REVIEW ARTICLE

Neuroplasticity and Post-Synaptic Rebound-Induced Spiking at Purkinje Cell-Deep Cerebellar Nuclei Synapses

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Abstract

Background: Within the cerebellum white matter are located four pairs of nuclei, collectively known as the deep cerebellar nuclei (DCN) (1). In the cerebellum, signal integration from pre-cerebellar structures via excitatory parallel fibers and climbing fibers in the cerebellar cortex occurs in GABAergic Purkinje cells (PC) (2). The main target of these PC cells is the DCN (2) and approximately 85% of GABAergic input on the DCN is from PCs (3). Furthermore, PCs outnumber DCN neurons (26:1) (2). Therefore, despite receiving substantial inhibition from Purkinje cells, DCN neurons are still active at rest showing regular spiking or spontaneous bursts (4). DCN neurons fire spontaneously at approximately 10-50 Hz (5). Given this unique anatomy of PC-DCN synapses, characterization of this synaptic circuit is important in understanding the overall role of the DCN in the brain.

Methods: The findings of 28 studies, including a few reviews, are reported in this paper. Studies selected focused principally on characterization of DCN circuitry properties and the role these properties have in the functioning of the DCN. Most studies employed in vivo and/or in vitro cellular recordings in rodents, among other models. Studies ranged from 1984 to 2013.

Summary: This review outlines current findings on the forms of plasticity found in the DCN, the function of the DCN and the connections between the DCN and other brain regions. In short, neurons in the DCN demonstrate both synaptic and non-synaptic plasticity. Cerebellar involvement in motor activity has been extensively studied therefore, not surprisingly; DCN neurons form connections with the motor cortex but also the prefrontal cortex. PC input on the DCN influences spike rate and timing through fluctuations in PC synchrony, and rebound depolarization.

Introduction

Nestled within the cerebellum are four pairs of nuclei, known as the deep cerebellar nuclei (DCN) (2). The cerebellum, in general, receives input from pre-cerebellar regions (2). This information is conveyed to the cerebellar cortex via excitatory MF and CF (2). Within the cerebellar cortex, these inputs are processed by the Purkinje cells (PC). Projections from PCs are the sole output of the cerebellar cortex. Notably, the DCN receive 85% of its inhibitory input from PCs (3). Furthermore, the DCN also receive excitatory input from MF and CF collaterals (2). Purkinje cells do not innervate the DCN in a uniform pattern (2). Of the types of neurons in the DCN, four are projection neurons (large and small) and two are interneurons (4). Large glutamatergic neurons have excitatory projections to extracerebellar non-olivary nuclei, small/medium nucleo-olivary GABAergic neurons have inhibitory projections to the inferior olive, large GABAergic and glycinergic neurons have inhibitory role in local circuitry and other glycinergic neurons have inhibitory feedback to cortex and feedforward to the brainstem nuclei (4,5). In turn, the DCN provide excitatory and inhibitory output to other brain regions such as the brainstem, thalamus and inferior olive (2). Not surprisingly, the DCN have connections to the motor cortex. However, connections between the prefrontal cortex and the DCN suggest that the DCN may also function within a wider behavioural context. While the anatomy and circuitry of the cerebellar cortex is well-studied, the circuitry of the DCN has received less attention. Nowadays, the DCN are often studied with very little differentiation between the individual nuclei and their circuitry within. More research must be done to map the connections within the DCN and the roles of the individual deep cerebellar nuclei. This paper aims to review current research on the circuitry and function of the DCN, with an emphasis on the PC-DCN synapse and plasticity. Briefly, the DCN has shown both changes in synaptic strength and intrinsic excitability mediated by changes in Ca^{2+} with PC synchrony, as well as rebound-induced spiking being proposed to influence DCN activity.

Neuroplasticity

Neuroplasticity can either return neurons to homeostasis or form a new set point such as non-homeostatic (6). Neuroplasticity in the DCN has mainly been studied in relation to its putative role in motor learning. Aizenman and Linden (7), who have studied both use-dependent synaptic plasticity and non-synaptic plasticity, propose that both forms of plasticity may work together to provide "a flexible and informationally rich engram" (7). An engram refers to the hypothetical representation of memory traces in the brain. In general, the DCN show bidirectional long-term synaptic plasticity, short-term synaptic depression and increases in intrinsic excitability.

Neurons in the DCN show bidirectional long-term synaptic plasticity

The PC-DCN synapses demonstrate long-term synaptic or use-dependent plasticity (8). This form of plasticity can cause a bidirectional change in synaptic strength – either enhancing the synapse's strength of depressing it. This bidirectional synaptic plasticity is induced by changes in post-synaptic Ca^{2+} influxes. Large Ca^{2+} transients induce long-term potentiation (LTP) and small transients induce long-term depression (LTD) (9).

Bidirectional synaptic plasticity at PC-DCN synapses has been studied by Aizenman *et al.* (9). They concluded, using intracellular recordings from the DCN of rats, that bidirectional long-term synaptic plasticity does exist at inhibitory synapses due to IPSP triggered Ca^{2+} influxes (9). Their results indicated that a burst of short, high frequency (10 pulses at 100 Hz) IPSPs applied at resting potential generated large Ca^{2+} transients - thereby inducing LTP for more than 20 minutes (9). Hyperpolarizing pulses also triggered LTP and generated large Ca^{2+} transients (9). However, when a burst of IPSPs (10 pulses at 100 Hz) is applied at a tonic hyperpolarized potential (-67 mV), this induces LTD with reduced Ca^{2+} transients (9). A burst of short, high frequency IPSPs at resting potential or at hyperpolarized potential also generated sizable rebound-induced spiking or limited rebound-induced spiking respectively (9). Rebound-induced spiking is a burst of spikes which are elicited at a depolarizing membrane potential following a release from inhibition (10). This long-term bidirectional synaptic plasticity is mediated in part by Ca^{2+} channels: blocking of Na^{+} spikes (using QX-314) also induces LTD with limited rebound spiking, (9) thereby showing that rebound is not mediated by Na^{+} channels. The contribution of Ca^{2+} influxes during rebound has been further studied: Dendrites in the DCN are capable of calcium-based excitation and dendritic calcium transients require T-type Ca^{2+} channels but not sodium channels (11). Both hyperpolarizing pulses and IPSPs (through inhibition of action potentials) induce a hyperpolarizing membrane potential. Furthermore, it is thought that rebound spiking induces the Ca^{2+} transients in DCN neurons. The amount of rebound spiking thereby determines whether LTP or LTD will be evoked, that is, in which 'direction' the change in synaptic strength will be (9).

Following Aizenman *et al.*'s (9) conclusion that IPSPs and hyperpolarization can elicit rebound-induced spiking, Aizenman and Linden (10) studied the conditions necessary to induce rebound in rats (10). Results indicated that IPSPs are more efficient at inducing rebound spiking than hyperpolarizing bursts (10). Rebound-induced spiking is evoked following a release from inhibition. Therefore, the more depolarization, the stronger rebound activation, with a peak activation at membrane potentials of -60 to -70 mV (this is within the low threshold, voltage-gated T-type Ca^{2+} channel's activation range (10). This provides further evidence that rebound-induced spiking is being mediated by Ca^{2+} channels, specifically T-type channels (9,10) being de-inactivated after hyperpolarization (9). T-type Ca^{2+} channels are involved in all forms of rebound activity exhibited in DCN cells (12). Furthermore, rebound-induced spiking is blocked in DCN cells when a T-type Ca^{2+} antagonist, mibefradil is applied (13) and rebound evoked by synaptic inhibitory input or current injection is suppressed by the T-type Ca^{2+} antagonist, TTA-P2 (12).

Nonetheless, Ca^{2+} transients can be mediated by more than just T-type Ca^{2+} channels. Plasticity may also depend upon NMDA receptors (6), as moderate or large Ca^{2+} influxes via activation of NMDA receptors as well as or L-type Ca^{2+} channels can also evoke cell-wide LTD or LTP of IPSC. L-type Ca^{2+} channels also play a role in eliciting LTP at MF-DCN synapses excitatory post-synaptic currents (EPSCs) (14). Hyperpolarization and disinhibition following high frequency excitation are necessary to generate LTP of EPSPs in DCN cells (15). Each of the above steps requires calcium regulation: Excitation activates calcium-dependent calcineurin while inhibition decreases L-type Ca^{2+} influxes (14). Lastly, disinhibition allows for calcium-activated α-CAMKII to triggers potentiation following the release from inhibition (14).

Neurons in the DCN show short-term depression

Short-term depression induces a less sustained decrease in synaptic strength than long-term depression. Because of the high PC to DCN convergence ratio, DCN cells are continuously bombarded with inhibitory input from PC neurons yet still have a constant basal firing rate (16). Short-term depression of PC-DCN synapses may therefore allow for such basal firing to occur in the DCN.

In a study by Telgkamp and Raman (16) identified two stages of short-term depression: A fast, frequency dependent stage and a slow, frequency independent stage (16). As a consequence, IPSC recovery from the first stage of depression is more rapid (~100 millisecond) than recovery from the second stage of depression (~10 second) (16). Increases in presynaptic activity therefore lead to "steady-state"-depressed IPSCs, most probably due to IPSCs never fully recovering from the second, slower stage of depression between the applications of high frequency stimuli (16). On the other hand, decreased presynaptic activity leads to larger IPSC that fully recover between applied stimuli (16). Inhibitory post-synaptic currents evoked at the sponta-

neous firing rate of PCs depress by 60% (16).

In all, the spontaneous activity of PC activity is thought to lead to short-term depression at the PC-DCN synapses allowing for basal DCN activity despite the high convergence of inhibitory PC cells (16). In this sense, short-term synaptic depression at the PC-DCN synapse functions to moderate inhibition of DCN cells (16). Such depression at the PC-DCN synapses occurs at varying firing frequencies and persists through glutamate blocking (MCPG blocker) but not through GABA blocking (SR95531 blocker) (16).

Neurons in the DCN show non-synaptic plasticity

Non-synaptic plasticity does not modify the strength of the synapse but induces changes in intrinsic excitability. Changes in the intrinsic excitability in DCN excitatory cells can manifest as an increase in firing rate or a decrease in intrinsic spike threshold (7). Tetanization protocols, NMDAR activation and depolarizing currents can all induce intrinsic excitability in DCN neurons (6,7,15).

In one study conducted by Aizenman and Linden (2000) (7), a tetanization protocol was applied. In their study, a tetanus of 10 high frequency bursts of 10 pulses at 100 Hz was applied at a frequency of 4 Hz (7). Results indicate that tetanization lead to sustained increases in intrinsic excitability of DCN cells compared to cells that did not receive a tetanus (7). Similarly, activation of NMDA receptors also lead to a sustained increase in intrinsic excitability of DCN cells recorded from rat cerebellar slices (7). Additionally, when cells are bathed in NMDA antagonist, D-AP5, no increase in spiking occurs (7), further supporting the role of NMDA receptors in intrinsic excitability. In both tetanization and NMDA receptor activation paradigms, Ca^{2+} is required. Ca^{2+} influxes can be achieved through depolarizing currents leading to Ca2+ voltage-gated calcium channel activation or Ca^{2+} coming into the cell via NMDA receptors (7). These calcium influxes might be a result of "burst-pause" input from PCs on DCN neurons (7).

Neuron spine index is correlated with the changes in intrinsic excitability in DCN cells

A study of neuronal morphology of mostly large and multipolar DCN projection neurons *in vivo* in rats between 6 to 9 post-natal days-old (P6-9) and P13-16 demonstrated a correlation between spine index (a measure of how spiny and sinuous dendrites are) and intrinsic excitability properties (8). An increase in spine index is correlated with a decrease in basal firing rate, larger after hyperpolarizing potentials (AHP) and a more negative resting membrane potential (8). Intrinsic excitability also increases with age. At P6-9 and P13-16, large DCN projection neurons have similar morphology, but cells at P6-9 show less intrinsic excitability (8). Furthermore, as Aizenman *et al.* (8) report, dendritic morphology of DCN projection neurons mature during pre-natal development and PCs innervate DCN cells in late pre-natal development (8). However, intrinsic excitability properties only mature later in post-natal development (8).

Neuroplasticity and Eye-Blink Conditioning

In general, long-term bidirectional synaptic plasticity is involved in associative learning (17). The role of neuroplasticity in the DCN has been studied in relation to eye-blink conditioning (EBC) (17,18,19). EBC is a form of classical conditioning of the eyelid or nictitating membrane (18) which involves the association of an unconditioned stimulus (US) and a conditioned stimulus (CS) (19). Naïve animals will blink in reaction to an US (e.g. puff of air) thus eliciting an unconditioned response (UR) (19). On the other hand, trained animals will also blink in reaction to a CS (e.g. tone) thus eliciting a response similar to the US known as a conditioned response (CR) (19). It has been proposed that MF and CF of the cerebellum convey information of the CS and US respectively (17). An early study by McCormick and Thompson (18) studied the relative contribution of the cerebellar cortex and the DCN, in particular the ipsilateral lateral cerebellum including the dentate and interpositus nuclei, in EBC. In this study, the dentate-interpositus region was shown to be necessary for learning the CR (18). Lesions in the dentate-interpositus region abolish CR while lesions in the cortex failed to abolish CR (18). This suggests that the lesions disrupt the output of the dentate-interpositus nuclei rather than the connection between the cortex and this DCN region (18). Furthermore, McCormick and Thompson proposed that these results suggest that plasticity necessary for EBC learning is restricted to the dentate-interpositus region (18). Chen *et al.* (17) reported similar results with lesions in the interpositus nucleus abolishing EBC learning (17). However, the cerebellar cortex is nonetheless involved in EBC. In a study by Chen *et al.* (17), because of the unique anatomy of the PC-DCN synapses, PC mutants mice have no neural output from the cortex to the DCN (17). These mutants showed impaired learning of CR compared to wild-types but with further training, were able to achieve minimal EBC (17), therefore the cerebellar cortex is also required for normal EBC. Various forms of synaptic plasticity may be involved in EBC (19). For example, Kim and Thompson (19) demonstrated that EBC impairment correlates with LTD at PF-PC synapses.

Function of the DCN

In general, the role of the cerebellum in motor activity and learning is well-studied. Both inhibitory and excitatory inputs from the cerebellar cortex influence DCN output and subsequently its function. In an early study by Llinas and Muhlethaler (20), intracellular recordings in guinea pigs demonstrated that DCN neurons generated EPSPs in response to input from CF collaterals, originated from the inferior olive, and MF collaterals, originated from precerebellar nuclei (2,20). DCN neurons also generate IPSPs in response to PC input (20), which can These PCs convey information via spike frequency alternations

and spike timing (5). Subsequently, the DCN provide excitatory output to the brainstem and thalamus, as well as inhibitory output to the inferior olive (2). Since PCs influence DCN activity, they subsequently affect motor activity. Graded PC activation leads to graded inhibition in DCN (21).

Influence of PC Synchrony on DCN

PCs convey information through inhibitory input from the cerebellar cortex to the DCN. Synchronized PC firing influences both spike rate and timing of DCN cells (22). An increase in PC synchrony leads to an increase in DCN spike rate (22). Synchrony of CF evoked spikes in PCs is due to gap junctions, which allow CFs that innervate separate PCs to be "electronically coupled" (5). PC synchrony plays a crucial role in information processing. Blocking olivary neuron coupling disrupts synchrony and rebound activity, leading to impaired and ill-timed reflex movements in some cases (5).

Furthermore, pauses in PC firing elicit DCN spikes with higher PC synchrony leading to more precisely timed DCN responses to inhibitory input (22). Spiking in PCs may also be generated intrinsically (23). Each of these spikes individually has a minimal influence on the DCN; however, due to high PC-DCN convergence, synchronized spikes can influence DCN firing via feed-forward inhibition (5).

Along with conveying information via spike rate, DCN neurons are thought to be able to transmit the timing of synchronized PC neurons spikes (24). Person and Raman (24) demonstrated that *in vitro*, desynchronized IPSPs which mimics PC input generate no spiking in DCN; while synchronized IPSPs do (24). As a consequence, DCN neurons fire spikes in-between the synchronized inhibitory PC input, that is, the DCN neurons fire spikes that are time-locked (24). Such as time-locked computational model may provide a model to describe the coordination of movement by the cerebellum, however, Medina (25) debates the generality of these results under physiological in vivo conditions. Medina (25) points out that further study is necessary to determine how the DCN balances both the synchronized, as Person and Raman (24) proposed, inhibitory PC input and excitatory MF and CF input (25). Khodakhah (25) also questions whether complete synchronization of two PC is probable and proposed optogenetic *in vivo* studies to increase specificity of PC activation to further test the time-locking model. Both Medina and Khodakhah (25) point out that the current model of cerebellar control of movement, rate code (an averaging of the rate of firing frequency to convey information) has not been refuted and thus time-locking may work in conjunction with a rate code computational model (25). In vivo, desynchronized IPSPs inhibit firing in DCN while synchronized IPSPs causes an increase in DCN spiking rate but only when performed at near physiological temperature (36 °C) (24). After synchronized IPSPs, there were short latency, well-timed action potentials generated because of the high PC-DCN convergence ratio (40:1), high post-inhibitory intrinsic firing rate (~90 Hz) and rapid IPSC decay (τ_{decay}=2.5 ms is significantly briefer than that at 22°C) (24). Faster IPSC decay allows for full decay of the inhibitory current between stimuli (24). Phase-locking of spikes to synchronized input also occurs in the DCN (24). DCN cells' spiking peaks at intervals corresponding to the intervallic generation of synchronized IPSPs allowing for the DCN to encode temporal information (24). As a consequence, faster decay periods would lead to more decay of IPSCs which may contribute to a fuller recovery from the second, slower state of short-term depression (16).

Influence of Rebound Activity on DCN

Rebound activity occurs following release of DCN cells from PC-generated IPSPs. Furthermore, rebound-induced spiking follows the offset of PC inhibition and not the onset (21). The release of this inhibitory input leads to an increase in firing (5,21). Mechanistically, rebound spiking is due to the opening of low-threshold, voltage-gated Ca^{2+} channels (10). Ca^{2+} channels de-inactivate with hyperpolarization and open with the return to a resting potential (20).

Synchrony of PC firing has an influence on generating rebound activity in the DCN. When individual PC neurons fire spikes together, there is both an increase in synchrony and an increase in the probability of eliciting rebound activity due to a decrease in PC background input (5,22). Computational models have postulated that rebound activity functions to trigger motor activity (22). GABAergic neurons in the DCN demonstrate rebound activity, which acts in an inhibitory feedback loop to the inferior olive (5). Non-GABAergic DCN neurons also demonstrate rebound activity which may act to influence motor and premotor areas (5).

A single, individual IPSP provides a small effect on the DCN (26). Therefore, concerted modulation from PC would be necessary to evoke rebound activity *in vivo* (26). With low PC synchrony, DCN cells are subject to a tonic inhibitory input (26). However, with synchrony of PC cells as discussed above, DCN cells produce large compound IPSP and rebound activity (26). Witter *et al.*'s (21) optogenetic study allowed for the synchronized activation of only PCs. In this method, a variant of the channelrhodopsin-2 is expressed in PCs in mice thus allowing for light to activate PCs specifically (21). Results confirmed that strong synchronized stimulus of PC led to more precisely timed rebound in the DCN (21). With this, the end of synchronized PC corresponded to movement in awake mice (21). Witter *et al.* (21) provide a PC control model of motor activity. In this model, a PC network is activated leading to graded control of rebound activity in the DCN which ultimately leads to the onset of motor activity (21).

The implications of PC activity triggering rebound-induced firing requires more study considering the majority of research (e.g. 9,10) has been conducted *in vitro*. As mentioned, a recent 2013 study by Witter *et al.* circumvented one limitation of electrophysiology, which is ensuring activation of specific cell types by using an optogenetic method (21). Using this method, Witter *et al.* (21) concluded that re-

rebound firing followed the offset of PCs activity and that even weak activation of PCs led to rebound *in vivo* (21). Nonetheless, further research is necessary as the exact role of rebound-induced spiking *in vivo* remains (13).

Connections to the prefrontal cortex

The cerebellum is known to be involved in motor activity, particularly motor learning (2). However, connections between the DCN and other physiological regions extend beyond motor function (27). While cerebellar involvement in motor activity and motor disorders has been well-studied, recent studies also indicate the DCN is involved in prefrontal activity. For example, multi-synaptic pathways have been found between the interpositus nucleus in rodents (equivalent to the fused emboliform and globose nuclei in humans), and the motor cortex and prefrontal cortex (27). Labelling neurons in the prefrontal cortex, area 46 and the motor area (M1) with rabies virus demonstrated that the interpositus nucleus has synaptic pathways to both the prefrontal cortex and the motor cortex (27). Neurons labelled from M1 were found in the dorsal portion of the posterior interpositus nuclei, in the anterior interpositus nucleus and in the dorsal portion of the dentate nucleus (27). On the other hand, neurons labelled from area 46 were found in the ventral portion of the posterior interpositus nucleus and in the ventral portion of the dentate nucleus (27). Moreover, the PCs from the C2 cerebellar cortex zone were found to project to the posterior interpositus nucleus, while PCs from the C1/C3 zones project to the anterior interpositus nucleus (27). Therefore, there are separate cerebellar output pathways to the prefrontal cortex and the motor cortex in the interpositus nucleus and the dentate nucleus (27).

Conclusions

The DCN receives excitatory input from MF and CF, and inhibitory input from the cerebellar cortex via PCs. Both synaptic and non-synaptic plasticity has been shown to occur in the DCN. For example, long-term synaptic changes occur at the inhibitory PC-DCN synapses and at excitatory PF-DCN synapses. Rebound-induced spiking is thought to mediate Ca^{2+} influxes which dictate whether long-term plasticity will involve an increase in synaptic strength or a decrease in synaptic strength. Short-term depression is also seen in DCN cells and can be broken down into two stages. Due to high PC inhibitory input on the DCN, spontaneous PC firing is thought to evoke short-term depression which allows for DCN cells to demonstrate basal firing. Furthermore, non-synaptic changes in large DCN projection neurons include changes in intrinsic excitability which correlates with dendritic spine index. Functionally, PC synchrony and IPSP-driven rebounds have been postulated to influence DCN function although the exact role that PC synchrony and rebound play is debated. PC synchrony may function to provide concerted PC firing on the DCN. The DCN firing has shown time-locking and phase-locking to synchronized PC firing which may allow for the DCN to convey temporal information. In addition to bidirectional plasticity, rebound may function to trigger motor activity. The cerebellum's involvement in motor activity has been extensively studied. The importance of the DCN in motor activity is demonstrated with congenital diseases which include DCN pathologies such as dentate nucleus atrophy and symptoms including a lack of coordination of movements, difficulties swallowing and difficulties articulating speech (28). However, the DCN also shows synaptic pathways to prefrontal cortex regions.

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