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The influence of synaptic activity on neuronal health

Karen F. S. Bell[1] and **Giles E. Hardingham**[1,*]
[1]Centre for Integrative Physiology, University of Edinburgh, Edinburgh EH8 9XD, UK.

Abstract

According to the theory of neuronal health, neurons exist in a spectrum of states ranging from highly resilient to vulnerable. An unhealthy neuron may be rendered dysfunctional or non-viable by an insult that would ordinarily be non-toxic to a healthy neuron. Over the years it has become clear that a neuron's health is subject to dynamic regulation by electrical or synaptic activity. This review highlights recently identified activity dependent signalling events which boost neuronal health through the transcriptional control of pro- and anti-apoptotic genes, the enhancement of antioxidant defences, and the regulation of mitochondrial and neurotrophic factor availability. Furthermore, activity dependent signals have recently been shown to influence a variety of events specific to individual neurodegenerative diseases, which will also be highlighted.

Introduction

Neuronal health is more complex than that offered by the binary classification of either dead or alive. It is better considered a dynamic spectrum of physiological states ranging from protected and fully functional to vulnerable and dysfunctional [1]. A neuron's position within this spectrum can be influenced by both detrimental and beneficial external cues (Figure 1). The concept that electrical activity promotes neuronal health, originated from studies in which activity blockade (either pharmacological or through deafferentation) caused death in the disconnected target neurons [2].

In vivo studies on the chick and later mammalian developing retinotectal/retino-superior collicular pathway revealed that neuronal survival required firing activity, as similarly seen in other systems such as the spiral ganglion [3,4]. Activity-dependent neuroprotection also appears relevant to mature neurons, despite this being difficult to assess in many brain regions given the complexity of incoming afferents. Deafferentation of adult cerebellar granule cells promotes apoptosis, and olfactory bulb ablation triggers deafferentation dependent apoptosis in piriform cortical neurons[2]. Activity-dependent survival has been recapitulated in multiple cultured neuronal types including those from the spinal cord, cerebellum (granule cells and Purkinje cells) hippocampus, neocortex, hypothalamus and several sensory ganglia [2]. Artificial manipulation of neuronal electrical activity both *in vivo* (principally spiral ganglion and retinal ganglion cells) and in culture also promotes neuronal survival in a variety of experimental systems and trauma models, including models of apoptosis, oxidative stress and excitotoxicity/ischemia [2,3,5-7].

Ca^{2+} influx is a key mediator of activity-dependent health-promoting pathways, and the synaptic N-methyl-D-aspartate receptor (NMDAR) is an important route for such influx. Impaired synaptic NMDAR activity promotes neuronal death *in vitro* and *in vivo* in development [8,9], in adults NMDAR blockade exacerbates neuronal loss during ongoing

*Correspondence to Giles.Hardingham@ed.ac.uk, Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK, EH8 9XD. Tel +44 131 6507961, Fax +44 131 6506576..

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neurodegeneration or post traumatic brain injury [10] and impairs survival of new-born neurons in the dentate gyrus [11]. The protective effects of physiological patterns of synaptic NMDAR activity are in marked contrast to the destructive effects of excessive NMDAR activity, particularly that mediated by extrasynaptic NMDARs [12,13].

Other sources of activity-dependent Ca^{2+} elevation are also relevant to neuroprotective signaling, including release from internal stores [14], as well as firing activity promoting influx through voltage-gated Ca^{2+} channels [15], indeed, different sources may cooperate in the creation of the transient. As will be discussed, neuronal activity triggers neuroprotection through the complimentary and coincident regulation of numerous health-promoting pathways that alter vulnerability to apoptotic, excitotoxic and oxidative insults, as will be outlined below. We will also discuss the emerging role of synaptic activity in influencing a number of processes specific to individual neurodegenerative diseases.

Synaptic activity induces expression of survival genes and suppresses pro-death genes

Neuronal activity and resultant Ca^{2+} influx is an important mechanism of dialogue between the synapse and nucleus, enabling both activation of second messengers and gene transcription. Activity-dependent induction of gene expression mediated by the transcription factor CREB is a classic example of an activity dependent health promoting process which confers resistance to both apoptotic and excitotoxic insults [16-18]. More recently, a group of genes termed the activity-regulated inhibitors of death (AID), with visible neuroprotective effects both *in vitro* and *in vivo*, were identified as being activity and nuclear Ca^{2+} regulated [19]. Some of these genes appear to be CREB targets, possibly promoting protection through an enhancement of mitochondrial resistance to stress or toxicity [19]. The Ca^{2+} responsive transcription factor NFAT (nuclear factor of activated T cells), was also recently implicated in NMDAR-dependent neuroprotection [20]. In addition to nuclear Ca^{2+} signalling, other neuroprotective signalling cascades are also triggered at the synaptic NMDAR, including the PI3K-Akt and Erk1/2 pathways [9], and the more recently identified nitric oxide synthase/Erk dependent activation of neuroprotective transcription factor NFI-A (nuclear factor I subtype A [21]). NFI-A joins CREB as a transcription factor implicated in mediating both NMDAR-dependent neuroprotection, as well as conferring resistance to NMDAR-dependent excitotoxicity.

Neuronal activity is also intimately involved in regulating the expression, processing, transport and release of neurotrophic factors, many of which have well-characterized neuroprotective effects. *In vivo* electrical stimulation upregulates fibroblast growth factor 2 (Fgf2) [22] and delays photoreceptor death, preserving retinal function [23], and also promotes IGF-1 secretion by Mueller glia. Elevated expression and release of BDNF is associated with elevated synaptic activity which contributes to neuroprotection [12,24,25], and BDNF is up-regulated by environmental enrichment *in vivo* [26]. The release and maturation of pro-NGF has also been identified as being activity-dependent [27]. Moreover, activity also promotes growth factor trafficking from the periphery in the case of IGF-1, enabling a coordinated delivery of trophic support to active areas [28].

In addition to pro-survival gene induction, synaptic activity results in the transcriptional suppression of core components of the intrinsic apoptotic cascade including *Puma*, *Apaf1*, *Casp9*, *Casp3*, and *Trp53*, leading to enhanced resistance to apoptotic insults [29,30]. While Puma suppression is central to apoptosis prevention, by preventing insult-induced cytochrome c release, additional downstream mechanisms such as the downregulation of Apaf-1 and caspase-9 also exist [29,30]. The transcriptional suppression of these apoptotic genes may be linked to the activity-dependent inactivation of the transcription factors that

control their expression, including p53 and the forkhead box protein O (FOXO) class of transcription factors [29,31,32]

Given that apoptotic features are found in a number of neurodegenerative conditions including Alzheimer's, Parkinson's and Huntington's diseases (AD, PD, HD respectively), the above findings are of clinical relevance, highlighting the possibility that less active neurons are more likely to undergo apoptosis in these conditions. Activity-dependent caspase regulation may be particularly relevant to AD as non-apoptotic, caspase-dependent events have been observed in several aspects of the pathology. Caspases have been shown to cleave the presenilin-1 subunit of γ-secretase, creating a complex which preferentially releases a higher yield of the more toxic 42-form of Aβ [33]. Moreover, caspases are activated following Death Receptor 6 binding by an APP cleavage product, leading to caspase-dependent axonal and cell body degeneration [34]. Caspase activation has also been linked to both tangle formation [35] and synaptic dysfunction [36] in animal models of AD. Given that neurodegeneration is a characteristic feature of AD, disrupted neuronal activity might be a contributing factor to resultant pathology through any of the above described mechanisms or through enhanced vulnerability to apoptosis itself. It should however be noted that caspases can mediate important non-apoptotic physiological events, including forms of long term depression and AMPA receptor internalization which rely on caspase-3 activation [37]. As such, the fact that the *Casp3* gene is itself subject to activity-dependent inactivation [30] may be relevant to physiological as well as pathological processes.

As well as restricting the apoptotic potential of neurons, synaptic activity also boosts neuronal health through an enhancement of intrinsic antioxidant defences. Previously active neurons withstand oxidative insults better than less active neurons, a mechanism which at least partially involves changes within the thioredoxin/peroxiredoxin antioxidant system [6]. Synaptic NMDAR activity reduces the level of oxidant-induced peroxiredoxin hyperoxidation and enhances expression of sulfiredoxin 1 (*Srxn1*) and sestrin 2 (*Sesn2*), the genes whose products are believed to mediate this. Interestingly, in addition to boosting expression of these genes, synaptic NMDAR activity also suppresses the expression of the thioredoxin inhibitor *Txnip*, a FOXO target gene [6]. Also relevant to the control of antioxidant defences is the influence of synaptic activity on gene expression promoted by the co-activator peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α), a master regulator of neuronal antioxidant defences [38,39]. Synaptic activity post-translationally enhances the transactivating potential of PGC-1α, induces transcription of the PGC-1α gene, and triggers the nuclear export of the corepressor SMRT [40] which, when nuclear, can block the antioxidant effects of PGC-1α [39].

Activity dependent regulation of mitochondrial availability and mitochondria related genes

Neuronal health is influenced by energy demands and Ca^{2+} homeostasis, two events which are regulated by mitochondria. By regulating mitochondrial fission/fusion and intracellular trafficking, neuronal activity triggers events which balance energy demands with localized availability [41]. For example, synaptic activity enhances mitochondrial fission, reduces mitochondrial mobility and localizes mitochondria to dendritic spines [42-44] and presynaptic sites [45] where energy demands are high, as is in line with the finding that mitochondrial mobility is accelerated in areas rich in ATP and slowed in areas high in ADP [46].

One mechanism through which mitochondria detect changes in intracellular Ca^{2+} and subsequently alter movement, involves the GTPase Miro, which has two EF-hand Ca^{2+} binding domains. Following Ca^{2+} influx, Miro unhinges mitochondria from transport

machinery, enabling stoppage in specific areas [45,47,48]. Mitochondrial movement into dendritic spines and filopodia is also activity-dependent and is mediated by Wiskott-Aldrich syndrome protein (WASP)-family verprolin homologous protein 1 (WAVE1) whose inhibitory phosphorylation by Cdk5 is in turn suppressed by NMDAR activity [49]. In addition to motility, neuronal activity also promotes gene transcription which enhances mitochondrial health, such as the previously mentioned activation of AID genes [19] or PGC1α [39] which is capable of controlling mitochondrial biogenesis [50].

Neuronal activity can influence aspects of disease pathology

We have hitherto focused on general neuroprotective events triggered by neuronal activity, which may be relevant to the survival of neurons in response to a variety of insults (Figure 2). However, recent studies have illustrated how activity can inhibit molecular events specific to individual neurodegenerative disease processes (Figure 3). As such, neuronal hypo-activity could be an exacerbating factor in certain diseases and since this could also be a consequence of disease pathology, could form a feed-forward cycle of disease progression.

Alzheimer's Disease

Neuronal activity, specifically that involving synaptic NMDAR activation, appears to have a suppressive effect on multiple aspects of AD-related amyloid processing. Synaptic NMDAR activation promotes protective non-amyloidogenic processing, over amyloidogenic processing, as seen by the activity-dependent recruitment of putative α-secretase ADAM-10 [51], increased non-amyloidogenic pathway components c83 and soluble APPα [52], reduced Aβ production and release [51,52], reduced APP695 mRNA expression [53] and reduced intraneuronal Aβ [54]. Interestingly, synaptic activity blockade *in vivo* in a transgenic mouse model of AD increased intraneuronal Aβ, reduced synaptophysin-immunoreactivity, increased synapse loss and worsened behaviour [55], highlighting the importance of neuronal activity in ameliorating pathology. Adrenergic neuronal activity may also be relevant, as β2 adrenergic receptor activation enhances glial Aβ uptake and degradation [56]. One can envisage that any stochastic or disease-related reduction in neuronal activity could worsen neuronal health and accelerate pathogenesis through the removal of the above-mentioned brakes on Aβ-related pathology.

Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis

Both Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS) are characterized by degeneration of motor neurons, an event which is influenced by modest levels of NMDAR activity. In a transgenic mouse model of SMA, exercise was found to delay motor neuron death, and upregulate NMDAR subunit NR2A, an effect which was ablated by NMDAR inhibition [57]. Daily *in vivo* NMDA administration to transgenic SMA-like mice, accelerated postnatal skeletal muscle maturation, reduced motor neuron death, improved neuromuscular junction morphology and motor behaviour and prolonged lifespan [58]. In an ALS-like transgenic mouse model, significant decreases in both NR2A and αCaMKII autophosphorylation were identified with coincident alterations in synaptic plasticity and reduced dendritic outgrowth, prior to symptom onset [59], alterations which led the authors to suggest that reduced glutamatergic signaling may contribute to disease pathogenesis.

Hungtington's Disease

Neuronal activity has also been shown to profoundly impact HD pathology, as largely demonstrated through the use of the YAC 128 HD mouse model. Synaptic activity increased formation of non-toxic mutant huntingtin (mtHtt) inclusions [60] via the NMDA-dependent transcriptional upregulation of chaperonin TRiC (T complex-1 (TCP-1) ring complex),

which mediates non-toxic inclusion formation in neurons, rendering neurons more resistant to mtHtt-mediated death [60]. Synaptic activity also enhances regulation of CREB target gene PGC1α, a co-activator which, as previously mentioned, regulates mitochondrial density and antioxidant defences [38,39,50], and which is lowered in the striatum of HD patients [61], an area particularly vulnerable to PGC1α deficiency [62]. Interestingly, mtHtt directly interferes with CREB-dependent PGC1α expression, leading to mitochondrial dysfunction and metabolic defects [61,63]. Blocking synaptic activity decreases both CREB activity and PGC1α protein levels, while activation has the opposite effect, suggesting a mechanism whereby synaptic NMDAR activity enhances neuronal health and resilience to insult via the protective CREB-PGC1α pathway and promotion of mtHtt inclusion formation [60]. Extrasynaptic NMDA receptor activation has been known for some time to dominate over protective CREB dependent signalling originating from synaptic NMDAR [12,13]. This is particularly relevant given that the YAC 128 mouse model displays an increase in extrasynaptic NMDAR expression and currents, along with an associated decrease in CREB activity [64]. Thus, the beneficial effects of synaptic NMDAR activity are negated by increased, dominating pro-death signalling from extrasynaptic NMDAR. Interestingly, *in vivo* low-dose memantine administration, which preferentially blocks extrasynaptic NMDAR while preserving synaptic NMDAR signalling [65], improved neuropathological and behavioural outcomes [60,64]. In contrast, higher doses of memantine, which also block synaptic NMDARs, exacerbated disease pathology and symptoms [60] highlighting the importance of maintaining synaptic activity to neuronal health and viability.

Conclusions

The myriad routes by which neuronal activity influences neuronal health are becoming clearer. Not only are general antioxidant, mitochondrial and apoptotic pathways subject to control, they are also central to a number of neurodegenerative diseases. Knowledge of such endogenous neuroprotective pathways points to ways in which they may be mimicked or boosted for therapeutic effect. Furthermore, they underline the fact that activity-dependent signals are important contributors to neuronal robustness and that successful therapies should leave these beneficial effects intact.

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* of special interest

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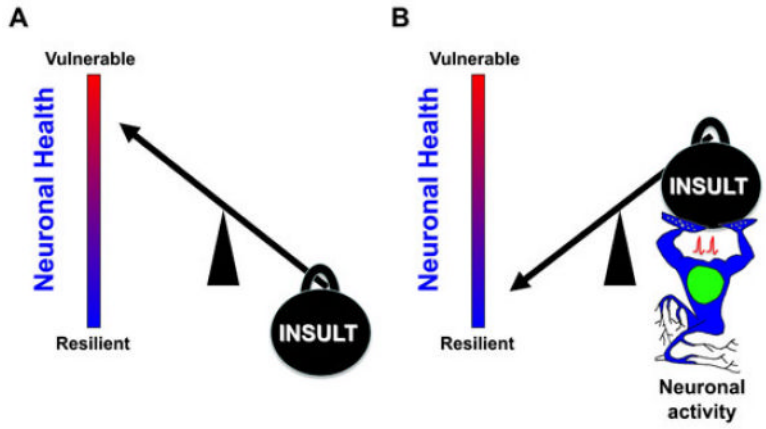

Figure 1.
Neurons exist within a dynamic spectrum of health ranging from vulnerable to resilient as shown by the red to blue gradients. A neuron's position within this spectrum is constantly influenced by a multitude of both beneficial and detrimental cues. In **(A)**, we see that the weight of an "INSULT", which represents a variety of detrimental events [e.g. oxidative stress, excitotoxicity, ischemia, pathology-associated burdens (amyloid beta protein, mutant huntingtin etc.)], burdens the neuron such that health is compromised and it is rendered vulnerable. In **(B)** however, neuronal activity, as represented by an active and muscular neuron, is able to boost neuronal health, enabling the neuron to withstand the same "INSULT" burden, whilst remain resilient, emphasizing the important neuroprotective influence of activity on neuronal health.

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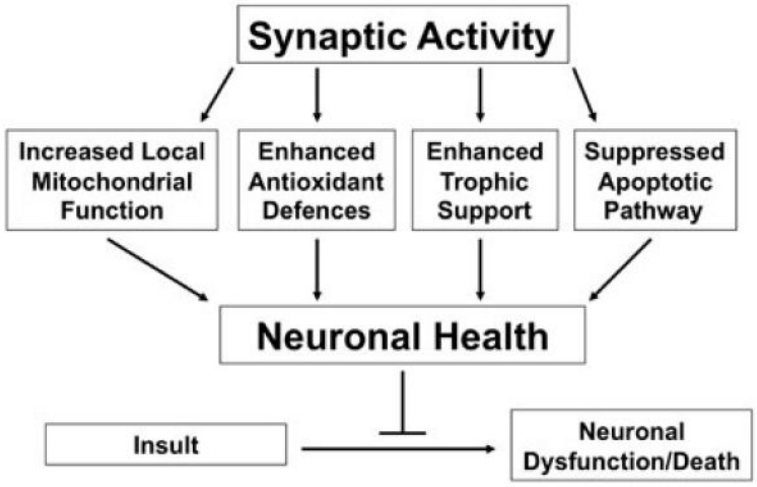

Figure 2.
Schematic demonstrating the mechanisms through which synaptic activity boosts neuronal health, enabling the cell to better resist dysfunction or death. For full description see text.

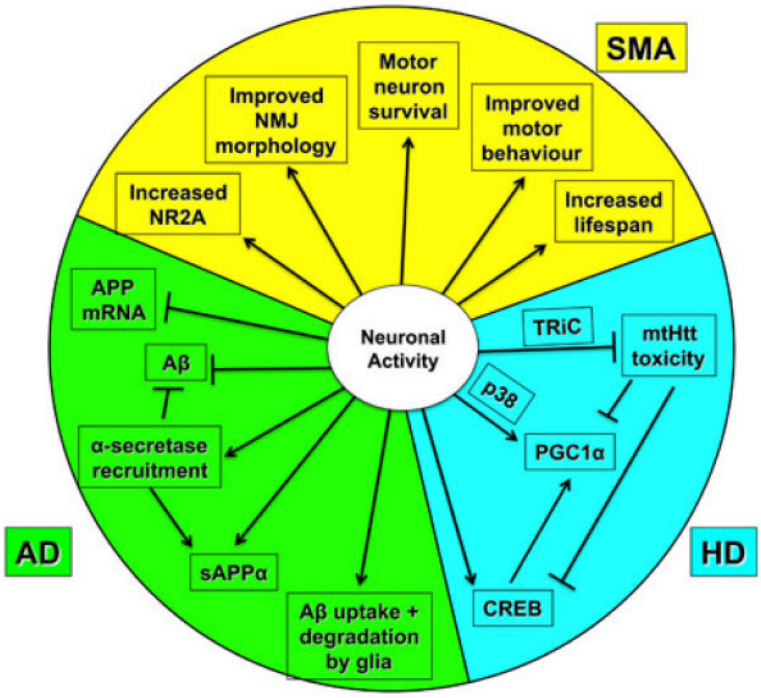

Figure 3.

Neuronal activity has been shown to influence specific disease processes in a number of experimental models of neurodegenerative disease. Summarized in graphic format are disease-specific pathways reported as being influenced by neuronal activity, in experimental models of Alzheimer's disease **(AD)**, Huntington's disease **(HD)** and Spinal Muscular Atrophy **(SMA)**, as reviewed in greater detail in the text. Aβ = amyloid beta protein, APP = amyloid precursor protein, mtHtt = mutant Huntingtin, NMJ = neuromuscular junction, PGC1α = peroxisome proliferator-activated receptor-γ co-activator 1α, sAPPα = soluble Amyloid Precursor Protein alpha, TriC = T complex-1 (TCP-1) ring complex.