Review

Security breach: peripheral nerves provide unrestricted access for toxin delivery into the central nervous system

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Abstract
We explore the hypothesis that a potential explanation for the initiation of motor neuron disease is an unappreciated vulnerability in central nervous system defense, the direct delivery of neurotoxins into motor neurons via peripheral nerve retrograde transport. This further suggests a mechanism for focal initiation of neuro-degenerative diseases in general, with subsequent spread by network degeneration as suggested by the Frost-Diamond hypothesis. We propose this vulnerability may be a byproduct of vertebrate evolution in a benign aquatic environment, where external surfaces were not exposed to concentrated neurotoxins.

Key Words: amyotrophic lateral sclerosis; bioaccumulation; neurodegeneration; neuropathology; neurotoxins; peripheral nerves; retrograde transport; retrotoxicity; suicide transport

Introduction
More than 15% of the worlds' population suffer from disorders of the central nervous system (World Health Organization, 2007) including major neuro-degenerative disease such as Alzheimer's disease, frontotemporal dementia, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis (ALS). The costs to society, financial and otherwise, are staggering, there are no cures and few therapies (Erkkinen et al., 2018), and disease prevention seems not possible (Global Burdon of Disease, 2019). While we continue to learn more about disease pathology, to date we simply do not know their initiating causes. For example, loss of myelin in multiple sclerosis is mediated by an autoimmune attack, and to date over 20 viruses have been falsely implicated in initiating the multi-focal 'plaque-like' onset. Similarly, in ALS the lateral spread of motor neuron (MN) loss follows accumulation of aggregated protein inclusion bodies, with an unknown relationship to principal risk factors including traumatic injury and environmental toxins. Like all neuro-degenerative diseases, ALS begins as a focal lesion (MN loss in the spinal column) with subsequent lateral spreading (Cudkowicz et al., 2004), a progression that is consistent with the Frost-Diamond "prionopathy" hypothesis (Frost and Diamond, 2010). Here we propose that one explanation for selective loss of MN in ALS represents an unappreciated vulnerability in central nervous system (CNS) defense, the direct delivery of neurotoxins to motor neurons via peripheral nerve retrograde transport. We suggest this represents a byproduct of vertebrate evolution in an aquatic environment where external surfaces were not exposed to high concentrations of neurotoxins. Mercury (Hg), for example, is present at only trace levels after release from point sources such as mining and industrial pollution. Inorganic Hg is not a significant neurotoxin until converted to organic methyl-mercury, by bacteria in anoxic aquatic environments, and subsequent bioaccumulation in the marine food chain (Hintelmann, 2010). Thus mercury neuro-toxicity is largely through ingestion rather than external contact.

The human body is exposed to a plethora of environmental toxins and pathogens including bacteria, viruses, and fungi. For somatic tissues, defense mechanisms include humoral immune surveillance and chemical detoxification in the liver. Unlike somatic tissue, neurons in the CNS live throughout our life span and, with limited exceptions (Berninger and Jessberger, 2016), retain the wiring connections established during development, and the CNS provides additional unique adaptations for their protection (**Figure 1**). The CNS is guarded by skull and spinal bones, and it is encased in a meningeal sac filled with cerebralspinal fluid (CSF) that acts like air bags to insulate from physical trauma. Since the skull creates a fixed space, the brain is also vulnerable to compression from within, and a dynamic flux between CSF and the cerebral vasculature stabilizes intra-cranial pressure from edema or arterial-venous pressure gradients generated in the cardiac pulse cycle (Wilson, 2016; Butler et al., 2017). The brain has another specialized cellular filtration system formed by astrocytes, the blood-brain barrier (BBB), that prevents microbes and toxins in the blood from entering brain parenchyma. Bone-marrow derived microglial scavengers also provide immune surveillance. Finally, neurons also withdraw from DNA replication and thus avoid accumulating spontaneous mutations, the hallmark of replicative senescence in somatic tissues. Neuronal axons are also wrapped in insulating myelin sheaths, an economy of size that allows fast conduction with 100-fold smaller axon diameters (Weatherby et al., 2000). Despite these protections, the CNS remains vulnerable to a spectrum of acquired neuro-degenerative diseases. To date only a few risk associated environmental agents have been identified, including viral and microbial invaders (Melton-Celsa, 2014; Parisi and Martinez, 2014) as well as environmental neurotoxins (Kang et al., 2014; Naughton and Terry, 2018). For example, ALS incidence is increased for Gulf War veterans (Horner et al., 2003) and populations with dietary accumulation of the neurotoxin beta-methylamino L-alanine (Murch et al., 2004; Bradley and Mash, 2009). However, the initiating cause for most neuro-degenerative diseases remains unknown.

Motor Neuron Pathology in Amyotrophic Lateral Sclerosis
ALS entails progressive loss of motor neurons in the CNS (Saberi et al., 2015). Like all of the major non-infectious neuro-degenerative diseases, ALS is associated with the accumulation of fibrillary protein aggregates that spread by apparent trans-cellular propagation along synapse connected pathways (Frost and Diamond, 2010). While the root cause is unknown, identified risk factors include genetic mutations (Taylor et al., 2016), environmental toxin exposure (Kang et al., 2014), sport injuries and smoking (Chio et al., 2014; Blecher et al., 2019). Some 10% of cases are 'familial' with inherited mutations in a small family of genes (Taylor et al., 2016), and the remaining 90% of ALS case are termed 'sporadic' (Ling et al., 2013; Tiryaki and Horak, 2014). For both forms the prognosis is the same, a devastating loss of motor function that is generally lethal within 5 years of diagnosis (Horner et al.,

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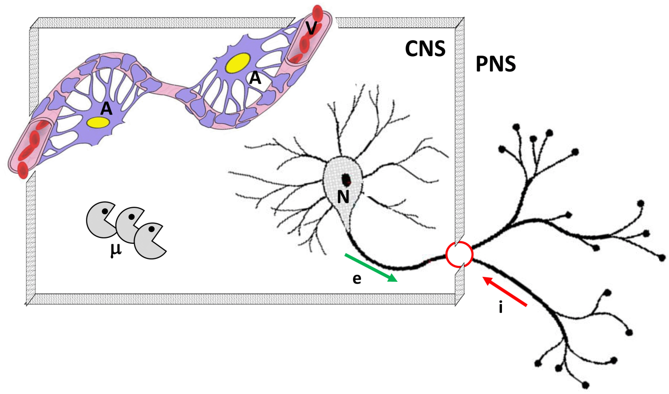

Figure 1 | Peripheral nerve security breach.
Schematic of central nervous system (CNS) motor neurons (N) with axons exiting to the periphery; axons are insulated with myelin sheaths generated by oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system (PNS, not shown). Motor neurons send electrical signals to somatic tissue [e] and receive trophic factor feedback information [i] by retrograde axonal transport. Neuronal defense mechanisms include the astrocyte (A) derived blood brain barrier surrounding blood vessels (v), and immune surveillance by microglia (μ). Retrograde transport can subvert these defense mechanisms to deliver toxins to neuronal soma, a process termed 'suicide transport'.

2003). The known genes provide insight into pathways and mechanisms associated with the pathology of motor neuron degeneration, and potential strategies to approach therapy. However, since their penetrance is low and not all allele carriers develop ALS (Chio et al., 2014), and for those who do the symptoms do not emerge early, these appear to be predisposition genes for disease progression and neither necessary nor sufficient for disease initiation (Hutten and Dormann, 2020).

The hallmarks of neuro-degenerative diseases such as ALS are the presence of inclusion bodies formed from mislocalization and aggregation of proteins in the nucleus or cytoplasm (Saberi et al., 2015; Taylor et al., 2016). These 'stress-granules' result from the deregulation of RNA and protein homeostasis and are a common effector mechanism for both sporadic and familial ALS (Ling et al., 2013). It is unknown whether these are causal or a result of the major degenerative phenotypes including mitochondrial dysfunction (Bose and Beal, 2016; Rahman and Copeland, 2019) and defective nucleo-cytoplasmic and/or axonal transport (Guo et al., 2020; Hutten and Dormann, 2020). Since movement of transport cargo is fundamental to maintaining the complex neuronal architecture, it seems evident that any insult which disrupts this process would be catastrophic for the cell (Perlson et al., 2010). In ALS, the main components of inclusion bodies are FUS (fused in sarcoma) and the trans-active response DNA binding protein TDP-43 (Suk and Rousseaux, 2020), a key element of non-homologous end joining and DNA repair. Since TDP-43 inclusion body aggregates are consistent across all cases of ALS (Suk and Rousseaux, 2020), its loss of function may be central to ALS progression. The mis-localization of TDP-43 is thought to be caused by protein mis-folding due to either inherited mutations in *tardbp* or mediated by mutant chaperone or modifying factors, such as superoxide dismutase (Cudkowicz et al., 2004) (familial ALS), or possibly initiated by exposure to environmental toxins (sporadic ALS). One model that may explain disease progression in sporadic ALS is a focal insult followed by the lateral spread of pathology, analogous to the progression of 'infectious' prion protein aggregates (Erkkinen et al., 2018) due to auto-catalytic mis-folding in Creutzfeld-Jakob disease (Prusiner, 1982), as proposed for the spread of alpha-synuclein aggregate Lewy bodies in Parkinson's disease (Frost and Diamond, 2010).

Neurotoxicity: Active Ingestion or Passive Exposure?

Two risk factors for ALS, sports injury and environmental toxins, provide valuable insight into ALS etiology. ALS is associated with injury prone sports (Chio et al., 2005; Blecher et al., 2019) played predominantly on grass fields (soccer, baseball), and its familiar name recognizes the professional baseball player Lou Gherig. Importantly, ALS clusters have not been identified in traumatic injury prone sports not conducted on grass such as basketball, boxing or ice hockey (Blecher et al., 2019). Thus the highest risk athletes experience abrasion injuries with peripheral nerve damage while exposed to agrochemicals. Of note, ALS is also strongly associated with other agrochemical rich environments such as farming (Kang et al., 2014), and it is more prevalent in farm laborers than in non-farming rural residents (Kang et al., 2014). Together these observations suggest that absorption of neurotoxins via skin abrasion presents a significant risk for ALS initiation.

As outlined below, one model that may explain these observations is contact exposure followed by the retrograde transport of neurotoxic chemicals along motor neuron axons. Toxins could either be passively entrapped in retrograde transport vesicles during assembly of 'signaling endosome' vesicles at the synaptic cleft (Maday et al., 2014), or actively inserted into auto phagosomes during autophagy, the lysosome degradation pathway in neurons (Perlson et al., 2010). Since the peripheral nervous system (PNS) lacks the protective blood filtering system of CNS glial (Reinhold and Rittner, 2020), ingested toxins also have unfiltered access to the PNS. In the dorsal root ganglion of the rat PNS, tight junction protein expression that constitutes the blood-nerve-barrier (BNB) is in the nerve fiber-rich area but not in the cell soma-rich area (Hirakawa et al., 2004). In both cases, chemicals that enter the distal end of an injured motor neuron axon, or evade the BNB in peripheral nerve ganglia, have direct access to neuronal cell bodies in the CNS. Thus the PNS is accessible to the plethora of neurotoxins in our environment, synthetic and otherwise. These include heavy metals such as lead and mercury (Deng et al., 2001; Neal and Guilarte, 2010; Pletz et al., 2016; Siblerud et al., 2019; Mezzaroba et al., 2019), and organophosphates (OP) including common agricultural pesticides, fire retardants and solvents (Naughton and Terry, 2018). Repeated exposure to OPs leads to acetylcholinesterase inhibition, defects in axonal transport, neuro-inflammation, oxidative stress and motor impairment, although to date there is no direct causal link between OP and neurodegenerative disease (Naughton and Terry, 2018). This unique toxin vulnerability may also underlie the exclusive PNS-sensitivity of chemotherapy-induced peripheral neuropathy (Trecarichi and Flatters, 2019). Further research is required to determine whether and which specific toxins may utilize suicide transport, and whether sensory involvement (Pugdahl et al., 2007) and early signs of neuromuscular junction instability (Moloney et al., 2014) represent peripheral nerve damage in ALS.

Retrotoxicity: Suicide Transport of Neurotoxins

Neurons extend axons up to several meters out of the CNS, and the maintenance of these processes depends on axonal transport to deliver cargo from the soma in the CNS to terminal synapses in the periphery and back (Maday et al., 2014; Guo et al., 2020). Thus axonal transport is a constitutive and essential component of neuronal survival. The retrograde transport system is exacerbated by nerve crush (Bisby and Bulger, 1977), it has been used as an experimental tool in pre-clinical studies of axon tracing (Card and Enquist, 2012), it has been co-opted by viruses as a route to establish latency (Koyuncu et al., 2018), and this feature has been manipulated as a strategy for viral vector mediated transgene delivery (Kaspar et al., 2003). Herpes Simplex virus enters latency in our nervous system via mucosal sensory nerves, and when the virus detects immune stress it reactivates, escapes down the same nerves to form cold sores, and finds a new host (Koyuncu et al., 2018). Thus the peripheral nerves present an open door for environmental exposure to both toxins and pathogens; they can bypass the intricate CNS defense mechanisms and have direct access to the CNS via peripheral nerve retrograde transport.

A variety of toxins have been used in studies of PNS axonal pathology and targeted neurotoxicity, and the resulting pathology is dependent on the insult used. Scholars focused on toxic lectins such as ricin (Wiley et al., 1982; Wiley and Oeltmann, 1986), which generate both peripheral and central nerve damage (Harper et al., 1980; Yamamoto et al., 1985; Wiley and Oeltmann, 1986). Ricin is a potent toxin that interferes with ribosomal protein synthesis (Lord et al., 1994) with broad scale tissue destructive effects, and this model has been limited by high lethality in rodents (Liang et al., 2018). Shiga toxin produced by *S. dysenteriae* works similarly to ricin in its toxic effects (Melton-Celsa, 2014). Another toxin utilized in this model, the anthracycline antibiotic doxorubicin, is a fluorescent compound which provides additional benefits for axonal tracing studies (Bigotte and Olsson, 1982; Koda and vander Kooy, 1983). However, doxorubicin is a broad spectrum toxin that is also used for chemotherapy, as it intercalates into DNA to interrupt replication and transcription. Thus many of the toxins used in retrotoxicity studies to date have broad scale tissue toxicity at both the site of injection and of retrograde delivery.

Our recent study (Liang et al., 2021) used the fungal toxin wortmannin, an inhibitor of phosphoinositol 3′-kinase that blocks a signaling pathway that is critical for neuronal survival. Our initial objective was to generate a spinal cord injury (SCI) that was minimal invasive, scalable and reproducible, and was motivated by the need for SCI injury models that were transparent and lacked experimental variability (Steward et al., 2012; Cheriyan et al., 2014; Lemmon et al., 2014; Snow, 2014). We demonstrated that retrograde transport of wortmannin via the sciatic nerve generated a focal loss of motor neurons, proportional to the level of drug administered, in the ipsilateral lumbar spinal cord. Co-injection of fluorescent viral tracers demonstrated that the immediate effects of acute wortmannin did not interfere with retrograde transport. The short half-life of wortmannin resulted in minimal wound spread, and the focal loss of MN resulted in a motor function defect, with both MN loss and motor function defect sustained through the length of the study. The retrograde delivery of wortmannin to motor neurons thus presents a reproducible model for quantitative studies on neural repair. Further, these results led to a surprisingly simple hypothesis for targeted motor neuron toxicity in diseases such as ALS (McKinnon, 2021). The least complex model for these findings would suggest that if you handle pesticides such as organophosphates with a cut on your finger, these neurotoxins can bypass the CNS defense mechanisms and be delivered into and destroy spinal cord motor neurons.

This back door direct entry channel circumvents the many elaborate systems that evolved to protect our CNS from ingested toxins, and this may indicate that our aquatic ancestors faced different challenges than we do for CNS protection. Our CNS is not protected from surface exposure and peripheral nerve transport, perhaps reflecting the low concentration of toxins in the aqueous environment from which we evolved. Since dilution prevented their outer surface from exposure to high concentrations of toxins, CNS defense mechanisms appear to have focused on preventing exposure to ingested toxins with adaptations such the blood brain barrier. In a similar vein, since buoyancy protected the early vertebrate spinal column from structural loads, we also inherited a spine that is poorly suited for vertical support during bipedal locomotion. Thus evolution appears to have given our house a defective frame and left the back door open to intrusion.

Harnessing Retrograde Transport for Delivery of Therapeutics

Retrograde neuro-toxicity may provide insight into how ALS starts, and this can lead to identifying environmental factors responsible for disease onset. This could also focus the many efforts being invested to identify small molecule therapeutics to prevent motor neurons loss. For example, increasing microtubule stability and targeting a family of protein kinase regulators of axonal transport may improve motor neuron function (Naughton and Terry, 2018; Guo et al., 2020). Despite these efforts, to date only four FDA drugs have been approved for ALS treatment, there is no ideal therapeutic, and there is no known cure (Tiryaki and Horak, 2014). Cell replacement also represents a potential therapeutic strategy to replace damaged neural cells (Kiel et al., 2008; Kadoya et al., 2016). However, grafted cells would also presumably be vulnerable to degeneration if the pathology is due to infectious prionopathy (Frost and Diamond, 2010), and engineering such cells to resist uptake (Puangmalai et al., 2020) or propagation of misfolded aggregates may be a prerequisite.

Therapy studies to date have used ingestion for drug delivery with the limitations of restricted access at the BBB and off target toxicity (Guo et al., 2020). The ability to deliver small molecules through retrograde transport may offer a novel avenue to circumvent the BBB by targeted delivery of therapeutics into the CNS. For example, retrograde transport of a viral vector encoding insulin-like growth factor, delivered into the hind limb quadriceps, delayed motor neuron force degeneration and age of death in a mouse model of ALS (Kaspar et al., 2003). This approach appears to have great potential to provide a novel route for targeted delivery of small molecule protective pharmaceuticals, to restore function, and to promote regeneration in many forms of neurodegenerative diseases.

Conclusions

The delivery of a toxin via peripheral nerves directly into the CNS demonstrates the potency of suicide transport and suggests that retrotoxicity can contribute to the etiology of neuro-degenerative diseases. This highlights the need to expand environmental toxicology studies beyond the current focus on ingested toxins. This also suggests that for activities that involve potential nerve injury during chemical exposure, adequate body coverings may decrease risk of disease onset. In addition to avoiding aerosol organophosphates or consuming mercury contaminated fish, we should protect our fingers and toes while fertilizing the lawn. Finally, since peripheral nerves can deliver toxins directly into the spinal cord, retrograde transport can also serve as an efficient vector for testing the neurotoxicity of suspect compounds and targeted delivery of potential therapeutics.

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