5 is more expressed in astrocytes than in neurons in the cortex.

3. mGluR cell signaling

Group I mGluRs are coupled to the activation of $G\alpha_{q/11}$ proteins, stimulating phospholipase Cβ1 (PLCβ1) and the formation of diacylghycerol (DAG) and inositol-1,4,5-triphosphate ($InsP_3$), which triggers the release of Ca^{2+} from intracellular stores through the activation of $InsP_3$ receptors (Fig. 1C). DAG remains at the plasma membrane and, together with Ca^{2+}, leads to the activation of protein kinase C (PKC), which has been proposed to activate phospholipase D (PLD), phospholipase A_2 (PLA_2) and mitogen activated protein kinases (MAPKs), as well as to modulate a variety of ion channels [56]. PKC activation via mGluR5 leads to stimulation of NMDAR by increasing open probability of the channel [57]. Interestingly, PKC activation can trigger PKC-mediated mGluR5 desensitization, which can be reversed by NMDAR-dependent activation of calcineurin, a Ca^{2+}-dependent phosphatase [58]. Moreover, mGluR1 can also upregulate NMDAR currents in cor-