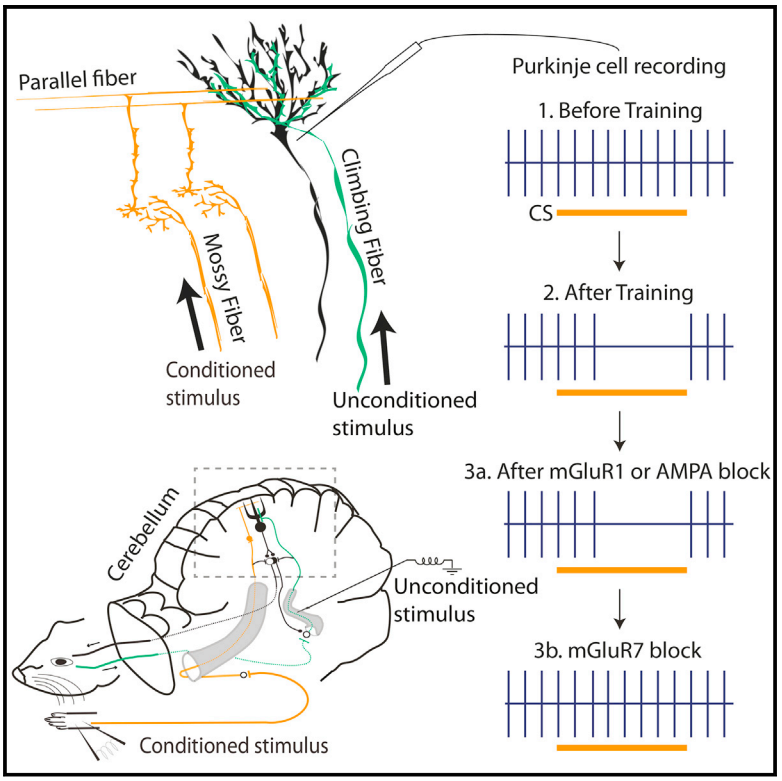
Report

Cell Reports

Activation of a Temporal Memory in Purkinje Cells by the mGluR7 Receptor

Graphical Abstract



Highlights

- Cerebellar cortical mGluR7 mediates an adaptively timed, learned response
- mGluR7 can activate cellular memories of temporal intervals
- mGluR7 mediates an inhibitory action of glutamate tied to a behavioral response
- Temporally modulated firing rates can be regulated by post-synaptic mechanisms

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In Brief

Johansson et al. show that a recently discovered temporal memory in cerebellar Purkinje cells, which takes the form of an adaptively timed inhibitory response to glutamate, can be tied to a specific metabotropic receptor subtype.

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Activation of a Temporal Memory in Purkinje Cells by the mGluR7 Receptor

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SUMMARY

Cerebellar Purkinje cells can learn to respond to a conditioned stimulus with an adaptively timed pause in firing. This response was usually ascribed to long-term depression of parallel fiber to Purkinje cell synapses but has recently been shown to be due to a previously unknown form of learning involving an intrinsic cellular timing mechanism. Here, we investigate how these responses are elicited. They are resistant to blockade of GABAergic inhibition, suggesting that they are caused by glutamate release rather than by a changed balance between GABA and glutamate. We show that the responses are abolished by antagonists of the mGlu7 receptor but not significantly affected by other glutamate antagonists. These results support the existence of a distinct learning mechanism, different from changes in synaptic strength. They also demonstrate in vivo post-synaptic inhibition mediated by glutamate and show that the mGlu7 receptor is involved in activating intrinsic temporal memory.

INTRODUCTION

Temporal precision is necessary in a wide range of tasks, from driving a car to anticipating the next step of a dance partner, and to control such behaviors the brain must produce complex temporal neural activity patterns. A simple form of timing-dependent learning can be studied in eyeblink conditioning. If a neutral conditioned stimulus (CS) repeatedly precedes an unconditioned blink-eliciting stimulus (US) with a fixed temporal delay (the interstimulus interval, ISI), it acquires the ability to elicit a timed blink response that peaks near the US onset (Kehoe and Macrae, 2002). Such timed conditioned responses depend upon the cerebellar cortex (Yeo et al., 1984). Purkinje cells in a specific, blink-controlling area of the ferret cerebellar cortex receive information about the CS and US via mossy/parallel fibers and climbing fibers, respectively (Hesslow, 1995; Hesslow et al., 1999; Hesslow and Yeo, 2002). During conditioning, Purkinje cells acquire a learned suppression of firing in response to the conditioned stimulus (Halverson et al., 2015; Hesslow, 1994b; Hesslow and Ivarsson, 1994; Jirenhed et al., 2007). This firing rate reduction releases tonic inhibition of cerebellar nuclear cells, which increase their firing rate to generate an overt, conditioned blink (Heiney et al., 2014; Hesslow, 1994b; Hesslow and Ivarsson, 1994; Jirenhed et al., 2007).

The conditioned behavioral responses and the conditioned reductions in Purkinje cell firing rate have critically similar properties. They are both adaptively timed, conditioned behavioral responses reach their maximum amplitude just before the anticipated onset of the US and the Purkinje cell's firing rate change is a few tens of milliseconds earlier, consistent with delays in the motor pathways (Lepora et al., 2010). Both response types usually end shortly after the ISI even if the conditioned stimulus lasts only a few milliseconds or if it outlasts the ISI by several hundred milliseconds (Jirenhed and Hesslow, 2011a, 2011b; Johansson et al., 2014). These properties strongly suggest a causal relationship between the conditioned Purkinje cell activity changes (henceforth called conditioned Purkinje cell responses) and the conditioned behavior (Jirenhed and Hesslow, 2015). This view is also supported by the findings that interfering with the conditioned Purkinje cell responses causes a disruption of the conditioned eyeblink (Hesslow, 1994b) and that eyeblinks can be elicited through optogenetic inhibition of Purkinje cells (Heiney et al., 2014).

The ability to time conditioned Purkinje cell responses correctly is usually ascribed to the availability of temporal information in the parallel fiber input signal arising from network dynamics that create time-varying activation of different granule cell subpopulations (Lepora et al., 2010; Medina and Mauk, 2000; Yamazaki and Tanaka, 2009). In these and many other models, pairing these parallel fiber signals with a US-elicited climbing fiber input would cause long-term depression (LTD) selectively of those parallel fiber-to-Purkinje cell synapses most activated by the CS around the time of US onset. These parallel fibers would then contribute to the conditioned response, which would therefore be correctly timed when the CS is re-applied. However, we have recently shown that even when the conditioned stimulus is a direct train of repetitive stimuli to the parallel fibers, such that temporal coding through network properties is ruled out, the Purkinje cell still learns an adaptively timed response (Johansson et al., 2014). So the timing of the conditioned response must here be due to a mechanism intrinsic to the Purkinje cell.

Traditionally, simple spike firing in a Purkinje cell is seen to be determined by the balance between a direct excitatory,