

PERSPECTIVES

Inhibition facilitates depressionRobert H. Cudmore^{1,2}, Jean-Marc Goiaillard^{1,2} and Dominique Debanne^{1,2}¹INSERM U641, Marseille, 13916 France²Université de la Méditerranée, Faculté de Médecine secteur nord, IFR 11, Marseille, 13916 France

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The release of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) and the subsequent activation of ligand-gated GABA_A receptors (GABA_AR) and G protein-coupled GABA_B receptors (GABA_BR) is generally thought to, as the name implies, inhibit neurons. On the postsynaptic side, the inhibition produced by GABA_BR activation is in part mediated by the opening of G protein-coupled inward rectifying potassium (GIRK) channels (Gähwiler & Brown, 1985). Functionally, synaptic activation of GABA_BR produces a long-lasting (~400 ms) window of inhibition in a large population of postsynaptic neurons when presynaptic neurons are coherently activated (Scanziani, 2000). A second function of GABA_BR is the presynaptic inhibition of neurotransmitter release at GABAergic and glutamatergic terminals. As a consequence of this presynaptic action, GABA_BRs have an influence on the gating of long-term potentiation (LTP) or long-term depression (LTD) in the hippocampus (Davies *et al.* 1991; Mott & Lewis, 1991; Wagner & Alger, 1995). Here, the spill-over of GABA produced by repetitive stimulation binds to GABA_BR to inhibit release of GABA during the conditioning and thereby suppresses the gating of LTP or LTD by inhibitory inputs.

Yet, outside hippocampus, the role of GABA_BR activation in the induction of synaptic plasticity remains largely an open question. In the cerebellum, the induction of parallel fibre LTD depends on the conjunctive glutamate-evoked activation of postsynaptic subtype 1 metabotropic glutamate receptors (mGluR1) and depolarization-evoked Ca²⁺ influx. By activating phospholipase C (PLC) and inducing subsequent release of internal calcium stores, mGluR1 provides an additional calcium influx that will reinforce

the activation of protein kinase C (PKC) by depolarization-evoked Ca²⁺ influx. mGluR1 and GABA_BR have different first order effectors (G_{q/11} and G_{i/o} protein activation, respectively) yet share many common downstream targets (e.g. IP₃R, PLC). An open question is if these common downstream targets endow postsynaptic GABA_BR with a functional role in the induction of LTD.

The exciting work of Kamikubo *et al.* (2007) in this issue of *The Journal of Physiology* shows that GABA_BR activation can facilitate LTD at the parallel fibre–Purkinje cell synapse of the cerebellum, thereby conferring a third major functional role to this receptor on the postsynaptic side (Fig. 1). This facilitation of LTD occurs via the activation of the $\beta\gamma$ subunits of the G_{i/o} protein which in turn activate PLC. This results in an augmentation of the mGluR1 response and an increase in postsynaptic Ca²⁺ via release from intracellular stores. Quite interestingly, in a study highly reminiscent of this it was shown that the induction of LTP at GABA_A synapses in hippocampus is gated by the cooperative activation of GABA_BRs and group I/II mGluRs via G-protein signalling and intracellular Ca²⁺ modulation (Patenaude *et al.* 2003). The similarity of these two studies might indicate that colocalization of GABA_BR and group I/II mGluRs is sufficient to obtain a cooperative effect of these receptors on synaptic plasticity (Hirono *et al.* 2001). The idea of cooperation between different G protein-coupled receptors and its role

in synaptic plasticity might be far more general than thought until now. Komatsu (1996) showed that the sign and magnitude of synaptic plasticity at cortical inhibitory synapses can be determined by the history of coactivation of GABA_BR and adrenergic or serotonergic receptors. Recently it was also shown that the magnitude and polarity of spike timing-dependent plasticity is determined not only by the timing between pre- and postsynaptic spikes but also by the recent activity of cholinergic and adrenergic neuromodulators (Seol *et al.* 2007).

With the discovery of spike timing-dependent plasticity emerged the idea that coincidence detection might be important for synaptic plasticity *in vivo*. By showing that coactivation of GABA and glutamate metabotropic receptors facilitates long-term synaptic plasticity in the cerebellum, the recent study from Kamikubo *et al.* (2007) brings the idea that coincidence of activation of several metabotropic pathways might also be needed *in vivo* to facilitate synaptic plasticity, or maybe even allow it. By studying the effect of coactivation of different receptor classes sharing common second messenger cascades, new rules for activity-dependent synaptic plasticity could emerge, and will probably reveal that synaptic plasticity relies on networks of proteins far more complex than is usually assumed.

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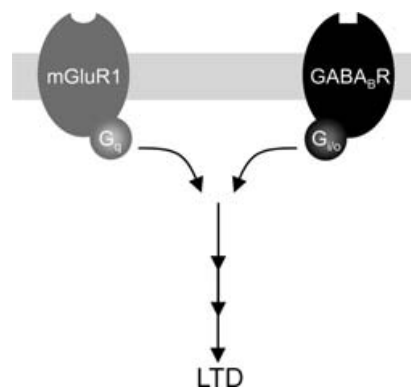


Figure 1. Co-activation of mGluR1 and GABA_BR facilitates induction of cerebellar LTD through the convergence of G_q and G_{i/o} signaling pathways