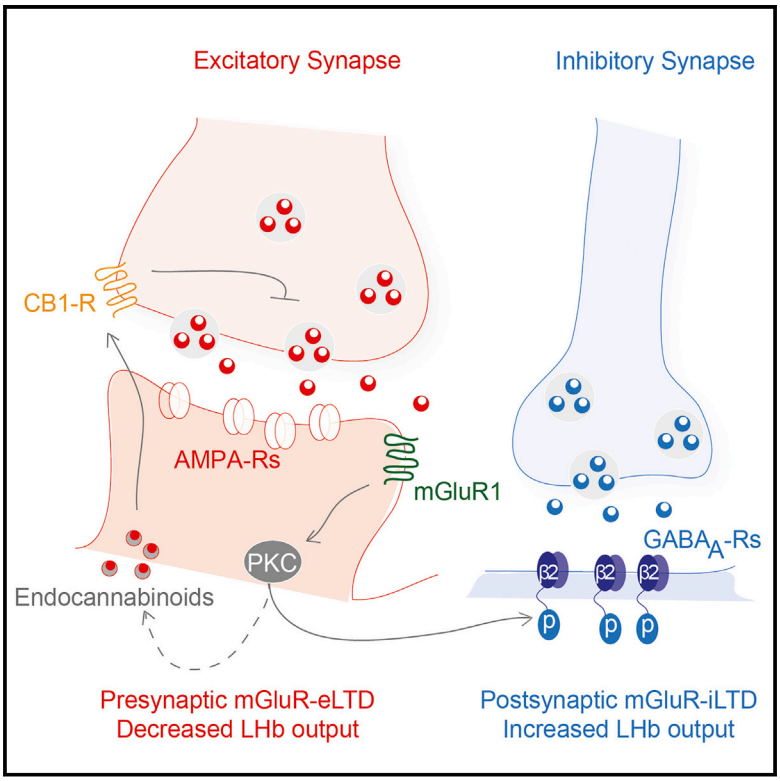
Report

Cell Reports

mGluR-LTD at Excitatory and Inhibitory Synapses in the Lateral Habenula Tunes Neuronal Output

Graphical Abstract



Authors

Kristina Valentinova, Manuel Mameli

Correspondence

manuel.mameli@inserm.fr

In Brief

Valentinova and Mameli show that mGluR1s in the lateral habenula (LHb) triggers PKC-dependent depression of excitatory and inhibitory transmission, allowing for bidirectional tuning of neuronal output via distinct presynaptic and postsynaptic mechanisms.

Highlights

- mGluR1 induces LTD of excitatory and inhibitory transmission in the LHb
- PKC mediates the induction of mGluR-LTD in the LHb
- Divergent expression mechanisms underlie mGluR-eLTD and -iLTD
- mGluR-eLTD and -iLTD decide the direction of LHb neuronal output

Valentinova & Mameli, 2016, Cell Reports *16*, 2298–2307
August 30, 2016
http://dx.doi.org/10.1016/j.celrep.2016.07.064

OPEN ACCESS
CellPress

Cell Reports
Report

mGluR-LTD at Excitatory and Inhibitory Synapses in the Lateral Habenula Tunes Neuronal Output

Kristina Valentinova[1,2,3] and Manuel Mameli[1,2,3,4,*]
[1]Institut du Fer à Moulin, 75005 Paris, France
[2]Inserm, UMR-S 839, 75005 Paris, France
[3]Université Pierre et Marie Curie, 75005 Paris, France
[4]Lead Contact
*Correspondence: manuel.mameli@inserm.fr
http://dx.doi.org/10.1016/j.celrep.2016.07.064

SUMMARY

Excitatory and inhibitory transmission onto lateral habenula (LHb) neurons is instrumental for the expression of positive and negative motivational states. However, insights into the molecular mechanisms modulating synaptic transmission and the repercussions for neuronal activity within the LHb remain elusive. Here, we report that, in mice, activation of group I metabotropic glutamate receptors triggers long-term depression at excitatory (eLTD) and inhibitory (iLTD) synapses in the LHb. mGluR-eLTD and iLTD rely on mGluR1 and PKC signaling. However, mGluR-dependent adaptations of excitatory and inhibitory synaptic transmission differ in their expression mechanisms. mGluR-eLTD occurs via an endocannabinoid receptor-dependent decrease in glutamate release. Conversely, mGluR-iLTD occurs postsynaptically through PKC-dependent reduction of β2-containing $GABA_A$-R function. Finally, mGluR-dependent plasticity of excitation or inhibition decides the direction of neuronal firing, providing a synaptic mechanism to bidirectionally control LHb output. We propose mGluR-LTD as a cellular substrate that underlies LHb-dependent encoding of opposing motivational states.

INTRODUCTION

Excitatory and inhibitory projections onto the lateral habenula (LHb) control the direction of neuronal output, contributing to the encoding of rewarding and aversive stimuli (Shabel et al., 2012, 2014; Stamatakis et al., 2013). Moreover, in rodent models of addiction and depression, glutamatergic and GABAergic synaptic plasticity modulates LHb neuronal firing, which is in turn instrumental for depression-like phenotypes (Lecca et al., 2016; Maroteaux and Mameli, 2012; Meye et al., 2015; Shabel et al., 2014). This highlights the behavioral relevance of synaptic adaptations in the LHb, heightening the need of understanding its underlying cellular processes.

Group I metabotropic glutamate receptor (mGluR) signaling and expression undergo modifications in disorders such as addiction and depression, disease states also characterized by aberrant LHb neuronal firing (Bellone and Mameli, 2012; Hovelsø et al., 2012; Lecca et al., 2014). Group 1 mGluRs consist of mGluR1 and mGluR5 subtypes (Lüscher and Huber, 2010). Their activation modulates the strength of excitatory and inhibitory synapses through G_q/G_{11}-mediated calcium mobilization and activation of downstream effectors, including protein kinase C (PKC) (Lüscher and Huber, 2010; Page et al., 2001). Pre- and postsynaptic mechanisms underlie mGluR-dependent long-term plasticity, but its relevance for controlling neuronal activity remains poorly understood (Galante and Diana, 2004; Kammermeier et al., 2000; Mameli et al., 2007).

We combine electrophysiology in LHb-containing acute slices with pharmacology and find that activation of mGluR1 receptors, but not of mGluR5, triggers long-term depression of excitatory and inhibitory synaptic transmission (mGluR-eLTD and mGluR-iLTD, respectively). mGluR-eLTD and -iLTD induction requires postsynaptic PKC signaling, but their maintenance relies on divergent expression mechanisms. mGluR-eLTD occurs via a presynaptic cannabinoid 1 receptor (CB1-R)-dependent decrease in glutamate release. In contrast, mGluR-iLTD is independent of presynaptic changes. Instead, mGluR-iLTD is postsynaptically expressed and requires PKC targeting onto $GABA_A$-R β2-subunits and a reduction in $GABA_A$-R single-channel conductance. The functional relevance of mGluR activation in the LHb is represented by opposing effects on neuronal output. Indeed, in the LHb, the mGluR-driven modulation of synaptic responses and output firing correlate positively. These data unravel the distinct molecular mechanisms underlying mGluR control of synaptic strength and the subsequent regulation of LHb neuronal activity.

RESULTS

mGluRs Drive Long-Term Synaptic Depression in the LHb

To examine the presence of group I mGluRs, we microdissected the LHb of mice and employed RT-PCR, which revealed mGluR1 and mGluR5 expression (Figure 1A). Accordingly, bath application (3–5 min) of the mGluR1/5 agonist