17

Wallerian Degeneration in Injury and Diseases: Concepts and Prevention

Bruno S. Mietto[1], Rodrigo M. Costa[1], Silmara V. de Lima[1], Sérgio T. Ferreira[1,2] and Ana M. B. Martinez[1]
[1]*Program of Basic and Clinical Neuroscience,*
[2]*Institute of Medical Biochemistry, Federal University of Rio de Janeiro, Brazil*

1. Introduction

The axon is a highly specialized compartment of neurons. Besides their basic function connecting neurons to their targets, axons play key roles in the nervous system. They are involved in the transport of several molecules indispensable to neuronal activity, act as sensors to guidance cues during development and regeneration, and are essential to maintain normal glial cell functions and myelin sheath assembly (Nave & Trap 2008). Recent evidence indicates that mRNA and Schwann cells-delivered ribosomes can be found within the axoplasm, suggesting that axons may be capable of synthesizing specific proteins (Court et al., 2008). However, most axonal structural proteins are synthesized in the neuronal cell body and transported along the length of the axon. Interruption of this supply leads to a degenerative process known as Wallerian degeneration (WD) in the distal portion of the axon (Coleman, 2005). WD is triggered by intrinsic degenerative pathways that are not correlated to cellular apoptosis (Finn et al., 2000). Axon degeneration is a final common pathway observed not only after a traumatic nerve injury, but also in many neurodegenerative disorders (e.g., Parkinson`s and Alzheimer`s diseases) and in demyelinating diseases such as multiple sclerosis (Coleman, 2005; Coleman & Freeman, 2010). Uncovering the mechanisms that trigger and control axon degeneration is extremely relevant, as such knowledge may offer novel tools to treat severed or damaged axons as well as several neurodegenerative disorders in which WD takes place. In this chapter, we will review the basic concepts of WD, with emphasis on the mechanisms that control axon degeneration following trauma. Next, we will address the issue whether or not current anti-degenerative strategies are efficient and can be envisioned to be applied to humans in the near future.

2. Overview of Wallerian degeneration

WD is classically referred to as a series of degenerative processes triggered in the distal portion of axons after a traumatic injury. WD was originally described by Augustus Waller in 1850 based on his observations in transected glossopharyngeal and hypoglossal nerves (Waller, 1850). Waller observed that, upon transection, the distal nerve stump underwent typical morphological alterations which resulted in total nerve fiber fragmentation followed

by disintegration. Although Waller`s description of WD was based on studies with transected peripheral nerves, the main features of WD are observed after many types of insults (crush, transection, chemical and/or toxic) both in the central nervous system (CNS) and in the peripheral nervous system (PNS), and are also present in the course of neurodegenerative and demyelinating diseases, suggesting a common triggering mechanism (Coleman & Perry, 2002).

Axons respond rapidly to an injury. Just a few hours after lesion, ultra-structural analysis reveals swollen axons with their axoplasms filled with an amorphous matrix (Figure 1) resulting from the fact that the major cytoskeleton proteins (microtubules and neurofilaments) are being degraded by activation of ubiquitin-proteasome system (UPS) and calcium-dependent proteases, respectively (to review, see Vargas & Barres, 2007). This event is called granular disintegration of the axonal cytoskeleton resulting in complete degradation of axonal organelles and proteins and is the main ultra-structural characteristic of axons undergoing WD in the PNS. In central nerve fibers, axon disruption may present in two distinct patterns of axoplasm degeneration, as based on the ultra-structural aspect of the axoplasm (Figure 1) (Narciso et al., 2001).

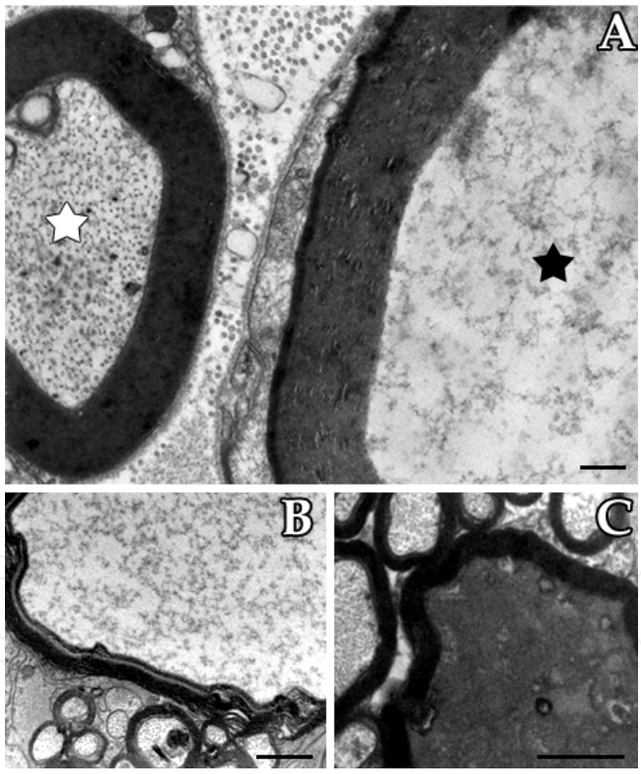


Fig. 1. Ultra-structural images showing different aspects of axon degeneration. Image A represents a sciatic nerve transverse ultra-thin section 48 hours after crush injury in C57BL/6 mice. Note a normal nerve fiber (white star) next to a fiber showing aspects of degeneration with the dissolution of its axoplasmic elements (black star). Images B and C show ultra-thin sections of rat optic nerve, 96 hours after crush injury. Note in B one fiber undergoing watery degeneration, whereas panel C shows a fiber undergoing dark degeneration. Scale bar = 0.3 μm (A) and 1 μm (B and C)

With the onset of WD, the axon will progressively deteriorate and the myelin lamellae will be disrupted into small fragments known as myelin ovoids (Lubińska, 1977) (Figure 2). To date, this criterion is widely used by several groups to study WD in different models (Farah et al., 2011; Narciso et al., 2009).

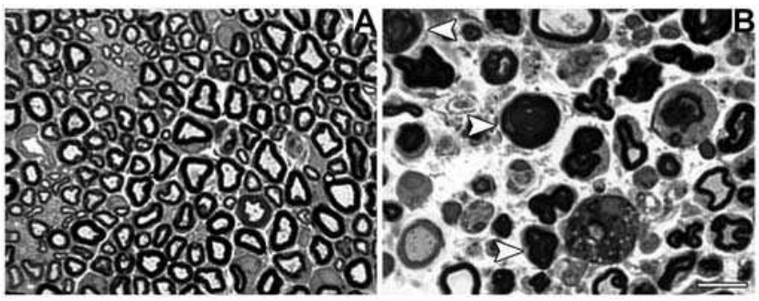


Fig. 2. Wallerian degeneration in C57BL/6 sciatic nerve after crush injury. A. Semi-thin transverse section (toluidine blue staining) from a normal mouse sciatic nerve. B. Semi-thin transverse section from an injured mouse sciatic nerve 96 hours after crush. Note the presence of myelin ovoids (arrowheads). Scale bar = 20 μm

At a later stage of degeneration, myelin and axonal debris will be removed by resident and newly-recruited inflammatory cells (monocytes/macrophages) and microglia (in the CNS) and by Schwann cells (in PNS). The clearance of debris is crucial to create a favorable microenvironment for axon regrowth, since myelin-proteins block axon regeneration by inducing growth-cone collapse (Yiu & He, 2006). During WD, there is an important inflammatory reaction which is highly regulated by immune cells (monocytes/macrophages, T and B lymphocytes, dendritic cells, neutrophils) and by resident non-neuronal cells (microglia and astrocytes in the CNS and Schwann cells in the PNS) (Hawthorne & Popovich, 2011; Sanders & Jones, 2006). Activation of these cells is temporally-orchestrated and triggers the release of several inflammatory molecules that may favor axon degeneration or regeneration. Whether an exacerbated or attenuated inflammatory reaction would be beneficial or harmful to lesioned nerves is still a matter of investigation. Several reports indicate that, in the damaged PNS, inflammation enhances axons regeneration by augmenting macrophages recruitment and myelin debris clearance (Barrete et al., 2008; Narciso et al., 2009). On the other hand, in the damaged CNS, the scenario is not simple: some reports show that recruited macrophages favor axon regeneration (Leon et al., 2000; Yin et al., 2006), while other studies show that it can also be toxic to neurons (Gensel et al., 2009; Popovich & Longbrake, 2008). These conflicting results are currently subject of an intense debate among neuro-immunological researchers and represent an important challenge in the field of neurotrauma (for a review, see Crutcher et al., 2006).

Since Waller`s seminal observations, much has been done in the field of WD. Much of this knowledge was produced with the development of the electron microscope, which allowed researchers to explore in detail the ultra-structural alterations of damaged axons. For a long time, much attention was given to the main mechanisms that control neuronal cell body death; however, to this date, there are several unsolved questions, many of them related to the molecular and cellular pathways that regulate axon destruction, that make this a challenging field for neuroscientists.

3. Molecular and cellular basis of WD

The cascade of events that takes place during axonal degeneration follows a very coordinated sequence determined by the type of nerve fiber affected (motor or sensory neurons, myelinated or unmyelinated fibers), the type and severity of injury, which may vary from a slight crush to complete transection, and by consequences such as deficits in axonal transport (Coleman, 2005) or demyelination (De Vos et al., 2008; Nave & Trapp, 2008). All these factors can affect limb function and recovery in different ways and with different timeframes. But, independently of how severe was the injury, axonal degeneration will occur in a defined fashion. The sequence of steps in axonal degeneration will be discussed in this section. In order to understand the process of axonal degeneration in more detail, however, we first need to cover some basic concepts on axon structure and function.

Each neuron has a highly specialized cylinder-like process that ensures the conduction of information from the cell body to the nerve terminals (Debanne et al., 2011). This process is called "axon" and differs from the other protrusions named "dendrites" in terms of its particular structure and function. The axon emerges from the cell body and varies in length and thickness depending on the function and region of the body it innervates (Wang et al., 2008). Another important feature of axon morphology is the presence or not of a myelin sheath, made by oligodendrocytes in the CNS and by Schwann cells in the PNS. The axonal cylindrical shape is due to the highly organized cytoskeleton components, mainly microtubules and neurofilaments, which are longitudinally aligned along axons. These cytoskeletal components are also responsible for maintenance of axon thickness and are directly implicated in axonal transport of cargoes in association with motor proteins such as dynein and kinesins (De Vos et al., 2008; Perrot et al., 2008).

As previously mentioned, WD is described as the degeneration of axons distal to the point of injury (Waller, 1850). Axonal degeneration is triggered by a large Ca^{2+} influx (George et al., 1995; Martinez & Ribeiro, 1998; Schlaepfer, 1971, 1974), attributed to reversal of the function of the plasma membrane Na^{+}/Ca^{2+} exchanger as a consequence of dysfunction of the Na^{+}-K^{+} ATPase (reviewed in LoPachin & Lehning, 1997). This intracellular Ca^{2+} overload is presumed to cause disruption of mitochondrial oxidative phosphorylation, excessive formation of free radicals (Anderson et al., 1995; Young et al., 1982) and activation of calpains, calcium-activated neutral cysteine proteases that are responsible for cytoskeleton breakdown and myelin protein degradation (Martinez & Canavarro, 2000; Stokes et al., 1983) (Figure 1). Cytoskeleton disruption leads to failure of axon structural integrity and of important intracellular mechanisms such as axonal trafficking of cargoes and energy supply (De Vos et al., 2008). Intracellular calcium stores are also involved in important cellular changes that boost secondary degeneration (Staal et al., 2010). Another intra-axonal degradation mechanism is the activation of the UPS, which has been implicated as a common mechanism for selective protein degradation in a variety of biological processes including axonal degradation during WD (Zhai et al., 2003). Axon swelling and myelin sheath degradation are the next steps in WD. At this stage, it is possible to observe a bead-like pattern formation along the degenerating axon, classically known as myelin ovoids; this is followed by disconnection and complete degradation of the distal stump (Vargas & Barres, 2007) (Figure 2).

One of the key events in WD is the clearance of axon and myelin debris. Immediately after axonal fragmentation and degradation, Schwann cells in the PNS enter continuous cell division, degrade their own membrane and phagocyte myelin and axonal debris (Liu et al.,

1995; Murinson et al., 2005). Besides, macrophage recruitment and infiltration is initiated via cytokine and chemokine signalling, enhancing myelin debris clearance and creating an appropriated environment for axonal regeneration in the PNS. A different scenario is observed in the CNS, where oligodendrocytes undergo apoptosis and are not involved in myelin debris phagocytosis and signaling for macrophage help. This results in delayed macrophage recruitment, exposure of myelin inhibitory proteins, formation of an astroglial scar and secretion of inhibitory molecules such as chondroitin-sulphate proteoglycans which result in a hostile microenvironment for axon regeneration (George & Griffin, 1994) and establish irreversible loss of function of the target organs. In contrast, microglia, which are considered the resident macrophages of the CNS, are activated after an injury by pro-inflammatory cytokines, among other signals, and undergo several rounds of cell division and morphological changes in order to help phagocytosis of dead cells and myelin debris (Ferrer et al., 1990; Kreutzberg, 1995).

An important tool to better understand the steps and mechanisms involved in WD was the discovery of the slow Wallerian degeneration mouse (Wld^S) (Lunn et al., 1989). In these mutant mice, the active process of neurodegeneration and synapse breakdown after an experimental injury presents a ten-fold delay (Lunn et al., 1989). The chimeric *Wld*^{S} gene resulted from a spontaneous mutation in the C57BL/6 mouse strain, causing a tandem triplication in the distal region of chromosome 4 (Conforti et al., 2000), and is known to protect axons in both CNS and PNS from degeneration induced by injury, neurotoxins and neurodegenerative diseases (Wang et al., 2001). The mutation on chromosome 4 comprises a stable 85-kb tandem triplication encoding the N-terminal 70 amino acids of the multiubiquitination factor Ube4b fused in frame to the nuclear nicotinamide adenine dinucleotide (NAD) producing enzyme nicotinamide mononucleotide adenylyltransferase (Nmnat1) (Coleman et al., 1998; Mi et al., 2003). Interestingly, some research groups have described a significant therapeutic potential for this mutation. The *Wld*^{S} gene can be used to confer neuroprotection using delivery methods such as gene therapy (Wang et al., 2001), with the advantage of no side or detrimental effects on other non-neuronal cell types (Wishart et al., 2009).

The differences between CNS and PNS, as pointed out here, include important features regarding molecular mechanisms in nervous system degeneration. Therapeutic approaches such as anti-degenerative strategies must thus be designed and tested according to the target region of the nervous system, type of injury and severity.

4. Anti-degenerative strategies

The main goal of an anti-degenerative strategy is to halt the progress of neurodegeneration in order to rescue neural and non-neural cells from death. Delaying degeneration can also represent a useful approach to open a time-window in which to introduce combinations treatments, e.g., administration of trophic factors. To achieve its goal, such approach should down-regulate genes related to cellular degeneration and up-regulate those related to regeneration. However, this scenario is not simple. During WD, innumerous signaling pathways are triggered within the neuron´s cell body, axon, synaptic terminals and also in glial cells. To make things worse, we still do not know with certainty the identities of the main proteins that control WD. Nonetheless, based on results from animal model experiments, promising strategies have been proven to be effective in modulating WD progression, raising hopes that they may, in the near future, be applied to humans.

Importantly, several studies have shown that the mechanisms that activate neuronal cell death pathways and axonal degeneration are different from each other. Blocking neuronal death does not prevent axonal degeneration, and inhibiting axonal degeneration does not necessarily block neuronal death (Beirowsky et al., 2008; Vohra et al., 2010). In an attempt to block or decrease tissue damage after neuronal injury, one should simultaneously take into consideration the need to inhibit neuronal death, prevent axonal degeneration and, finally, stimulate neuronal regeneration.

4.1 Neuronal survival

Following a lesion to peripheral nerves, there are molecular and cellular events that occur within the axons acutely after injury and that are followed by other alterations in non-neuronal and neuronal cells. These changes culminate in the activation of signals responsible for initiating the regeneration program but also activate neuronal death pathways (Chen et al., 2007; Makwana & Raivich, 2005). The interruption of axonal transport is one of the first events that take place after injury and its impact on the flow of trophic factors, specially the retrograde transport of ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) from target areas, promotes neuronal death (Koliatsos et al., 1993; Sendtner et al., 1997). On the other hand, activation of the signal transducer and activator of transcription 3 (STAT3) and its retrograde transport activates genes important for axonal regeneration (Cafferty et al., 2004). The main components of the axoplasm, the microtubules and neurofilaments, are degraded through the UPS and calpain, respectively (Ehlers, 2004; Zhai et al., 2003), leading to disconnection of the neuronal cell bodies to their targets (Makwana & Raivich, 2005).

Numerous studies have shown the effects of neutrophic factor and neurotrophins (NT) on neuronal survival after injury (Arenas & Persson, 1994; Koliatsos et al., 1993; Yan et al., 1992). Administration of NGF after sciatic nerve transection completely prevented cell loss of dorsal root ganglia neurons (Otto et al., 1987). CNTF and BDNF also prevent death of motor neurons after axotomy (Koliatsos et al., 1993; Yan et al., 1992). This role in preventing neuronal death is important to preserve a certain amount of neuronal cells that can potentially regenerate, resulting in better functional recovery (Chen et al., 2007). The importance of NT in neuronal survival after injury was first appreciated when researchers found that the levels of some NT and neurotrophic factors, and also their receptors, change after lesion and this could account for the roles of different NT on neuronal survival and regeneration (Funakoshi et al., 1993). Funakoshi and collaborators (1993) demonstrated changes in the profile of NT and their receptors at different times after lesion to the sciatic nerve. They showed that levels of BDNF mRNA in the neuronal cell body did not change after sciatic nerve transection but, in contrast, there was a marked increase in the proximal stump. They also found an increase in BDNF mRNA levels at the target, the gastrocnemius muscle, two weeks after lesion. In the case of NT-3, mRNA levels decreased in the cell body after injury but returned to baseline levels 3 days after, while levels in the sciatic nerve dropped within hours after lesion and came back to baseline levels by 2 weeks after the injury. For NT-4, there was no change in the levels of mRNA in the cell body, but there was a 5 -fold increase in the proximal stump and a strong decrease in the neuronal target; this latter event suggests that expression of NT-4 by target organs depends upon neuronal stimulation. Concomitant with changes in the expression of NT, the levels of their receptors also changed and this occurred specially in the nerve's proximal stump. All these changes are important to support neuronal survival after damage and they imply that these factors

are produced by glial cells and targets organs in an attempt to promote neuronal survival, regeneration and re-myelination of the growing axons (Chan et al., 2001; Cosgaya et al., 2002).

Another strategy that has been used to prevent cell death is the use of apoptotic and necrotic blockers with the aim of inhibiting activation of cell death pathways. However, the outcomes from these strategies have only impacted on neuronal survival, and not on axonal neuroprotection and regeneration. For example, overexpression of Bcl-2, a mitochondrial protein that inhibits the intrinsic pathway of caspase activation, enhances retinal ganglion cell (RGC) survival after injury, but its effect is only temporary (for a review, see Isenmann et al., 2003). Moreover, BCL-2 overexpression results only in histological improvement after traumatic brain injury without better behavior outcomes (Tehranian et al., 2006). Calpains are also involved in cell death after injury and are implicated in necrotic and apoptotic pathways (McKernan et al., 2007; Paquet-Durand et al., 2007). *In vitro* studies have shown that by inhibiting calpain activation it is possible to attenuate apoptosis in RGC after injury to the optic nerve (Smith et al., 2011). Although calpain inhibition can affect neuronal survival and provide axonal neuroprotection, there is no evidence that its inhibition can promote axonal neuroprotection and neuronal survival at the same time, which is another indicative that neuronal death and axonal degeneration are triggered and controlled by distinct pathways.

4.2 Axonal neuroprotection

As mentioned above, one of the first events triggered upon injury is the degradation of cytoskeleton proteins by calpains. Several studies have shown positive effects of calpain inhibition in different types of lesion and animal models of CNS and PNS disorders, but the precise relationship between calpain activation and neuronal death is not fully understood (Couto et al., 2004; Kieran & Greensmith, 2004; McKernan et al., 2007). It has been shown that use of calpain inhibitors improves the outcomes of muscle function and cell survival after PNS injury (Kieran & Greensmith, 2004). Application of a calpain inhibitor in the distal target organ improved the rate of cell survival and muscular function 12 weeks after a crush lesion of the sciatic nerve (Harding et al., 1996). To test whether calpain inhibition in neuronal cell bodies would have an impact on neuronal survival and muscle function, Kieran & Greensmith (2004) delivered a calpain inhibitor to the spinal cord after injuring the sciatic nerve. Twelve weeks later they observed an improvement in neuronal survival and muscle function, suggesting that calpain inhibition plays an important role on both neuronal survival and axonal neuroprotection. Couto and collaborators (2004) showed that a calpain inhibitor applied to the site of a crush injury had a neuroprotective effect on optic nerve fibers 4 days after injury (Figure 3), while Silmara de Lima and collaborators (unpublished dada) observed that the delay in axonal degeneration promoted by calpain inhibition had no effect on RGC survival 14 days after optic nerve lesion. These results are important since the delay in the onset of WD can create a time-window to add other strategies and investigate whether different types of combinational treatments can lead to better results.

Sodium or calcium channel blockers have also been used in anti-degenerative strategies to prevent axonal disintegration. Lo and colleagues (2003) demonstrated that neuroprotection to spinal cord axons was achieved using a sodium channel blocker in a model of experimental allergic encephalomyelitis. Those authors reported that, besides preventing axonal degeneration, nerve fibers from animals treated with the sodium channel blocker maintained the ability to conduct action potentials. Calcium channel blockers also proved

effective in protecting axons from degeneration and improving neuronal survival in models of spinal cord and optic nerve injury, with loss of myelin basic protein and alterations in spinal cord evoked potentials attenuated in the former case (Winkler et al., 2003), and RGC survival increased in the latter (Karim et al., 2006).

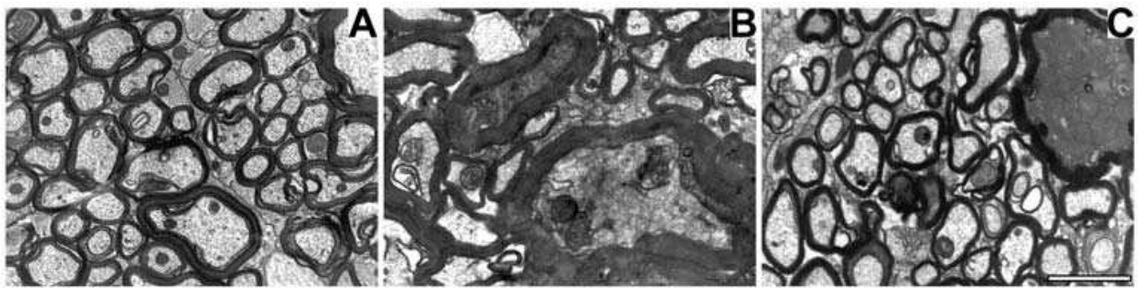


Fig. 3. Transverse ultrathin section from rat optic nerve. A represents a normal optic nerve. B shows a 4 day-injured optic nerve with numerous axons undergoing WD. C shows a 4 day post-injury optic nerve treated with calpain inhibitor prior to the lesion and during the survival time. Note that there are more intact fibers with preserved axoplasm when compared to the image in B. Scale bar = 2 μm

Another important system involved in WD is the UPS, which has been implicated in many biological processes including protein degradation and axonal pathfinding (Campbell & Holt, 2001). The involvement of UPS in the early stages of WD was demonstrated in explanted superior cervical ganglion neurons by Zhai and collaborators (2003), who showed that they could delay axonal degeneration by using a UPS inhibitor. In the same study, they showed that by combining UPS and calpain inhibitors there was also a delay in axonal degeneration. However, better results were obtained when the UPS inhibitor was used prior to the lesion, suggesting that the UPS is involved in the early phase of WD. According to Walker and collaborators (2001), microtubule degradation is sufficient to trigger axonal degeneration, whereas neurofilament disruption *per se* does not affect the distribution of microtubules and other elements of the axon cytoskeleton. For these reasons, maintaining the integrity of axons and improving neuronal survival may be a way to promote a better outcome after nerve fiber injury and to accelerate functional recovery. Therefore, the combined use of calpain and UPS inhibitors may be a promising approach for testing in clinical trials, as inhibitors can be applied peripherally onto neuronal targets.

Another promising strategy is to prevent or slow down axonal degeneration using pharmacological agents. For example, Da Costa et al. (2010) recently showed that intra-peritoneal injections of 2,4-dinitrophenol (DNP) every 24 hours following injury significantly reduced axonal degeneration in a mouse model of sciatic nerve crush injury.

Besides, expression of amyloid precursor protein (APP) and neuregulin-1 (NRG1) were increased in sciatic nerve longitudinal sections after DNP treatment. APP is related to neuronal development, growth and survival (reviewed in Gralle & Ferreira, 2007) and NRG1 plays important roles in development and neurodegeneration (Falls, 2003) and is involved in myelin thickness control (Michailov et al., 2004). DNP is a well-known uncoupler of mitochondrial oxidative phosphorylation (Parascandola, 1974). However, at low concentrations, insufficient to produce mitochondrial uncoupling, DNP has been shown to be a powerful neuroprotective agent against a variety of insults (reviewed in De Felice & Ferreira, 2006; De Felice et al., 2007).

5. Conclusions and perspectives

Since Waller's first experiments and important observations, huge advances have been made in terms of imaging technology, molecular biology tools, genomics and chemical compound synthesis and screening. All this progress has allowed a detailed view of the mechanisms and molecular intimacy of degenerating axons. From accurate freehand drawings to live 3D multiphoton microscopy, researchers have unveiled some of the mysteries behind the dynamics of morphological changes of injured nerves. However, we still face some basic questions regarding axon degeneration: What are the main molecular pathways that trigger axon breakdown after injury? Can we manipulate these key molecules in order to prevent axon degeneration? Furthermore, although it is possible to precisely monitor specific events during degeneration, there are still many open questions about how efficient and which is the best anti-degenerative strategy depending on the type of injury, lesioned region (PNS or CNS) and how far from the cell bodies were the axons damaged. The time between the injury and the beginning of treatment is also a big issue in terms of WD progression and is an important factor regarding limb function recovery. The crosstalk between basic and clinical research is one of the key points in developing new strategies and testing therapeutic hypothesis. Longitudinal screenings on different types of injuries and evaluations of therapies that were applied to each single subject may help to create a blueprint for a personalized nervous system injury treatment.

6. Acknowledgements

Work in the author´s laboratories is funded by grants from the Brazilian agencies Conselho Nacional de Desenvolvimento Científico e Tecnológico, Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro and Instituto de Neurociência Translacional.

7. References

Anderson, D.K.; Means, E.D.; Waters, T.R. & Spears, C. J. (1995). Spinal cord energy metabolism following compression trauma to the feline spinal cord. *J. Neurosurg*. 53:375–380.

Arenas, E. & Persson, H. (1994). Neurotrophin-3 prevents the death of adult central noradrenergic neurons in vivo. *Nature*. 6461:368-71.

Barrete, B.; Hébert, M.A.; Filadi, M.; Lafortune, K.; Vallières, N.; Gowing, G.; Julien, J.P. & Lacroix, S. (2008). Requirement of myeloid cells for axon regeneration. *J. Neurosci*. 38:9363-9376.

Beirowski, B.; Babetto, E.; Coleman, M.P. & Martin, K.R. (2008). The WldS gene delays axonal but not somatic degeneration in a rat glaucoma model. *Eur. J. Neurosci*. 6:1166-79.

Cafferty, W.B.; Gardiner, N.J.; Das P, Q.J.; McMahon, S.B. & Thompson S.W. (2004). Conditioning injury-induced spinal axon regeneration fails in interleukin-6 knock-out mice. *J. Neurosci*. 18:4432-43.

Campbell, D.S. & Holt, C.E. (2001). Chemotropic responses of retinal growth cones mediated by rapid local protein synthesis and degradation. *Neuron*. 6:1013-26.

Chan, J.R.; Cosgava, J.M.; Wu, Y.J. & Shooter, E.M. (2001). Neurotrophins are key mediators of the myelination program in the peripheral nervous system. *Proc. Natl. Acad. Sci*. 25:14661-8. 2001.

Chen, Z.L.; Yu, W.M. & Strickland, S. (2007). Peripheral regeneration. *Annu. Rev. Neurosci.* 30:209-33.

Coleman, M. (2005). Axon degeneration mechanisms: commonality amid diversity. *Nat. Rev. Neurosci.* 6:889–898.

Coleman, M.P. & Freeman, M.R. (2010). Wallerian degeneration, Wlds and Nmnat. *Annu. Rev. Neurosci*. 33:245-267.

Coleman, M. P.; Conforti, L.; Buckmaster, E.A.; Tarlton, A.; Ewing, R.M.; Brown, M.C.; Lyon, M.F. & Perry, V.H. (1998). An 85-kb tandem triplication in the slow Wallerian degeneration (Wlds) mouse. *Proc. Natl. Acad. Sci. USA*. 95:9985-9990

Coleman, M.P. & Perry, V.H. (2002). Axon pathology in neurological diseases: a neglected therapeutic target. *Trends Neurosci*. 25:532-537.

Conforti, L.; Tarlton, A.; Mack, T.G.; Mi, W. & Buckmaster, E. A. (2000). A Ufd2/D4Cole1e chimeric protein and overexpression of Rbp7 in the slow Wallerian degeneration (WldS) mouse. *Proc. Natl. Acad. Sci. USA*. 97: 11377–11382.

Cosgaya, J.M.; Chan, J.R. & Shooter, E.M. (2002). The neurotrophin receptor p75NTR as a positive modulator of myelination. *Science*. 5596:1245-8.

Court, F.A.; Hendriks, W.T.J.; MacGillavry, H.D.; Alvarez, J. & Van Minnen, J. (2008). Schwann cell to axon transfer of ribosomes: toward a novel understanding of the role of glia in the nervous system. *J. Neurosci*. 43:11024-11029.

Couto, L.A.; Narciso, M.S.; Hokoç, J. N. & Blanco Martinez, A. M. (2004). Calpain inhibitor 2 prevents axonal degeneration of opossum optic nerve fibers. *J Neurosci Res*. 77: 410-419.

Crutcher, K.A.; Gendelman, H.E.; Kipnis, J.; Perez-Polo, J.R.; Perry, V.H.; Popovich, P.G. & Weaver, L.C. (2006). Debate: "is increasing neuroinflammation beneficial for neural repair?". *J Neuroimmune Pharmacol*. 1:165-211.

Da Costa, R.M.; Martinez, A.M.B. & Ferreira, S.T. (2010). 2,4-Dinitrophenol blocks neurodegeneration and preserves sciatic nerve function after trauma. *J. Neurotauma*. 5:829-841.

De Felice, F.G. & Ferreira, S.T. (2006). Novel neuroprotective, neuritogenic and anti-amyloidogenic properties of 2,4-dinitrophenol: The gentle face of Janus. *IUBMB Life* 58:185–191.

De Felice, F.G.; Wasilewska-sampaio, A.P.; Gomes, F.A.; Klein, W.L. & Ferreira, S.T. (2007). Cyclic AMP enhances Abeta oligomerization blockers as potential theraqpeutics agents in Alzheimers diseases. *Curr. Alzheimer Res.* 3:263-271.

De Vos, K.J.; Grierson, A.J.; Ackerley, S. & Miller, C.C. (2008). Role of axonal transport in neurodegenerative diseases. *Annu. Rev. Neurosci.* 31:151–73.

Debanne, D.; Campanac, E.; Bialowas, A.; Carlier, E. & Alcaraz, G. (2011). Axon physiology. *Physiol. Rev.* 91(2):555-602.

Ehlers, M.D. (2004). Deconstructing the axon: Wallerian degeneration and the ubiquitin-proteasome system. *Trends. Neurosci.* 1:3-6.

Falls, D.L. (2003). Neuregulins: Functions, forms, and signaling strategies. *Exp. Cell. Res.* 284:14–30.

Farah, M.H.; Pan, B.H.; Hoffman, P.N.; Ferraris, D.; Tsukamoto, T.; Nguyen, T.; Wong, P.C.; Price, D.L.; Slusher, B.S. & Griffin, J.W. (2011). Reduced BACE1 activity enhances clearance of myelin debris and regeneration of axons in the injured peripheral nervous system. *J. Neurosci*. 15:5744-5754.

Ferrer, I.; Bernet, E.; Soriano, E.; Del Rio, T. & Fonseca, M. (1990). Naturally occurring cell death in the cerebral cortex of the rat and removal of dead cells by transitory phagocytes. *Neuroscience.* 39:451–458.

Finn, J.T.; Weil, M.; Archer, F.; Siman, R.; Srinivasan, A. & Raff, M.C. (2000). Evidence that wallerian degeneration and localized axon degeneration induced by local neurotrophin deprivation do not involve caspases. *J. Neurosci*. 20:1333-1341.

Funakoshi, H.; Frisén, J.; Barbany, G.; Timmusk, T.; Zachrisson, O.; Verge, V.M. & Persson, H. (1993). Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. *J. Cell. Biol.* 2:455-65.

Gensel, J.C.; Nakamura, S.; Guan, Z.; Rooijen, N.V.; Ankeny, D.P. & Popovich, P.G. (2009). Macrophages promote axon regeneration with concurrent neurotoxicity. *J. Neurosci*. 12:3956-3968.

George, R. & Griffin, J.W. (1994). Delayed macrophage responses and myelin clearance during Wallerian degeneration in the central nervous system: the dorsal radiculotomy model. *Exp. Neurol.* 129:225–36.

George, E.B.; Glass, J.D. & Griffin, J.W. (1995). Axotomy-induced axonal degeneration is mediated by calcium influx through ion-specific channels. *J. Neurosci.* 15:6445–6452.

Gralle, M. & Ferreira, S.T. (2007). Structure and functions of the human amyloid precursor protein: The whole is more than the sum of its parts. *Prog. Neurobiol.* 82:11–32.

Harding, D.I.; Greensmith, L.; Connold, A.L. & Vrbová, G. (1996). Stabilizing neuromuscular contacts increases motoneuron survival after neonatal nerve injury in rats. *Neuroscience.* 3:799-805.

Hawthorne, A.L. & Popovich, P.G. (2011). Emerging concepts in myeloid cell biology after spinal cord injury. *Neurotherapeutics*. 2:252-261.

Isenmann, S.; Kretz, A. & Cellerino, A. (2003). Molecular determinants of retinal ganglion cell development, survival, and regeneration. *Prog. Retin Eye Res*. 4:483-543.

Karim, Z.; Sawada, A.; Kawakami, H.; Yamamoto, T. & Taniguchi, T. (2006). A new calcium channel antagonist, lomerizine, alleviates secondary retinal ganglion cell death after optic nerve injury in the rat. *Curr. Eye Res*. 3:273-283.

Kieran, D. & Greensmith, L. (2004). Inhibition of calpains, by treatment with leupeptin, improves motoneuron survival and muscle function in models of motoneuron degeneration. *Neuroscience*. 2:427-39.

Koliatsos, V.E.; Clatterbuck, R.E.; Winslow, J.W.; Cayouette, M.H. & Price, D.L. (1993). Evidence that brain-derived neurotrophic factor is a trophic factor for motor neurons in vivo. *Neuron*. 3:359-67.

Kreutzberg, G.W. (1995) The First Line of Defense in Brain Pathologies. *Drug Research.* 45: 357–360

Leon, S.; Yin, Y.; Nguyen, J.; Irwin, N. & Benowitz, L.I. (2000). Lens injury stimulates axon regeneration in the mature rat optic nerve. *J. Neurosci*. 12:4615-4626.

Liu, H.M.; Yang, L.H. & Yang, Y.J. (1995). Schwann cell properties: 3. C-fos expression, bFGF production, phagocytosis and proliferation during Wallerian degeneration. *J. Neuropathol. Exp. Neurol.* 54:487–96.

Lo, A.C.; Saab, C.Y.; Black, J.A. & Waxman, S.G. (2003). Phenytoin protects spinal cord axons and preserves axonal conduction and neurological function in a model of neuroinflammation in vivo. .*J Neurophysiol*. 5:3566-71.

LoPachin, R.M. & Lehning, E.J. (1997) Mechanism of calcium entry during axon injury and degeneration. *Toxicol. Appl. Pharmacol.* 143:233–244

Lubińska, L. (1977). Early course of wallerian degeneration in myelinated fibers of the rat phrenic nerve. *Brain Res*. 1:47-63.

Lunn, E.R.; Perry, V.H.; Brown, M.C.; Rosen, H. & Gordon, S. (1989). Absence of Wallerian degeneration does not hinder regeneration in peripheral nerve. *Eur. J. Neurosci.* 1:27–33.

Makwana, M. & Raivich, G. (2005). Molecular mechanisms in successful peripheral regeneration. *FEBS. J.* 11:2628-38.

Martinez, A.M.B. & Canavarro, S. (2000). Early myelin breakdown following sural nerve crush: a freeze-fracture study. *Braz. J. Med. Biol. Res.* 12:1477-1482.

Martinez, A.M.B. & Ribeiro, L.C.V. (1998). Ultrastructural localization of calcium in peripheral nerve fibers undergoing Wallerian degeneration: an oxalate-pyroantimonate and x-ray microanalysis Study. *J. Submicrosc Cytol Pathol.* 3:451-458.

McKernan, D.P.; Guerin, M.B.; O'Brien, C.J. & Cotter, T.G. (2007). A key role for calpains in retinal ganglion cell death. *Invest. Ophthalmol. Vis. Sci*. 12:5420-5430.

Mi, W.; Glass, J. D. & Coleman, M. P. (2003). Stable inheritance of an 85-kb triplication in C57BL/WldS mice. *Mutat. Res.* 526:33-37.

Michailov, G.V.; Sereda, M.W.; Brinkmann, B.G.; Fischer, T.M.; Haug, B.; Birchmeier, C.; Role, L.; Lai, C.; Schwab, M.H. & Nave, K.A. (2004). Axonal neuregulin-1 regulates myelin sheath thickness. *Science* 304:700–703.

Murinson, B.B.; Archer, D.R.; Li, Y. & Griffin, J.W. (2005). Degeneration of efferent myelinated fibers prompts mitosis in Remak Schwann cells of uninjured C-fibers afferents. *J. Neurosci.* 25:1179-1187.

Narciso, M.S.; Hokoç, J.N. & Martinez, A.M.B. (2001). Watery and dark axons in Wallerian degeneration of the opossum`s optic nerve: different patterns of cytoskeletal breakdown?. *An. Acad. Bras. Cienc*. 2:231-243.

Narciso, M.S.; Mietto, B.S.; Marques, S.A.; Soares, C.P.; Mermelstein, C.S.; El-Cheikh, M.C. & Martinez, A.M.B. (2009). Sciatic nerve regeneration is accelerated in galectin-3 knockout mice. *Exp. Neurol*. 217:7-15.

Nave, K.A. & Trapp, B.D. (2008). Axon-glial signaling and the glial support of axon function. *Annu. Rev. Neurosci.* 31: 535–561.

Otto, D.; Unsicker, K. & Grothe, C. (1987). Pharmacological effects of nerve growth factor and fibroblast growth factor applied to the transectioned sciatic nerve on neuron death in adult rat dorsal root ganglia. *Neurosci. Lett.* 1-2:156-60.

Paquet-Durand, F.; Johnson, L. & Ekström, P. (2007). Calpain activity in retinal degeneration. *J. Neurosci. Res.* 4:693-702.

Parascandola, J. (1974). Dinitrophenol and bioenergetics: A historical perspective. *Mol. Cell Biochem*. 5:69–77.

Perrot, R.; Berges, R.; Bocquet, A. & Eyer, J. (2008). Review of the multiple aspects of neurofilament functions, and their possible contribution to neurodegeneration. *Mol. Neurobiol.* 38:27–65.

Popovich, P.G. & Longbrake, E.E. (2008). Can the immune system be harnessed to repair the CNS?. *Nat. Rev. Neurosci.* 6:481-493.

Sanders, V.M. & Jones, K.J. (2006). Role of immunity in recovery from a peripheral nerve. *J. Neuroimmune. Pharmacol*. 1:11-19.

Schlaepfer, W.W. (1971). Experimental alterations of neurofilaments and neurotubules by calcium and other ions. *Exp. Cell Res.* 67:73–80.

Schlaepfer, W.W. (1974). Calcium-induced degeneration of axoplasm in isolated segments of rat peripheral nerve. *Brain Res*. 69:203–215.

Sendtner, M.; Götz, R.; Holtmann, B. & Thoenen, H. (1997). Endogenous ciliary neurotrophic factor is a lesion factor for axotomized motoneurons I adult mice. *J. Neurosci.* 18:6999-7006.

Smith, A.W.; Das, A.; Guyton, M.K.; Ray, S.K.; Rohrer, B. & Banik N.L. (2011). Calpain inhibition attenuates apoptosis of retinal ganglion cells in acute optic neuritis. *Invest. Ophthalmol. Vis. Sci*. 7:4935-41.

Staal, J.A., Dickson, T.C., Gasperini, R., Liu, Y., Foa, L. & Vickers, J.C. (2010) Initial calcium release from intracellular stores followed by calcium dysregulation is linked to secondary axotomy following transient axonal stretch injury. *J. Neurochem.* 112:1147-1155.

Stokes, B.T.; Fox, P. & Hollinden, G. (1983). Extracellular calcium activity in the injured spinal cord. *Exp. Neurol*. 80:561–572.

Tehranian, R.; Rose, M.E.; Vagni, V.; Griffith, R.P.; Wu, S.; Maits, S.; Zhang, X.; Clark, R.S.; Dixon, C.E.; Kochanek, P.M.; Bernard, O. & Graham, S.H. (2006). Transgenic mice that overexpress the anti-apoptotic Bcl-2 protein have improved histological outcome but unchanged behavioral outcome after traumatic brain injury. Brain Res. 1:126-35.

Vargas, M.E. & Barres, B.A. (2007). Why is Wallerian Degeneration in the CNS so slow? *Ann. Rev. Neurosci.* 30:157-179.

Vohra, B.P.; Sasaki, Y.; Miller, B.R.; Chang, J.; DiAntonio, A. & Milbrandt J. (2010). Amyloid precursor protein cleavage-dependent and -independent axonal degeneration programs share a common nicotinamide mononucleotide adenylyltransferase 1-sensitive pathway. *J. Neurosci.* 41:13729-13738.

Walker, K.L.; Yoo, H.K.; Undamatla, J. & Szaro, B.G. (2001). Loss of neurofilaments alters axonal growth dynamics. *J Neurosci.* 24:9655-66

Waller, A. (1850). Experiments on the section of glossopharyngeal and hypoglossal nerves of the frog and observations of the alternatives produced thereby in the structure of their primitive fibers. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 140:423–29.

Wang, M.S.; Fang, G.; Culver, D.G.; Davis, A.A.; Rich, M.M. & Glass, J.D. (2001). The WldS protein protects against axonal degeneration: a model of gene therapy for peripheral neuropathy. *Ann. Neurol.* 50:773-9.

Wang, S.S.; Shultz, J.R.; Burish, M.J.; Harrison, K.H.; Hof, P.R.; Towns, L.C.; Wagers, M.W. & Wyatt, K.D. (2008). Functional trade-offs in white matter axonal scaling. *J. Neurosci.* 28:4047–4056.

Winkler, T.; Sharma, H.S.; Stålberg, E.; Badgaiyan, R.D.; Gordh, T. & Westman, J. (2003). An L-type calcium channel blocker, nimodipine influences trauma induced spinal cord conduction and axonal injury in the rat. *Acta Neurochir. Suppl.* 86:425-32.

Wishart, T.M.; Brownstein, D.G.; Thomson, D.; Tabakova, A.M.; Boothe, K.M.; Tsao, J.W. & Gillingwater, T.H. (2009) Expression of the neuroprotective slow Wallerian degeneration (WldS) gene in non-neuronal tissues. *BMC Neurosci*. 10:148.

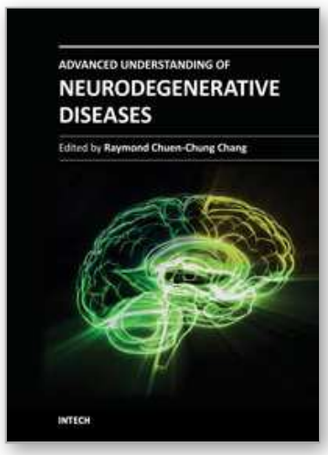
Yan, Q.; Elliott, J. & Snider, W.D. (1992). Brain-derived neurotrophic factor rescues spinal motor neurons from axotomy-induced cell death. *Nature*. 6406:753-755.

Yin, Y.; Henzl, M.T.; Lorber, B.; Nakazawa, T.; Thomas, T.T.; Jiang, F.; Langer, R.; Benowitz, L.I. (2006). Oncomodulin is a macrophage-derived signal for axon regeneration in retinal ganglion cells. *Nat. Neurosci.* 6:843-852.

Yiu, G. & He, Z. (2006). Glial inhibition of CNS axon regeneration. *Nat Rev Neurosci*. 8:617-627.

Young, W.; Yen, V. & Blight, A. (1982) Extracellular calcium ionic activity in experimental spinal cord contusion. *Brain Res.* 253:105–113.

Zhai, Q.; Wang, J.; Kim, A.; Liu, Q.; Watts, R.; Hoopfer, E.; Mitchison, T.; Luo, L. & He, Z. (2003). Involvement of the ubiquitin-proteasome system in the early stages of wallerian degeneration. *Neuron*. 2:217-25.



Advanced Understanding of Neurodegenerative Diseases

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-529-7
Hard cover, 442 pages
Publisher InTech
Published online 16, December, 2011
Published in print edition December, 2011

Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Bruno S. Mietto, Rodrigo M. Costa, Silmara V. de Lima, Sérgio T. Ferreira and Ana M. B. Martinez (2011). Wallerian Degeneration in Injury and Diseases: Concepts and Prevention, Advanced Understanding of Neurodegenerative Diseases, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-529-7, InTech, Available from: http://www.intechopen.com/books/advanced-understanding-of-neurodegenerative-diseases/wallerian-degeneration-in-injury-and-diseases-concepts-and-prevention

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen