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Type 1 metabotropic glutamate receptor and its signaling molecules as therapeutic targets for the treatment of cerebellar disorders

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Neurodegenerative diseases such as spinocerebellar ataxias and autoantibody-associated disorders of the central nervous system often affect the cerebellum, resulting in motor deficits. Recent studies have revealed that most of these disorders impair type 1 metabotropic glutamate receptor (mGluR1) and/or the closely associated signaling molecules in cerebellar Purkinje cell. Since the signaling pathway triggered by mGluR1 activation in Purkinje cell plays a pivotal role in coordinated movements and motor learning, pharmacological repair of aberrant mGluR1 signaling in Purkinje cell is critical for mitigation of cerebellar symptoms. Here we review recently identified pathophysiology underlying the neurodegenerative and autoimmune diseases affecting mGluR1 signaling in Purkinje cell and possible therapeutic interventions.

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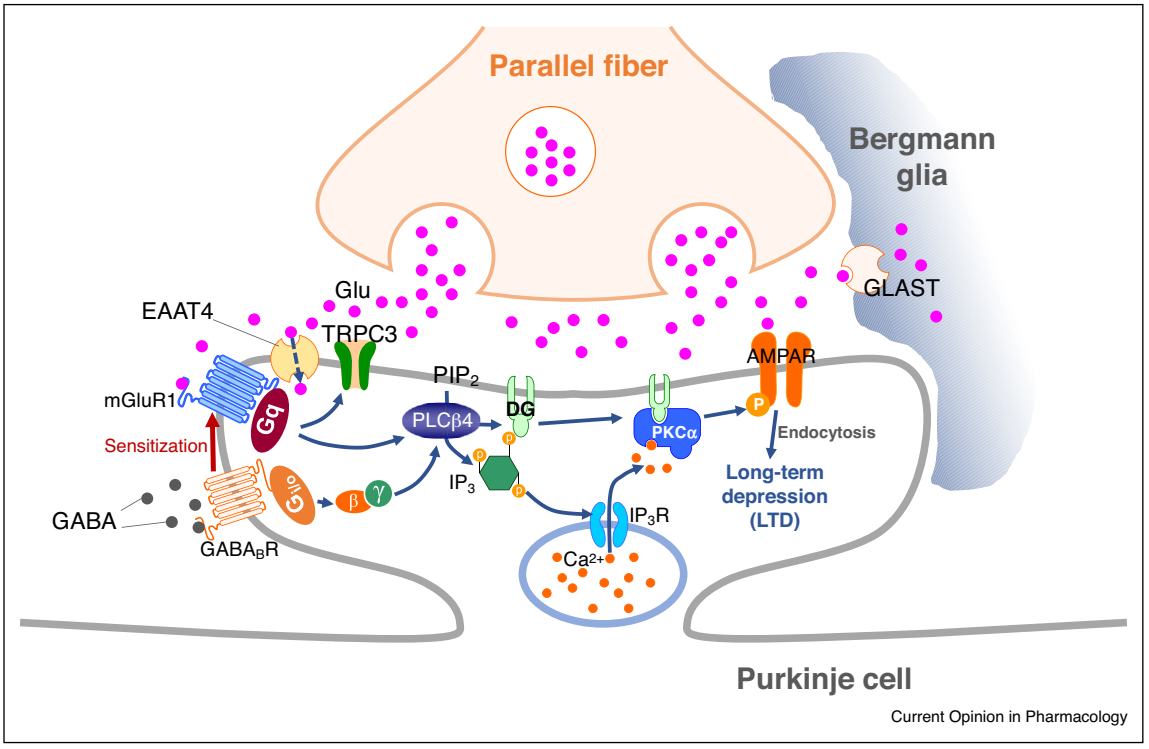
Introduction

Each Purkinje cell in the cerebellum receives two distinct excitatory inputs from numerous (more than one hundred thousand) parallel fibers and only one climbing fiber: each parallel fiber forms one or two synaptic contacts on each of the spines emerging from the dendritic branchlets, while a single climbing fiber makes several hundreds of synapses on the relatively proximal dendritic regions. Glutamate is released from presynaptic terminals of parallel fibers and a climbing fiber to the synaptic clefts and activates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors (Figure 1, see right side), which mediates fast synaptic transmission. The type 1 metabotropic glutamate receptor (mGluR1), which is one of the two members of group 1 mGluR and is known to be essential for various aspects of Purkinje cell functions [1,2], is richly expressed at perisynaptic sites of dendritic spines receiving parallel fiber inputs (Figure 1, left side). Normally, glutamate released from parallel fibers cannot reach mGluR1 since Bergmann glial processes ensheathing the synaptic clefts quickly take up the majority of glutamate via the glial glutamate transporter GLAST (Figure 1, right side). However, repetitive activation of parallel fibers releases large amount of glutamate which surpasses the uptake capacity, causes glutamate to spill over from the synaptic clefts, and allows it to access and activate mGluR1 (Figure 1).

Upon binding of glutamate, mGluR1 activates Gq protein and phospholipase Cβ4 (PLCβ4) (or presumably phospholipase Cβ3 (PLCβ3)), leading to the production of diacylglycerol (DG) and inositol 1,4,5-trisphosphate (IP_3) through hydrolysis of the membrane phospholipid. The IP_3 binds to the type 1 IP_3 receptor (IP_3R1) richly expressed on the endoplasmic reticulum (ER) of Purkinje cell, and triggers Ca^{2+} release from the internal stores, which, together with the DG, activates protein kinase C (PKC), a serine/threonine-protein kinase. Purkinje cells express two classical PKC isoforms, PKCγ and PKCα [3]. PKCγ is essential for pruning supernumerary climbing fibers from Purkinje cells during postnatal development [4], while PKCα plays a critical role in the expression of long-term depression (LTD) at parallel fiber–Purkinje cell synapses (Figure 1) [5•].

The DG, which is generated by PLCβ4 (or presumably PLCβ3) activation following mGluR1 stimulation or large Ca^{2+} influx through the membrane depolarization, is converted to the endocannabinoid 2-arachidonoylglycerol (2-AG) by DG lipase α. The 2-AG is released to extracellular space, and retrogradely binds to Gi/o protein-coupled cannabinoid CB_1 receptor present on the parallel fiber terminal, leading to transient suppression of glutamate release from there. This short-term synaptic plasticity initiated by mGluR1 activation or depolarization-induced Ca^{2+} influx is called synaptically evoked suppression of excitation (SSE) and depolarization evoked suppression of excitation (DSE), respectively [6,7]. In addition to the events above, mGluR1 activation triggers opening of transient receptor potential canonical 3

Figure 1



Regulation of mGluR1 signaling at parallel fiber–Purkinje cell synapses. Glutamate is released from parallel fiber terminals to the synaptic clefts, and activates postsynaptic AMPA receptors that mediate fast synaptic transmission. The released glutamate is primarily taken up by GLAST, a glutamate transporter localized on Bergmann glial processes. Residual glutamate is incorporated into Purkinje cells via EAAT4, a glutamate transporter localized adjacent to mGluR1, and thus, the extent of mGluR1 activation is suppressed. However, superfluous release of glutamate surpasses the uptake capacity, leading to activation of G_q protein-coupled mGluR1, which triggers slow synaptic transmission via opening of TRPC3, a non-selective cation channel. mGluR1 activation also produces DG and IP_3 from phosphatidylinositol 4,5-bisphosphate (PIP_2) via activation of PLCβ4 or presumably PLCβ3. IP_3 binds to IP_3R1 on the ER, which, in turn, triggers release of Ca^{2+} from the internal store. The released Ca^{2+} together with DG activates PKC. The activated PKCα phosphorylates the intracellular C-terminal region of the AMPA receptor, which initiates endocytosis of AMPA receptor, resulting in LTD of synaptic transmission. The $GABA_B$ receptor is closely associated with mGluR1, and augments the mGluR1 function.

(TRPC3), a non-selective cation channel (Figure 1), which is observed as slow excitatory postsynaptic currents (EPSCs) after repetitive parallel fiber stimulation in a whole cell-voltage-clamped Purkinje cell.

Around the postsynaptic membrane at parallel fiber to Purkinje cell synapses, B-type γ-aminobutyric acid ($GABA_B$) receptor, a Gi/o protein-coupled receptor for the inhibitory transmitter GABA, is expressed and closely associated with mGluR1 (Figure 1). Previous studies have shown that pharmacological activation (or inhibition) of the postsynaptic $GABA_B$ receptor increased (or decreased) amplitude of slow EPSCs in cerebellar slice preparation, and enhanced (or reduced) LTD of a glutamate-evoked current [2,8]. These results suggest that ambient GABA sensitizes mGluR1 via closely localized $GABA_B$ receptor, and pharmacological stimulation of $GABA_B$ receptor can further enhance the mGluR1 sensitization.

Pathophysiology underlying aberrant mGluR1 signaling in Purkinje cells

Disruption of retinoid-related orphan receptor α (RORα)-mediated transcription

RORα, which is most highly expressed in Purkinje cells [9], binds to the retinoic acid-related orphan receptor response element (RORE), and upregulates expression of multiple genes including *SLC1A6* encoding excitatory amino-acid transporter 4 (EAAT4), *ITPR1* encoding IP_3R1, and *PCP2/L7* encoding PcP2/L7 protein [10]. In addition to these genes, RORα is thought to be involved in mGluR1 expression, since *staggerer* mouse, which is a RORα loss of function mutant [11], showed significant reduction of mGluR1 expression in the cerebellum [12,13]. Indeed, patch clamp analysis using cerebellar slices from 3-week-old *staggerer* mice revealed almost complete loss of mGluR1 signaling such as slow EPSC and SSE with fast EPSC and DSE relatively preserved [12]. RORα makes a transcriptional complex with the