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Review

Cerebellar learning mechanisms

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ABSTRACT

The mechanisms underlying cerebellar learning are reviewed with an emphasis on old arguments and new perspectives on eyeblink conditioning. Eyeblink conditioning has been used for decades a model system for elucidating cerebellar learning mechanisms. The standard model of the mechanisms underlying eyeblink conditioning is that there two synaptic plasticity processes within the cerebellum that are necessary for acquisition of the conditioned response: (1) long-term depression (LTD) at parallel fiber-Purkinje cell synapses and (2) long-term potentiation (LTP) at mossy fiber-interpositus nucleus synapses. Additional Purkinje cell plasticity mechanisms may also contribute to eyeblink conditioning including LTP, excitability, and entrainment of deep nucleus activity. Recent analyses of the sensory input pathways necessary for eyeblink conditioning indicate that the cerebellum regulates its inputs to facilitate learning and maintain plasticity. Cerebellar learning during eyeblink conditioning is therefore a dynamic interactive process which maximizes responding to significant stimuli and suppresses responding to irrelevant or redundant stimuli.

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1. Introduction

The cerebellum plays a role in learned adjustments to movement amplitude and timing. The most intensively investigated cerebellar learning paradigms include eyeblink conditioning (Freeman and Steinmetz, 2011; McCormick and Thompson, 1984a), conditioned limb flexion (Mojtahedian et al., 2007; Voneida, 2000), learned adjustments to load change (Gilbert and Thach, 1977), gaze-reach calibrations (Norris et al., 2011), gain and timing modification of the vestibulo-ocular reflex (Boyden et al., 2004; Raymond et al., 1996a), and learned smooth pursuit eye movements (Medina and Lisberger, 2008). The current review will focus primarily on old arguments and new perspectives on the mechanisms underlying cerebellum-dependent eyeblink conditioning.

2. Early theories of the neural mechanisms underlying cerebellar learning

The mechanisms underlying cerebellar learning were first addressed in computational models by Marr (1969) and Albus (1971). These models posit that modification in the efficacy of parallel fiber-Purkinje cell synapses is the primary mechanism underlying cerebellar learning. A key component of the Albus (1971) model is that cerebellar Purkinje cells undergo learning-related inhibition. Purkinje cell axonal projections are the sole output of the cerebellar cortex and are exclusively inhibitory. Thus, learning-related inhibition of Purkinje cells releases the cerebellar deep nuclei and vestibular nuclei from inhibition and drives learned. The current interpretation of this inhibitory mechanism is that parallel fiber-Purkinje cell synapses undergo long-term depression (LTD) during learning (Ito and Kano, 1982; Linden, 1994; Linden and Connor, 1991, 1995; Linden et al., 1991). One of the first studies to show an LTD-like mechanism *in vivo* found decreases in Purkinje cell simple spike activity during a task requiring monkeys to modify wrist movements to compensate for changes in load (Gilbert and Thach, 1977). This demonstration of an LTD-like reduction in Purkinje cell activity is consistent with the Albus model, but it does not prove that the LTD-like mechanism or the cerebellar cortical circuitry is necessary for learning.

3. Neural mechanisms of cerebellar learning in eyeblink conditioning

In the standard delay eyeblink conditioning procedure a conditioned stimulus (CS) that does not elicit eyelid closure before training, typically a tone or light, is followed by an unconditioned stimulus (US) that elicits an eyeblink reflex before training, such as a puff of air to the cornea or a brief shock in the periorbital area (Deaux and Gormezano, 1963; Gormezano et al., 1962; Schneiderman et al., 1962). Repeated paired presentations of the CS and US result in the development of an "eyeblink" conditioned response (CR) which includes eyelid closure, nictitating membrane movement, and eyeball retraction (Deaux and Gormezano, 1963; Gormezano et al., 1962; Schneiderman et al., 1962). This complex of adaptive responses occurs during the CS with maximum eyelid closure, nictitating membrane movement, and eyeball retraction occurring at the onset of the US (Fig. 1). The eyeblink conditioning CR is therefore determined by an association in which the CS predicts the presentation of the US and when it will occur.

3.1. *Essential role of the cerebellum in eyeblink conditioning*

Richard Thompson and his colleagues were the first to show that the cerebellum is necessary for eyeblink conditioning (McCormick et al., 1982). They found that lesions of the cerebellum ipsilateral to the conditioned eye block acquisition and abolish retention of eyeblink conditioning (Lincoln et al., 1982; McCormick et al., 1982; McCormick and Thompson, 1984a). Conditioning of the contralateral eye is completely intact following ipsilateral cerebellar lesions. Subsequent studies found that lesions localized to the dorsolateral anterior interpositus nucleus and medial dentate nucleus abolish eyeblink CRs (Clark et al., 1984; Lavond et al., 1985; Yeo et al., 1985). The lesion studies showed that the cerebellum is necessary for acquisition and retention of eyeblink conditioning, but did not prove that the memory underlying the CR is stored within the cerebellum.

The strongest evidence that the memory underlying eyeblink conditioning is stored within the cerebellum comes from a series of studies that used reversible inactivation methods. Inactivation of the intermediate cerebellum ipsilateral to the conditioned eye results in blockade of acquisition and the rate of learning following cessation of the inactivation is the same as in naïve animals, indicating that no savings was established during training with cerebellar inactivation (Fig. 2) (Clark et al., 1992; Freeman et al., 2005; Krupa et al., 1993; Nordholm et al., 1993). This is a critical point because inactivation could have suppressed expression of the CR but still allowed associative learning to occur upstream or downstream of the cerebellum. These effects alone are not sufficient to demonstrate that the

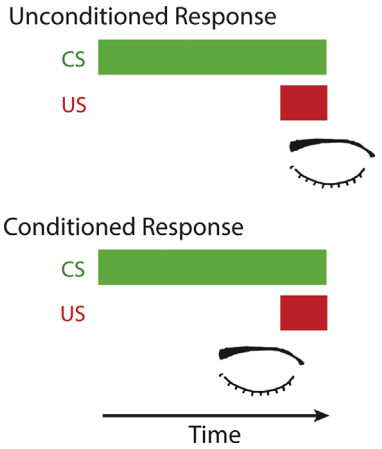

Fig. 1 – Diagram of eye-blink conditioning procedure and timing of the conditioned response. At the start of training an unconditioned response (eyelid closure) occurs after the onset of the unconditioned stimulus (US). With repeated presentations of the conditioned stimulus (CS) and the US a conditioned eyelid closure starts before the onset of the US.

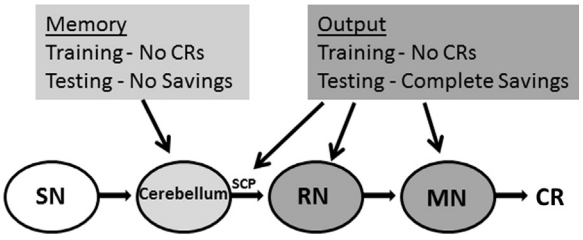

Fig. 2 – Diagram summarizing the effects of reversible inactivation on different parts of the neural circuitry necessary for eyeblink conditioning. Reversible inactivation of the cerebellum blocks conditioned responses (CRs) during acquisition and results in no savings. In contrast, reversible inactivation of the red nucleus (RN), superior cerebellar peduncle (SCP), or motor nuclei (MN) that generate eyelid movement block CRs during acquisition but result in complete savings after inactivation is terminated. The findings indicate that the cerebellum is the primary site of memory storage and the SCP, RN, and MN are necessary for the output necessary to generate the eyelid closure CR.

memory is stored exclusively within the cerebellum. It was necessary to examine the effects of inactivating areas downstream of the cerebellum as well. Inactivation of the contralateral red nucleus or the superior cerebellar peduncle completely block CR expression during eyeblink conditioning, but complete savings is found after the cessation if inactivation (Krupa et al., 1993, 1996; Krupa and Thompson, 1995). Inactivation of the cerebellum therefore blocks memory, whereas inactivation of the superior cerebellar peduncle or red nucleus blocks *expression* of memory (Fig. 2). Another approach has been to examine the effects of cerebellar inactivation after training sessions to assess memory consolidation mechanisms. Yeo and colleagues demonstrated that cerebellar cortical inactivation shortly after each eyeblink conditioning session impaired memory, which was evident by a lack of savings from one training day to the next (Attwell et al., 2002; Cooke et al., 2004). This is a particularly important finding because the post-training inactivation effects cannot be attributed to deficits in sensory or motor function during eyeblink conditioning. Evidence that the memory underlying eyeblink conditioning is stored within the cerebellum also comes from numerous studies of cerebellar plasticity mechanisms, as discussed below.

3.2. *Evidence for an LTD-like mechanism at parallel fiber-Purkinje cell synapses during eyeblink conditioning*

Neurophysiological studies of Purkinje cell activity during eyeblink conditioning have found learning-related changes in simple spike firing (Berthier and Moore, 1986; Gould and Steinmetz, 1994, 1996; Green and Steinmetz, 2005; Hesslow and Ivarsson, 1994; Jirenhed et al, 2007; Jirenhed and Hesslow, 2011; Katz and Steinmetz, 1997; Nicholson and Freeman, 2004). Pauses in simple spikes develop as eyeblink conditioning progresses, which is consistent with an LTD-like mechanism. The pauses in simple spike activity increase in magnitude during conditioning and decrease during extinction (Jirenhed et al., 2007). These learning-related changes in Purkinje cell simple spike activity suggest that pauses in simple spike firing during the CS release the deep nuclei from tonic inhibition and thereby facilitate CR expression, as would be expected for and LTD-like mechanism (Mauk and Donegan, 1997; Raymond et al., 1996b).

The feasibility of parallel fiber LTD as a putative mechanism underlying eyeblink conditioning was examined *in vitro* with forward paired presentations of parallel fiber and climbing fiber stimulation (Chen and Thompson, 1995; Freeman et al., 1998b; Schreurs and Alkon, 1993; Schreurs et al., 1996). The cellular and molecular mechanisms underlying Purkinje cell LTD were then examined *in vivo*. Purkinje cell LTD *in vitro* is PKC-dependent (Freeman et al., 1998b; Linden and Connor, 1991) and eyeblink conditioning in rabbits is associated with an increase in PKC activation in the molecular layer of the cerebellar cortex (Freeman et al., 1998a). LTD at parallel fiber-Purkinje cell synapses is associated with a decrease in AMPA receptors *in vitro* and a decrease in cerebellar cortical AMPA receptors has been found in rabbits given eyeblink conditioning relative to controls given unpaired presentations of the CS and US or naïve rabbits (Hauge et al., 1998). Eyeblink conditioning is also associated with a decrease in excitatory synapses within the outer half of the molecular layer, which are primarily parallel fiber synapses on Purkinje cell dendrites and dendritic spines (Connor et al., 2009). Moreover, genetic manipulations that impair cerebellar cortical LTD generally impair eyeblink conditioning (Aiba et al., 1994; Ichise et al., 2000; Kishimoto et al., 2002; Lee et al., 2009; Shibuki et al., 1996). The findings from a wide variety of methodological approaches therefore indicate that eyeblink conditioning is associated with an LTD-like mechanism in the cerebellar cortex.

3.3. *Evidence for an LTP-like mechanism at mossy fiber-interpositus nucleus synapses during eyeblink conditioning*

The release of the deep nuclei from inhibition during pauses in Purkinje cell firing is thought to promote plasticity within the anterior interpositus nucleus (Mauk and Donegan, 1997; Medina and Mauk, 1999; Ohyama et al., 2006). *In vivo* neurophysiological studies have shown that neurons in the anterior interpositus nucleus increase firing during the CS as the CR emerges across training. The burst of interpositus neuronal firing correlates with the amplitude and timing of the CR and precedes it within training trials (Campolattaro et al., 2011; Choi and Moore, 2003; Freeman and Nicholson, 1999, 2000; Gould and Steinmetz, 1996; Halverson et al., 2010). The results of the *in vivo* neurophysiological studies suggest that the burst of activity in the interpositus nucleus plays a causal role in the production of the CR. Furthermore, electrical stimulation of the anterior interpositus nucleus can elicit eyelid closure before or after eyeblink conditioning, suggesting that the interpositus nucleus can drive the CR through its projections to the red nucleus (Freeman and Nicholson, 2000; McCormick and Thompson, 1984b).

What are the cellular and molecular mechanisms underlying the learning-related bursts of interpositus nucleus activity? Neurons in the deep cerebellar nuclei show increases in intrinsic excitability and EPSPs following stimulation of their excitatory inputs *in vitro* (Aizenman and Linden, 2000). Synaptic potentiation may be related to an increase in the number or size of mossy fiber-interpositus nucleus excitatory synapses. A quantitative electron microscopy study found that the number of excitatory synapses per neuron within the anterior interpositus nucleus is significantly elevated following 5 days of eyeblink conditioning in rats (Kleim et al., 2002). This finding was replicated by counting mossy fiber varicosities within the anterior interpositus nucleus/dorsolateral hump in mice after 5 days of training (Boele et al., 2013). An increase in the size of excitatory synapses was found within the anterior interpositus nucleus in rabbits following less extensive training (Weeks et al., 2007).

Thus, there is an initial increase in the size of excitatory synapses within the anterior interpositus nucleus followed by an increase in synapse number as eyeblink conditioning becomes consolidated. Pharmacological blockade of memory consolidation mechanisms such as protein synthesis, NMDA receptors, and kinase activity within the interpositus nucleus impair eyeblink conditioning, suggesting that these molecular processes may play a role in the learning-related enhancement of mossy fiber-interpositus synaptic function (Bracha et al., 1998; Chen and Steinmetz, 2000a, 2000b; Gomi et al., 1999). The enhancement of mossy fiber-interpositus nucleus synapses coupled with pauses in Purkinje cell activity is thought to produce the burst of activity during the CS that drives the CR.

4. New perspectives on cerebellar plasticity: Purkinje cell excitability and LTP

The standard view of cerebellar learning mechanisms underlying eyeblink conditioning in which paired CS–US presentations result in LTD in parallel fiber-Purkinje cell synapses and LTP at mossy fiber-anterior interpositus nucleus synapses may need updating. The Purkinje cell LTD hypothesis was initially based upon the anatomical and physiological properties of the cerebellar circuitry and subsequently gained support from numerous empirical studies, as detail above. A critical source of evidence for the LTD hypothesis has been the demonstration of pauses in simple spike activity during the CS (Green and Steinmetz, 2005; Jirenhed et al., 2007). Many of the *in vivo* recording studies have also found Purkinje cells with increases in simple spike activity during the CS (Berthier and Moore, 1986; Gould and Steinmetz, 1996; Green and Steinmetz, 2005; Katz and Steinmetz, 1997; Nicholson and Freeman, 2004). This enhancement of simple spike firing has typically been dismissed as reflecting interneuron activity or Purkinje cell activity that is not relevant to the eyeblink CR. An alternative explanation for the Purkinje cells with increased activity is that they may be involved in inhibiting cerebellar output to the levator palpebrae muscle, which raises the upper eyelid. Purkinje cells that increase simple spike activity during the CS increase inhibition of the cerebellar deep nuclei and may thereby decrease excitatory output to motor neurons that activate the levator palpebrae. An elegant study by Delgado-Garcia and colleagues found that different classes of neurons in the interpositus nucleus are excited or inhibited during eyeblink conditioning in cats (Sanchez-Campusano et al., 2012). They found that type-A neurons in the interpositus nucleus increase firing during eyelid closure, whereas type-B neurons fire tonically when the eyelid is open and reduce firing when the eyelid is closing. This antagonistic action of the different types of interpositus neurons is thought to be necessary for the normal kinematic properties of the eyelid closure CR (Sanchez-Campusano et al., 2012). What is the mechanism underlying the pause in type-B neuron activity during eyelid movement? It is proposed here that some of the Purkinje cells that show an increase in simple spike activity during the CS inhibit type-B neurons and thereby reduce excitatory input to the levator palpebrae motor neurons. Thus, Purkinje cells that have pauses *vs.* increases in simple spike activity work cooperatively to facilitate expression of the CR through the interpositus nucleus (Fig. 3).

What are the mechanisms underlying the increase in Purkinje cell activity during eyeblink conditioning? Increased simple spike activity in these Purkinje cells might be the result of LTP at parallel fiber-Purkinje cell synapses or increased intrinsic excitability. Bernard Schreurs and colleagues were the first to show that eyeblink conditioning results in an increase in Purkinje cell excitability (Schreurs et al., 1997, 1998, 1991). These authors trained rabbits with eyeblink conditioning and then performed intracellular recordings from cerebellar cortical slices *in vitro*. Rabbits given paired CS–US training showed an increase in intrinsic excitability in Purkinje cell dendrites, whereas rabbits given unpaired CS and US presentations did not show changes in excitability. The increase in Purkinje cell excitability is caused, at least in part, by inactivation of I_A K^+ channels (Schreurs et al., 1998). More recent studies have shown that small-conductance Ca^{2+}-activated K^+ (SK2) channels are necessary for increased excitability *in vitro* and facilitate parallel fiber-Purkinje cell LTP (Belmeguenai et al., 2010; Hosy et al., 2011; Ohtsuki et al., 2012). Downregulation of SK2 and I_A channels as a result of eyeblink conditioning might, therefore, contribute to the facilitated spike firing in some of the Purkinje cells that influence levator palpebrae activity.

Pre-synaptic and post-synaptic LTP have been demonstrated for parallel fiber-Purkinje cell synapses (Hansel et al., 2001; Jorntell and Hansel, 2006; Salin et al., 1996). Moreover, reversible plasticity at these synapses has been

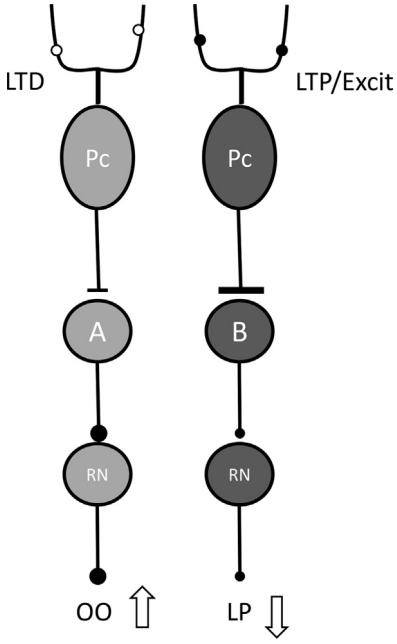

Fig. 3 – Diagram depicting how different plasticity mechanisms in Purkinje cells might influence expression of the conditioned response during eyeblink conditioning. Purkinje cells (Pc) that undergo long-term depression (LTD) decrease inhibition of type-A neurons in the interpositus nucleus (A) resulting in stronger excitatory output to the red nucleus (RN) and increased activity in the orbicularis oculi (OO) motor neurons, which causes eyelid closure. Purkinje cells that undergo long-term potentiation (LTP) and/or increases in intrinsic excitability (Excit) increase inhibition of type-B interpositus neurons (B) thereby decreasing excitatory output to the RN and downstream to the levator palpebrae (LP) motor neurons, facilitating eyelid closure. Inhibitory synapses are depicted by a flat ending. All other synapses are excitatory.

proposed as crucial for extinction and other aspects of learning (Medina et al., 2002). Parallel-fiber LTP also causes increases in intrinsic excitability (Belmeguenai et al., 2010). A recent study found that mice with a Purkinje cell-specific knockout of protein-phosphatase-2B (L7-PP2B) had a severe deficit in LTP but no deficit in LTD *in vitro* (Schonewille et al., 2010). The L7-PP2B knockout mice were also impaired in acquisition of delay eyeblink conditioning (Schonewille et al., 2010). The findings of this study provide compelling evidence that an LTP-like mechanism at parallel fiber-Purkinje cell synapses may play a substantial role in eyeblink conditioning. This LTP-like mechanism could act on its own or in concert with increased excitability to increase Purkinje cell activity during the CS and inhibit type-B neurons in the anterior interpositus nucleus, thereby reducing input to the downstream levator palpebrae motor neurons during CRs (Fig. 3).

It is possible that other types of plasticity mechanisms within the cerebellum (Hansel et al., 2001) play a role in eyeblink conditioning but relatively limited information on this topic is currently available. A more systematic approach examining the effects of genetic and pharmacological manipulations on specific plasticity mechanisms in animals trained on eyeblink conditioning is needed. This kind of systematic approach has been fruitful for examining the plasticity mechanisms underlying various forms of VOR adaptation (Gao et al., 2012).

5. Purkinje cell entrainment of deep nucleus activity

Another recently discovered property of cerebellar circuitry that may play a role in learning is that deep nucleus neuronal firing can be entrained to synchronously active Purkinje cells (Person and Raman, 2012). In conditions where Purkinje cells are activated synchronously deep nucleus neurons are not tonically inhibited; rather, their activity is entrained to the Purkinje cell activity (Person and Raman, 2012). It is not clear how this property of cerebellar function affects the CR during eyeblink conditioning but it is possible that synchronously activated Purkinje cells, presumably *via* LTP or increased excitability, might entrain oscillations in interpositus nucleus activity and in turn cause oscillations in the kinematic properties of the CR (Gruart et al., 2000). Eyelid CRs show oscillations that differ in frequency across species (Gruart et al., 2000). These oscillations might be driven by synchronously activated Purkinje cells during the CS. The specific oscillation during the CR could be influenced by learning-related plasticity of SK2 channels since their function influences the temporal pattern of Purkinje cell spikes (Belmeguenai et al., 2010; Hosy et al., 2011). Purkinje cells synchronously activated by the CS might therefore play a role in the microstructure of the CR by producing oscillations in type-A neuronal activity as well as inhibiting type-B neurons in the interpositus nucleus during eyeblink conditioning.

6. Cerebellar interactions with the CS and US pathways

The neural pathways that transmit sensory information from the CS and US to the cerebellum during eyeblink conditioning have been identified (Freeman and Steinmetz, 2011; Mauk et al., 1986; Steinmetz et al., 1987).

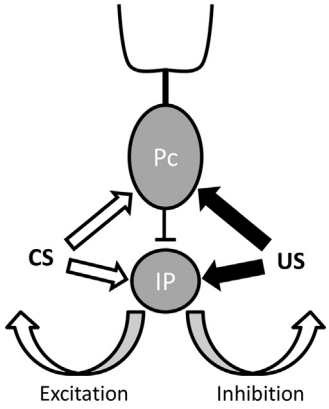

Fig. 4 – Diagram depicting interactions between the cerebellum and the conditioned stimulus (CS) and unconditioned stimulus (US) pathways. Purkinje cells (Pc) and neurons in the interpositus nucleus (IP) received input from the CS and US pathways during eyeblink conditioning. As plasticity develops in the cerebellum and the conditioned response starts to be expressed cerebellar output through the interpositus nucleus sends inhibitory feedback to the US pathway at the level of the inferior olive and excitatory feedback to the CS pathway at the level of the pontine nuclei and the medial auditory thalamus. Inhibitory feedback to the inferior olive regulates climbing fiber activity and thereby prevents learning to redundant stimuli and maintains learning-related synaptic plasticity. Excitatory feedback to the CS pathway facilitates conditioning to stimuli that predict the US. Inhibitory synapses are depicted by a flat ending. All other synapses are excitatory.

These pathways are subcortical for delay eyeblink conditioning and provide the inputs necessary for establishing associative plasticity. The cerebellum is not simply a passive recipient of these sensory inputs; it interacts with the CS and US pathways to modulate its own inputs and learning mechanisms (Fig. 4).

6.1. *The US pathway*

Early models of cerebellar learning posited that the climbing fiber axons of the inferior olive could serve as the teaching or error detection input to the cerebellum. The US pathway was subsequently identified by a combination of several experimental approaches. Neuronal activity in the inferior olive or complex spike activity in Purkinje cells is synchronized to US presentations, typically firing 1–3 times following US onset (Jirenhed et al., 2007; Kim et al., 1998; Nicholson and Freeman, 2000, 2003a, 2003b; Rasmussen et al., 2008). Lesions of the inferior olive following eyeblink conditioning cause a decrease in CRs across training trials that parallels extinction, suggesting that the loss of climbing fiber input to the cerebellum is functionally equivalent to omitting the US during extinction training (McCormick et al., 1985). A critical experiment for identifying the climbing fiber pathway as the US input to the cerebellum used electrical stimulation of the inferior olive as a US paired with a tone CS (Mauk et al., 1986). This experiment found that stimulation of the inferior olive, if located properly, is sufficient for eyeblink conditioning.

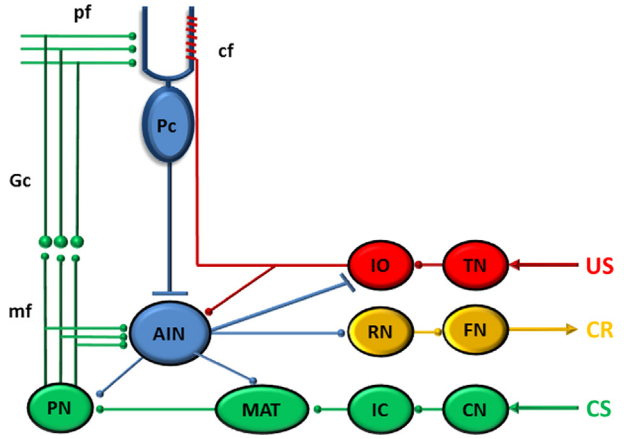

Fig. 5 – Diagram of the neural circuitry underlying delay eyeblink conditioning. The cerebellar anterior interpositus nucleus (AIN) and Purkinje cells (Pc) in the cerebellar cortex receive convergent input from the conditioned stimulus (CS, green) and unconditioned stimulus (US, red) neural pathways. The CS pathway for an auditory CS includes the cochlear nuclei (CN), superior olive (not shown), lateral lemniscus (not shown), inferior colliculus (IC), medial auditory thalamus (MAT), basilar pontine nuclei (PN), mossy fiber (mf) projection to the AIN and cortical granule cells (Gc), and the parallel fiber (pf) projections to Purkinje cells. The US pathway includes the trigeminal nucleus (TN), dorsal accessory division of the inferior olive (IO), and the climbing fiber (cf) projection to the AIN and Pc. The output pathway for performance of the conditioned blink response (orange) includes the AIN projection to the red nucleus (RN) and its projection to facial motor nucleus (FN) which causes the eyelid closure conditioned response (CR). Feedback projections from the AIN to the PN, MAT, and IO regulate CS and US input to facilitate acquisition and maintain plasticity within the cerebellum. Inhibitory synapses are depicted by a flat ending. All other synapses are excitatory.

These findings and many others indicate that US information is transmitted to the cerebellum *via* the climbing fiber pathway (Fig. 5).

6.2. *Cerebellar feedback to the US pathway*

The cerebellar nuclei send an inhibitory projection to the inferior olive (Andersson et al., 1988; Bengtsson and Hesslow, 2006; Bengtsson et al., 2004; Hesslow and Ivarsson, 1996; Nicholson and Freeman, 2003a). This inhibitory pathway can be thought of as providing negative feedback, in the context of eyeblink conditioning. Cerebellar inhibitory feedback pathway has been shown to have a progressively stronger effect on the climbing fiber pathway during eyeblink conditioning as bursts of interpositus nucleus activity and the CR develop (Kim et al., 1998; Nicholson and Freeman, 2003a; Sears and Steinmetz, 1991). Learning-related inhibition of the US pathway is important for associative learning because it blocks redundant associations with other stimuli (Kim et al., 1998; Thompson et al., 1998). Moreover, inhibitory regulation of the US pathway at the level of the inferior olive influences the maintenance of synaptic plasticity in Purkinje cells (Kenyon et al., 1998; Medina et al., 2002). Inhibitory feedback from the cerebellum is also necessary for the induction of plasticity mechanisms underlying extinction (Medina et al., 2002).

6.3. *The CS pathway*

The pontine mossy fiber projection is the most proximal part of the neural pathway that conveys CS input to the cerebellum. Pontine mossy fibers project through the middle cerebellar peduncle to the deep nuclei and the granule cell layer in the cortex. The parallel fiber axons of the granule cells then project to the molecular layer of the cortex. The pontine mossy fiber projection is necessary for eyeblink conditioning with auditory, visual, or tactile CSs (Lewis et al., 1987). The auditory pathway is primarily within the lateral and dorsolateral nuclei (Halverson and Freeman, 2010a; Steinmetz et al., 1987). Lesions or inactivation of the lateral pontine nuclei impair eyeblink conditioning with an auditory CS (Halverson and Freeman, 2010a). Moreover, stimulation of the lateral pontine nuclei is a sufficient CS for eyeblink conditioning (Freeman and Rabinak, 2004, 2005; Steinmetz et al., 1986a, 1986b, 1989). Neuronal activity within the lateral pontine nuclei initially shows sensory responses to an auditory CS but then develops learning-related activity during conditioning that is similar to the learning-related activity in the anterior interpositus nucleus (Bao et al., 2000; Campolattaro et al., 2011; Clark et al., 1997; McCormick et al., 1983).

The lateral pontine nuclei receive input from the medial auditory thalamus (Campolattaro et al., 2007; Halverson and Freeman, 2010a). The medial auditory thalamus is necessary for acquisition and retention of eyeblink conditioning with an auditory CS. Like the lateral pontine nuclei, neuronal activity in the medial auditory thalamus initially shows sensory elicited responses but then develops learning-related activity during subsequent training. Stimulation of the medial auditory thalamus is also an effective CS for eyeblink conditioning (Campolattaro et al., 2007). The medial auditory thalamus receives critical input from the inferior colliculus but thalamic input from the cochlear nucleus and superior olive also plays a role in eyeblink conditioning (Freeman et al., 2007). CS input is thus transmitted in parallel from brainstem auditory nuclei to the medial auditory thalamus and then to the lateral pontine nuclei.

The visual CS pathway is within the medial pontine nuclei (Halverson and Freeman, 2010b). Inactivation of the medial pontine nuclei severely impairs eyeblink conditioning and stimulation of this pathway is an effective CS (Halverson and Freeman, 2010b; Halverson et al., 2009). The medial pontine nuclei receive parallel input from the nucleus of the optic tract and ventral division of the lateral geniculate (Halverson and Freeman, 2010b; Steinmetz et al., 2013). The nucleus of the optic tract and ventral lateral geniculate receive direct retinal input. Neurons in the LGNv show learning-related plasticity, but it differs from the plasticity observed in the medial auditory thalamus. LGNv neurons initially show sensory responses to a visual CS and then show maintained responding during eyeblink conditioning relative to control conditions. Thus, the LGNv shows a lack of habituation during eyeblink conditioning rather than facilitation in responding to the CS.

6.4. *Cerebellar feedback to the CS pathway*

As mentioned above, neurons in the lateral pontine nuclei develop learning-related increases in activity during eyeblink conditioning that resembles the learning-related activity in the anterior interpositus nucleus (Bao et al., 2000; Campolattaro et al., 2011; Freeman and Nicholson, 1999; McCormick et al., 1983). The learning-related activity in the pontine nuclei develops more slowly with training than cerebellar learning-related activity. Inactivation of the interpositus nucleus abolishes this learning-related pontine activity, suggesting that excitatory feedback from the cerebellum is driving the pontine learning-related activity (Bao et al., 2000; Clark et al., 1997). Medial auditory thalamic neurons also show learning-related activity that develops more slowly than learning-related activity in the anterior interpositus nucleus. The learning-related burst of activity in the medial auditory thalamic nuclei during the CS follows the burst of activity in the anterior interpositus nucleus within training trials (Halverson et al., 2010). These findings suggest that the cerebellum provides excitatory feedback to the medial auditory thalamus that drives the thalamic learning-related activity. A monosynaptic projection from the anterior interpositus nucleus to the medial auditory thalamus was identified, which may be the primary pathway for cerebellar feedback. The CS pathway therefore receives excitatory feedback at the level of the pontine nuclei and the medial auditory thalamus.

The precise role of cerebellar feedback to the CS pathway has not been determined but it is hypothesized that the cerebellum enhances its own input for significant stimuli; in the context of eyeblink conditioning, a significant stimulus is the best predictor of the US (Kim et al., 1998; Thompson et al., 1998). Good stimulus predictors of the US are thus amplified through excitatory feedback to the CS pathway to facilitate cerebellar plasticity, whereas plasticity mechanisms are suppressed for redundant stimuli through inhibitory feedback to the inferior olive (Kim et al., 1998).

7. Summary and conclusions

Eyeblink conditioning has been studied for decades as a model system, resulting in a wealth of data regarding the neural circuitry and cellular mechanisms underlying associative learning. The standard view of the neural mechanisms underlying eyeblink conditioning is that there are two essential types of synaptic plasticity: (1) an LTD-like mechanism at parallel fiber-Purkinje cell synapses and (2) an LTP-like mechanism at mossy fiber-anterior interpositus nucleus synapses. The LTD-like mechanism causes pauses in Purkinje cell activity during the CS which releases the deep nuclei from tonic inhibition. The release of the anterior interpositus nucleus from Purkinje cell inhibition promotes the development of LTP which, combined with the reduction of Purkinje cell inhibition, causes a burst of firing in projection neurons that then activate the red nucleus and thereby activate motor neurons that produce the eyeblink CR. There is a substantial amount of evidence supporting the standard view but additional plasticity mechanisms might also play role in eyeblink conditioning. Increased Purkinje cell intrinsic excitability and parallel fiber-Purkinje cell LTP might contribute to eyeblink conditioning by suppressing activity of interpositus nucleus neurons that activate the levator palpebrae motor neurons. Purkinje cells with increased activity might also entrain deep nucleus neurons to produce oscillations in eyelid movements. The CS and US pathways that support LTD and LTP within the cerebellum have been identified. These pathways are not simply relays for sensory stimulation; they develop learning-related activity during eyeblink conditioning that is driven by feedback from the cerebellar nuclei. The cerebellum, therefore, regulates its own inputs to facilitate conditioning to stimuli that predict the US and to maintain plasticity when the learning situation has not changed. Tremendous progress has been made toward elucidating the mechanisms underlying eyeblink conditioning and cerebellar learning, but there is still much to be learned. Hypotheses presented in this review regarding the role of facilitated Purkinje cell activity and cerebellar feedback in eyeblink conditioning can only be addressed adequately by continuing the tradition of systematic investigation that was initiated by Thompson and colleagues in the 1970s (Thompson, 1976).

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