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Rebound from Inhibition: Self-Correction against Neurodegeneration?

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Abstract

Neural networks play a critical role in establishing constraints on excitability in the central nervous system. Several recent studies have suggested that network dysfunction in the brain and spinal cord are compromised following insult by a neurodegenerative trigger and might precede eventual neuronal loss and neurological impairment. Early intervention of network excitability and plasticity might therefore be critical in resetting hyperexcitability and preventing later neuronal damage. Here, the behavior of neurons that generate burst firing upon recovery from inhibitory input or intrinsic membrane hyperpolarization (rebound neurons) is examined in the context of neural networks that underlie rhythmic activity observed in areas of the brain and spinal cord that are vulnerable to neurodegeneration. In a non-inflammatory rodent model of spongiform neurodegenerative disease triggered by retrovirus infection of glia, rebound neurons are particularly vulnerable to neurodegeneration, likely due to an inherently low calcium buffering capacity. The dysfunction of rebound neurons translates into a dysfunction of rhythmic neural circuits, compromising normal neurological function and leading to eventual morbidity. Understanding how virus infection of glia can mediate dysfunction of rebound neurons, induce hyperexcitability and loss of rhythmic function, pathologic features observed in neurodegenerative disorders ranging from epilepsy to motor neuron disease, might therefore suggest a common pathway for early therapeutic intervention.

Keywords: Post-inhibitory rebound firing; Rhythmic neural networks; Calcium buffering; Calcium channels; Motor neuron degeneration; Microglia; NG2 glia; Astrocytes

Introduction

In human and animal neurodegenerative diseases, neurons undergo functional alterations that lead to cell death and eventual morbidity. Despite widespread CNS occurrence of etiologic triggers, such as abnormal, foreign or misfolded proteins, degenerative mechanisms often select for certain neuronal populations over others. Defining the nature of neuronal vulnerability to the trigger has focused primarily on understanding interactions between the pathogenic proteins and neuronal targets such as cell surface receptors, neurotransmitter transporters, intracellular signal transduction cascades, epigenetic gene regulatory elements, neuron selective endoplasmic reticulum protein folding and degradation pathway components, calcium homeostasis, and/or the activity and kinetics of voltage-gated currents [1-4]. Impaired neurological function can also arise through dysfunction in neural networks, which, by contrast, is not necessarily associated with neuronal loss. Aberrant neuronal activity, which can result from misfolded proteins found, for example, in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS), and alter signaling pathways, are suggested to lead to network dysfunction and eventual neurological failure [5,6]. Given the complex interplay between direct, indirect, inflammatory and non-inflammatory mechanisms, sorting out elements critical in initiating damage in specific neuron types or unique circuitry, and determining when they come into play, constitutes a challenging task.

One approach towards understanding the bases for neuron-selective pathogenesis is to consider neurodegenerative systems where the identification of etiologic triggers is not confounded by inflammatory/neuroinflammatory components. In mice, one such neurodegenerative disease is caused by the murine retrovirus, CasBrE, first described by Gardner et al. [7,8].

Because this virus is transmitted from infected dams to newborn offspring through mammary secretions, immune-naïve pups fail to recognize it as foreign and fail to develop an active immune response. Upon entry into the host, CasBrE infects blood-forming tissues, leading to the high serum virus levels necessary to facilitate entry into the CNS before endothelial restriction prevents CNS infection [9,10].

In the CasBrE disease paradigm, retrovirus-induced neurodegeneration targets pre-motor and motor areas as well as auditory and vestibular nuclei [11,12]. Overt clinical manifestations include tremor, spasticity, stilted gate, altered posture, progressive paralysis and ultimately death, a picture analogous to ALS in humans [13-15]. In addition, auditory deficits, which include raised hearing thresholds [16], suggest a loss of synchronous network activity in brainstem circuits. We therefore used the CasBrE model to examine the susceptibility of different neuronal types and networks to degeneration. Our model system was the inferior colliculus, a midbrain nucleus in the central auditory pathway. Cell types in the inferior colliculus can be differentiated by their intrinsic firing patterns [17,18] and local microcircuits are activated by input from the lower brainstem as well as by intrinsic connections between collicular neurons [19-22], providing a system in which to determine why

particular neuronal populations succumb to neurodegenerative triggers.

Our results demonstrate that a combination of two factors, the intrinsic firing pattern of a neuron and its incorporation into a specific microcircuit, can be critical in determining vulnerability to degeneration. Neurons that respond to the cessation of an inhibitory input by generating bursts of spikes (referred to as rebound neurons) are particularly susceptible to dysfunction and loss.

Following systemic infection with the virus, rebound firing is abolished and neurons exhibit prolonged spontaneous hyperexcitability that is not tied to inhibition. In addition, the loss of rebound firing in individual neurons propagates into the local network and causes widespread failure of rhythmic activity in the colliculus. In this system, viral infection is restricted to glia and is not observed in neurons, suggesting that the etiologic triggers for failure of the rhythmic neural network, and for progressive neurodegeneration, are glial signals that regulate the ability of neurons to rebound from inhibition [16].

Loss of rhythmic network activity during neurodegeneration

Rhythmic neural circuits are present in many areas of the brain and spinal cord concerned with sensory and motor coordination [22-30]. Circuit activity is maintained by an oscillating excitatory-inhibitory network that can include rebound neurons, which reset excitation in a periodic manner. When rebound neurons receive an inhibitory input, they respond with a burst of spikes that acts as the signal for network activity. Rebound neurons that release the neurotransmitter GABA convey a strong inhibitory signal during the rebound burst period to the connected neurons in the network [31-36]. The signal conveyed by rebound from inhibition therefore acts as a switch to stop or reset excitation in the network. Rebound neurons that release inhibitory neurotransmitters are themselves intrinsically oscillating [37,38], thus, as individual neurons, they have the capacity to set phase transitions between excitation and inhibition. An added benefit of this excitatory-inhibitory oscillation is the limiting of activity to the restricted locus of neurons that form the feedback connections of the network [39].

The loss of rebound firing in a neurodegenerative milieu translates into a breakdown of rhythmic circuits, and an inability to reset the excitatory state of the network, resulting in a prolonged hyperexcitable state. Indeed, in several rodent models of neurodegeneration, hyperexcitability of single neurons co-exists with a loss of rhythmic activity. For example, in the mutant superoxide dismutase (SOD1) rodent model of motor neuron degeneration and ALS, motor neurons in the spinal cord become persistently hyperexcitable. In addition, these mice show deficits in rhythmic behavior that normally originates in rebound firing [40,41] and which manifests as abnormal ventral root rhythms that correlate with disease pathology [42,43]. Neurodegeneration is also associated with altered network activity in brain regions that regulate sleep (basal forebrain, hippocampus) [44] and breathing [45], both of which involve rhythmic circuits. In our model of retrovirus infection, a primary readout of neuronal synchrony, the auditory brainstem response, is severely attenuated and delayed in the inferior colliculus [16]. Taken together, these several studies suggest that a loss of rhythmic behavior coincides with the neurodegenerative state.

The calcium-rebound connection and its failure in neurodegeneration

In normal conditions, the rhythmic cycle is maintained when rebound firing is temporally locked to the preceding inhibition or membrane hyperpolarization [17,22]. Inhibition and the subsequent rebound firing form a temporal gate, during which spike rates are elevated compared to that before the inhibitory input [46,47]. Two critical characteristics of the inhibition-rebound window give the rhythmic network the capacity to adjust its level of excitation to the level of inhibition. First, the amplitude of preceding inhibition determines both the latency and duration of rebound firing. With increasing inhibition, rebound latency decreases, while rebound firing becomes prolonged [17]. Loss or down-regulation of inhibitory input can therefore result in loss or delay of rebound firing. In our retrovirus model of degeneration, rebound neurons in the inferior colliculus lose rebound firing despite normal levels of inhibitory input or intrinsic hyperpolarization [16]. Rebound loss therefore results from the second determinant of the temporal nature of the inhibition-rebound window, namely changes in the behavior of intrinsic ion channels. These changes are discussed below.

Intrinsic ion channels affected by the retrovirus appear to be voltage-gated L-type calcium channels that are activated during rebound from inhibition. When the internal concentration of free calcium is decreased by dialyzing cells with the calcium buffer EGTA, rebound firing is restored. In control mice, in contrast, decreasing internal free calcium abolishes rebound firing [16]. A comparison of the effects of EGTA on the rebound window between infected and uninfected mice reveals that the generation of rebound firing requires an interaction between L- type channels (I_L) and the lower-threshold T-type calcium channel (I_T), also present in rebound neurons. Calcium influx through I_T is unaffected in infected mice, whereas calcium influx through I_L is absent. The restoration of rebound firing by EGTA in infected mice indicates no permanent loss of I_L subunits. Instead I_L is blocked due to a calcium-dependent inactivation of these channels from the cytoplasmic side of the cell membrane. I_L thus provides the regenerative current needed to drive rebound firing, and its inactivation in infected mice suggests raised internal calcium levels. Since I_T is not subject to calcium-dependent inactivation [48], it is unaffected by increases in the internal calcium concentration. However, since the initial influx of calcium into rebound neurons occurs through I_T, the subsequent block of I_L suggests that I_T must provide the regenerative drive to activate I_L from the cytoplasmic side of the membrane. The requirement for calcium entry through both I_T and I_L during the rebound window, which has been demonstrated in other studies [49,50], and the block of I_L, but not I_T, following viral infection in the inferior colliculus, indicates that neurodegenerative triggers act at the site of interaction between I_T and I_L. Firing properties of other neuronal types in the inferior colliculus are unaffected by EGTA dialysis, suggesting that rebound cells must be less capable than other cell types of handling high calcium loads. EGTA dialysis, and the application of nimodipine, an antagonist of I_L, also blocks hyperexcitability in rebound neurons, providing strong support for the hypothesis that calcium buffering in rebound neurons is compromised [16]. The retrovirus model of degeneration therefore demonstrates that the vulnerability of rebound neurons arises from a calcium buffering capacity that is normally lower than that of other neuronal cell types in the inferior colliculus.

The importance of calcium buffering in neurodegenerative disorders is well established [51]. In ALS mouse models, for example, motor

neurons with low levels of endogenous calcium buffers display enhanced susceptibility to degeneration [52]. The type of endogenous calcium-binding protein as well as the presence of more than one calcium-binding protein in a cell might also be important in resisting degeneration. In this regard, a recent comparison between ALS-resistant ocular motor neurons and vulnerable hypoglossal and spinal motor neurons showed that parvalbumin levels correlated with resistance levels [53]. The presence of multiple calcium-binding proteins within neurons might also confer resistance to degeneration. For example, neurons in regions of the inferior colliculus that are resistant to virus-induced degeneration appear to contain both calbindin and calretinin, whereas collicular neurons vulnerable to degeneration contain only parvalbumin [54,55]. Neurons in the deep cerebellar nucleus, which undergo virus-induced degeneration [12] also contain parvalbumin [56], while resistant cerebellar cortex neurons [11] contain parvalbumin, calbindin and calretinin [57]. Calretinin- and calbindin-deficient cerebellar granule cells display rapid spiking and fast neuronal oscillations, alterations of normal rhythmic states and ataxia, which are reduced by increasing calcium-buffering through added cytoplasmic calcium chelators [58,59], suggesting a direct role for calcium-binding proteins in altered rhythmic activity, hyperexcitability and motor coordination.

Does glial-neuronal miscommunication underlie the loss of rhythmic networks?

The retrovirus-induced degenerative model is particularly interesting from the perspective of how glial-neuronal communication may initiate neurodegeneration. Although degenerating neurons appear to be permissive for virus entry events [60], they are not permissive for virus replication or gene expression because the reverse transcribed genome cannot integrate into the chromosomal DNA of non-dividing cells. Moreover, chimeric brain reconstitution experiments demonstrated that early virus replication events are insufficient to precipitate neurodegeneration but rather require expression of the viral ENV protein within host glia to cause disease [61,62]. CNS infection is most prominent in microglia and NG2 glia [11,60,63], however, infection of these two cell populations alone does not appear to be sufficient to cause disease [60]. A third glial cell type, most likely astrocytes, appears to be required for neurodegeneration, but its identity remains in question since virus expression in this cell type appears to be down-regulated upon their differentiation from glial progenitor cells [64,65]. Interestingly, infection of glial progenitor cells with either neurovirulent of non-neurovirulent ectopic viruses inhibits their differentiation into mature oligodendrocytes, however, the neurovirulent virus appears to bias differentiation towards an astrocytic fate, whereas the isogenic non-neurovirulent virus appears to suspend cells in a progenitor-like state [64]. How this alteration of glial differentiation may affect neuronal excitability and circuit behavior remains unexplored.

Importantly, direct infection by CasBrE or related neurovirulent viruses is not directly cytotoxic to any glia or their progenitors, however, NG2 cells (aka, oligodendrocyte progenitor cells; OPCs) appear to be particularly vulnerable to the excitotoxic milieu of dysregulated circuits and hyperactive neurons [64,66]. NG2/OPC-induced cell damage is characterized by effacement of the cytoplasm, while largely sparing nuclear structures. This secondary "spongiform" pattern follows initial post-synaptic vacuolation associated with the dendrites of susceptible neurons [11,16,67,68]. It is now well-established that both excitatory and inhibitory neurons make synaptic contact with NG2 glia, and that these cells possess a variety of neurotransmitter receptors and ion channels [69]. Although these cells have been observed to exhibit action potentials, regenerative events are infrequent and thus, arguably inconsequential [69,70].

It is presently unclear how a non-functional NG2-neuron connection could lead to hyperexcitability and loss of rhythmic networks. An attractive hypothesis might stem from the primary characteristic of NG2 cells, namely their polyfunctionality [71]. Because NG2 cells can differentiate into oligodendrocytes, astrocytes and, in some cases, neurons, and they connect synaptically to neurons [72], virus-induced dormancy could result in large-scale dysregulation of external calcium levels, with consequences for resting calcium levels in both glia and neurons, regulated by calcium leak channels. It has been shown that buffering calcium concentrations within astrocytes prevents neurons from generating rhythms; and rhythmic activity is restored by adding astrocytic calcium-binding proteins to the extracellular space [73]. Whether NG2 cells participate in direct ionic buffering remains to be determined, but their ion channel/transporter expression profile suggests it is possible [69]. Alternatively, NG2 infection could act indirectly to affect astrocyte density, since CasBrE appears to bias glial differentiation towards astrocytes [64]. Whether differentiating astrocytes effectively buffer extracellular calcium in CasBrE-induced disease has not been addressed, since infection of these cells is not readily observable in the CasBrE model [11,60,65]. Nonetheless, this scenario is reminiscent of HIV CNS infection, where astrocyte infection is infrequent and non-productive, but nevertheless appears to be responsible for disruption of the blood brain barrier and death of certain gap junction-connected cells [74,75].

Regardless of whether the etiologic mechanism involves NG2 glia or astrocytes, a non-functional glial-neuronal connection might act in two ways to further degeneration. First, it might serve as a critical point of failure to regulate resting neuronal calcium levels, and second, it might be the factor that is responsible for the neuron selective aspect of neurodegeneration, namely that neurons with a low calcium buffering capacity, such as rebound neurons, are targeted for degeneration (Figure 1). An example of glia as a critical point may be represented by recent findings on perisynaptic schwann cells (PSCs), glial cells present at the neuromuscular junction (NMJ). PSCs decode motor neuron firing to muscles that can be translated into their detection of synaptic damage. Through synaptically-evoked PSC calcium transients, PSCs can shift to an activated state that initiates synapse-repairing processes. Examination of this feature of PSCs in the G37R mutant SOD1 transgenic ALS mouse model suggests that PSCs abnormally decode hyperexcitability at the neuromuscular junction, fail to transition into their reparative state, and thus contribute to NMJ denervation [76]. Since NG2 cells also integrate global and dendritic calcium signals and display calcium transients in response to neural activity [77], it suggests that similar mechanisms may be operating at rebound neuron synapses during rhythmic circuit disruption. Interestingly, deletion of NG2 cells in the CNS has no obvious neuropathologic sequelae *per se* [78], however, a detailed examination of associated neuronal activities has yet to be examined under conditions where they have been knocked out globally, so it may be premature to speculate on whether their presence is critical for normal circuit function. Thus, the function of NG2 cells in the CNS, beyond their ability to act as glial precursors, remains enigmatic.
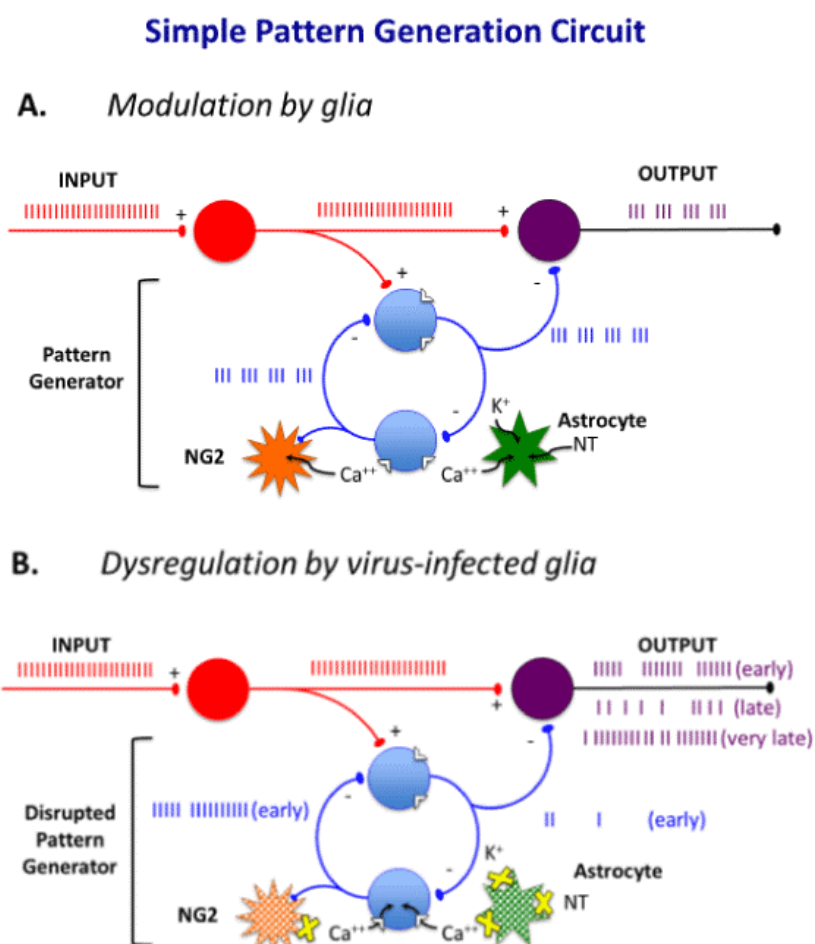
Figure 1: Model of glial-mediated loss of rhythmic activity following retroviral infection. Excitatory input (red spikes, red neuron) to a circuit consisting of recurrently connected rebound neurons (blue neurons) results in an output of periodic oscillating bursts (violet output neuron, violet spikes). Both rebound neurons are inhibitory, forming a recurrent inhibitory circuit that converts a sustained excitatory input to a bursting pattern due to the alternation between inhibition and rebound firing. **A)** In the uninfected condition, increases in calcium concentrations in the extracellular space, which result from activity in the rebound network, are sequestered by surrounding glia. Glial activation required to begin the process of calcium-sequestration is initiated by NG2 cells through their synaptic connections to rebound neurons, their ability to transduce signals through action potential generation, and their connections to other glial cells. As a result, there is minimal calcium entry into rebound neurons through neuronal calcium leak channels. L-type Ca^{++} channels underlying rebound spiking recover rapidly from calcium-dependent inactivation and the rebound-initiated rhythm is maintained during constant excitatory input. The consequent alternation between inhibition and rebound spiking that result in rhythmic bursting in the output neuron also serves to prevent activation of excitatory conductances in the output neuron that could evoke arrhythmic firing. **B)** Following infection and subsequent loss of NG2 function, an excitatory input to the rebound network may evoke an initial rebound response (not illustrated). However, calcium concentrations build up in the extracellular space, as a result of which, calcium enters rebound neurons through calcium leak channels. Increased cytoplasmic calcium leads to prolonged inactivation of L-type Ca^{++} channels, with subsequent failure to generate rebound spiking following inhibition. Inhibition within the rebound network is therefore no longer able to convert a sustained excitatory input to a rhythmic output. Consequently, the output neuron responds to the sustained excitation both as a follower neuron and with added intrinsic conductances that prolong firing and can result in hyperexcitability. At early times following glial disruption and subsequent accumulation of calcium ions in the extracellular space, rhythm-generation remains but is abnormal (Output: early). As the accumulation of extracellular calcium increases, calcium entering rebound neurons through calcium leak channels is unable to be buffered sufficiently. Rebound neurons become hyperexcitable and their inhibitory effect on the output neuron is transiently elevated, resulting in loss of spiking and arrhythmic firing (Output: late). The loss of rebound neurons in the network at later times results in the absence of their inhibitory modulation, and the output becomes non-rhythmic and prolonged (Output: very late).

Despite the parallel occurrence of glial infection and neuronal vacuolation, a functional glial-neuronal link in retrovirus-induced degeneration is currently tenuous. In the inferior colliculus, for example, infected microglia and NG2 cells are observed in close proximity to degenerating neurons [11,16,60,64]. Their infection rates increase alongside the increased loss of rebound activity, suggesting that glial-neuron connections might be critical to disease or its progression. A disconcerting finding in this model is that infected microglia are immunologically and reactively blind to infection by CasBrE, both *in vitro* and *in vivo* [11,60,62,79,80]. Similarly, astrocytes are not activated by CNS virus infection [11], but astrogliosis can arise later in the pathogenic process if the disease kinetics are slowed [12]. These findings imply that microglial and astrocytic neuroinflammation arises as a response to neuronal damage rather than a causative factor in disruption of rebound firing or rhythmic circuits. However, because glial infection rates are high following the systemic administration of retrovirus [11,16,66,81], normal glial regulation of neuronal activity, which involves glial vesicle trafficking, ionic gradients and calcium levels [82], particularly in the extracellular space surrounding neurons, might be compromised. Consequently, associated glial pathways, such as downstream activation of NG2 cells by microglia [83] could become nonfunctional if infected microglia become insensitive to neuronal signaling. It has been demonstrated that CNS damage signals readily activate infected microglia *in vivo*, which in turn inhibits CasBrE induced neurodegeneration [84], a finding that is consistent with the idea that infected microglial cells remain functional but not activated [80]. Thus, it is likely that microglia fail to recognize hyperactive rebound neurons and/or rhythmic circuit alterations *per se*, but do respond once overt cell damage arises. Whether they contribute to this dysregulation is a more challenging question, especially when considered in the context of neurovirulent amphotropic retrovirus CNS infection, where NG2 cells and microglia are together insufficient to precipitate neurodegenerative changes [60]. If select intercellular signaling functions of microglia (reviewed in [85]) are compromised, like their ability to signal to astrocytes *via* ATP release [86,87], and/or signal to NG2 glia by transforming growth factor beta-1 [83], and this alteration is combined with altered NG2 glia and astrocyte functions, it might create a situation where neuronal and circuit functions are inappropriately modulated. Thus, retroviral infection might trigger large-scale degeneration of neurons through the disruption of an intrinsic inter-dependence of glial cell communication.

Concluding Remarks

Computational models suggest that the recruitment of a certain criterion number of neurons is necessary to initiate and maintain rhythms. If neuronal recruitment in the rhythmic circuit drops below 1 neuron/ms, the network is no longer able to generate spontaneous rhythms [88]. This suggests that neuronal loss is not required for network dysfunction; instead a slowing down of the network is sufficient to prevent feedback rhythmic behavior. Of particular note is work showing that the use of a treadmill to re-establish push-pull modulation between excitatory and inhibitory inputs during locomotor rhythmic activity [89], when combined with stem cell transplantation, improves recovery by supplying the inhibitory component of the locomotor rhythm [90]. Thus, despite the presence of neurodegenerative triggers, inhibitory plasticity in neural networks may be important in the restoration or recovery of neurological function. Rhythmic connections in the central nervous system cross long distances. For example, the output of pacemaker neurons in the cerebellum [91] is translated into oscillations of the same frequency in the thalamus through long-distance propagation of oscillating excitatory activity [92]. Alterations in local rhythmic networks are therefore likely to affect distant brain regions. Enhancing network plasticity might prevent propagation of abnormal rhythms from local neuronal populations to large scale networks.

Our studies in the retroviral model indicate that neurological impairments resulting from neurodegenerative triggers may be caused by dysfunctional neuron-glia interactions rather than neuronal loss in rhythmic networks. Simple C-type gamma retroviruses, like CasBrE, require nuclear membrane breakdown for viral integration, and thus in the postnatal CNS, viral infection is restricted to dividing glia and neuronal progenitors that persist in the cerebellar cortex, the hippocampal dentate gyrus, and olfactory bulbs [11,65]. Interestingly, neurons that do become infected by CasBrE do not degenerate despite expressing high levels of viral protein, although it has yet to be examined if infection alters their neurophysiological properties.

We speculate that the degenerative cascade may be initiated by a failing NG2-neuron connection. NG2 cells become altered and die in response to CasBrE-altered regulation of neuronal excitability rather than due to direct infection [64,66]. It is of interest that this cellular damage is not recognized as a damage associated molecular pattern (DAMP) signal by the innate immune system to activate a broad neuroinflammatory response as suggested by others [93]. Perhaps in the context of a different (mouse) genetic background [94,95], or if this cascade were initiated under conditions where immune system development and antigen tolerance was not operating, these changes could constitute an inflammatory initiator, such as has been speculated about viral triggers of multiple sclerosis (MS) [96]. Several recent lines of evidence have implicated human endogenous retrovirus (HERV) expression in MS etiology [97]. This includes findings showing viral protein and particle expression in association with blood and MS brain lesions [96], genetic linkage analyses showing MS association with several HERV loci [98-101], HERV Env viral transduction mouse models showing neuroinflammatory pathology similar to MS [97], and studies showing how HERV-W Env/Syncitin expression in astrocytes is toxic to oligodendrocytes [97,102]. Similarly, HERV-K expression has been implicated in sporadic ALS [103], and HERV-K Env transgenic mice show an ALS-like motor neuron disease phenotype [104]. The parallels in these systems raise the possibility that disruption of selective rhythmic neural circuits could underpin a variety of inflammatory and non-inflammatory neurodegenerative diseases, and highlight the utility of investigating circuit properties and their unique neuronal make-up and their modulation by associated glial components.

Acknowledgements

Conflict of Interest

The authors declare no competing financial interests.

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