ASPECTS OF RETINAL AND OPTIC NERVE PATHOLOGY AFTER EXCITOTOXIC RETINAL INJURY

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Chapter 10: IMMUNOHISTOCHEMICAL CHANGES IN MICROGLIAL AND ASTROCYTIC CELL MARKERS

10.1 Introduction

Numerous glial cells support the retinal neurons and optic nerve axons. Main glial cells in the retina consists of microglia and two types of macroglial cells, astrocytes and specialized Müller cells.[674] The small oval-shaped retinal microglial cells are distributed mainly in the INFL, IPL and OPL of the retina. Astrocytes are limited to the inner retinal surface, mainly located within the INFL and GCL. Müller cells, on the other hand, have wider distribution and they extend radially between the inner and outer limiting membranes. As all retinal neurons including the RGC neurons in INFL are unmyelinated, no oligodendroglia are seen in the retina. As Müller cells are restricted only to the retina, the glial cell population in optic nerve consists of astrocytes, microglia and oligodendrocytes which are distributed between the axons along the whole length.

Microglia, the smallest glial cells representing the innate immune system, are derived from myeloid progenitor cells. They are the immunocompetent cells, related to the macrophage-phagocytic system. They act as phagocytes and protect the brain from the invading micro-organisms. They provide first line of defense in response to any form of neuronal injury and play an important role in neuroprotection. Astrocytes have the classical morphology, with part of the cell in contact with a blood vessel, and many fine processes interwoven around neuronal cell bodies and processes. They play a vital role in neuronal signaling by maintaining ionic equilibrium, as well as by protecting the retina by contributing to the blood-retinal barrier.[675] Besides regulating the neuronal metabolism and maintaining neuronal function, astrocytes in the optic nerve provide mechanical support to the axons.[676, 677] They protect

axons against various sources of damage by forming a protective blood nerve barrier and once damaged, they participate in the scarring and repair of the nervous system.[677] Similarly, müller cells in the retina provide structural support to the retinal neurons and regulate their function through various mechanisms.[101]

In neural injury, microglia and astrocytes transform into their 'activated' phenotypes. This process of activation of glial cells is termed as 'reactive gliosis'.[124] Under pathological conditions, such as trauma, stroke or any inflammation-mediated degeneration of the central nervous system, the resting microglia proliferate and change their shape to become rod-shaped 'activated microglia', which possess numerous lysosomes and phagosomes and release pro-inflammatory and neurotoxins such as cytokines, eicosanoids, ROS and NO.[123] This microglia-driven neuroinflammatory response has been identified in conditions such as Alzheimer's disease.[678] multiple sclerosis [679] and stroke and NMDA induced neurotoxicity.[680] Astroglial cells undergo proliferation and differentiation to support axons in CNS injury as seen in various inflammatory and demyelinating autoimmune diseases.[681, 682] Their proliferation results in the formation of a scar in distal stump following axotomy.[512]

Detection of glial activation provides diagnostically useful information on the site and progression of the disease or neurodegeneration.[683] Besides relevance to clinicians, markers of glial activation are important for researchers. Imaging tools using positron emission tomography with relative selectivity for activated microglia, are under development to study and diagnose in vivo neuropathology.[683] Although, nerve degeneration is classically evaluated using histopathological techniques, gliosis can be assessed using specific antigenic biomarkers.

There are only a few specific microglial antigens. Therefore, most of the antibodies used for the detection are raised against macrophage-cell line. Common molecular biomarkers in immunological detection of microglia use antibodies OX-42 [684], MAC-1 [685] and ED-1 (CD68). ED-1 is a monoclonal antibody (mAb) that recognizes a single chain glycoprotein of 90-110kDa expressed predominantly on the lysosomal membranes of the fixed and wandering macrophages including microglia in the nervous system and expression of this antigen in cells increases during phagocytic activity.[686] Similarly, one of the best known markers for the altered macroglial cell activity is GFAP.[113, 687] GFAP is a 51-kDa intermediate filament protein found in the astrocyte and Müller cell end feet and processes. Although, Müller glial cells in normal rat retinas express little or no GFAP,[688] they show increased expression in retinal injuries including ischemia,[689] glaucoma [690] and kainite induced neurotoxicity.[469]

Based on the results obtained in the present and previous studies, it is obvious that the injection of NMDA into the rat vitreous humor causes degeneration of the inner retinal neurons as well as optic nerve axons. Although gliosis is a common phenomenon seen in neural injury, whether this is primary or secondary factor contributing to the axon damage remains to be determined. In order to solve the mystery, the current part of the study focused on these glial cell changes secondary to axon damage as a result of NMDA induced retinal insult. These glial cell changes will be studied using immunolabelling with ED-1 for microglia and GFAP for astrocytes and müller cells. This immunohistological study focused on the temporal changes in the expression profile of these two molecular markers so as to better understand the role of astrocytes and microglial cells in the excitotoxin-induced somagenic optic nerve degeneration.

10.2 Results

10.2.1 ED-1 immunostaining in the retina

No ED-1 immunostaining was observed in the saline-treated retinas at all the time intervals examined.[See Figure 52] Negative and positive controls showed no damage at any time point.

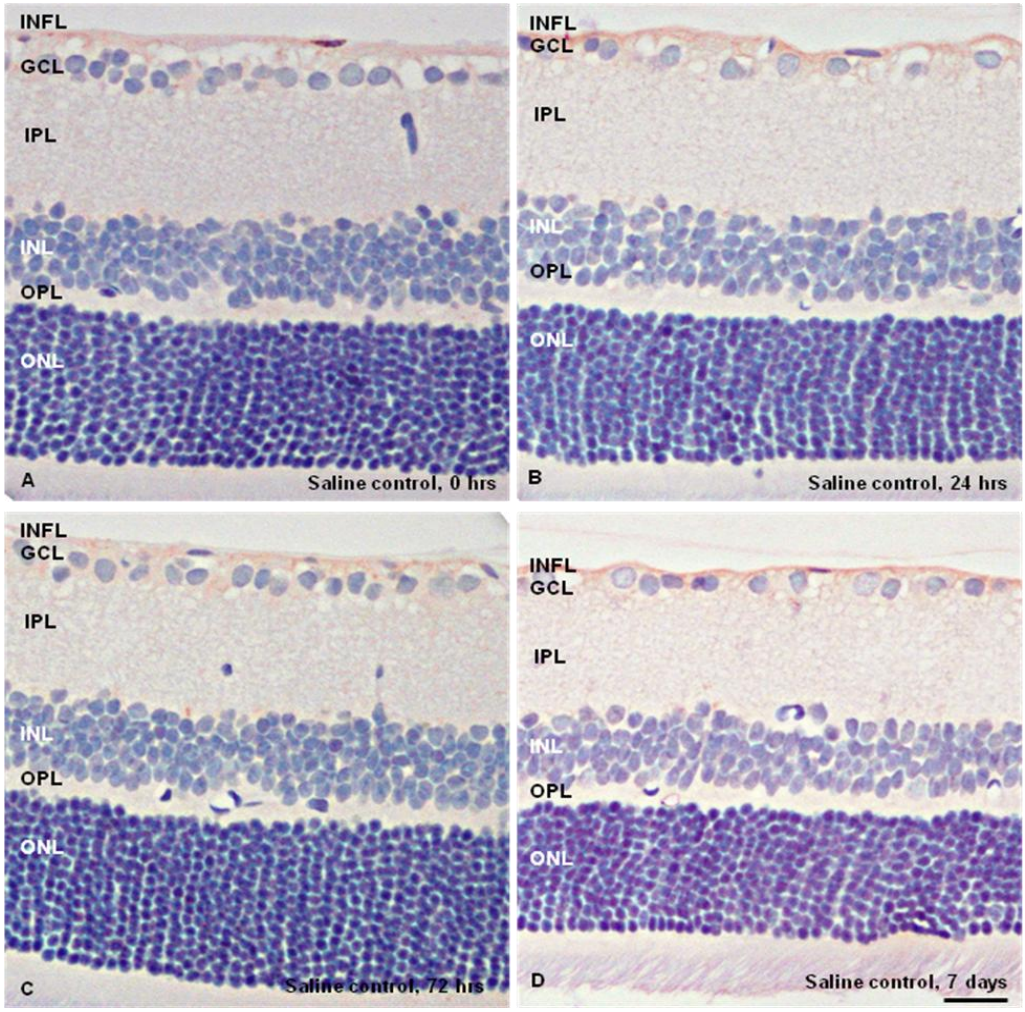

Figure 52. ED-1 immunoreactivity of saline-injected retinas of rat. Soon after injection no immunoreactivity was detected (A). X200 magnification. Bar= 50μm

No ED-1 immunostaining was seen in the retina immediately after the NMDA injection. At 1 day after NMDA injection, punctate ED-1 immunoreactive products were seen confined to the INFL, GCL and inner IPL. ED-1 positive cells with round profile were also noticed in the vitreous. At 3 days post NMDA injection, amoeboid or pleomorphic ED-1 immunoreactive cells, with many of them showing thin and stout processes, were seen distributed in the INFL, GCL and IPL. The immunoreactivity increased further at 7 days, when ED-1 positive cells became more numerous in these layers as well as the vitreous. [See Figure 53]

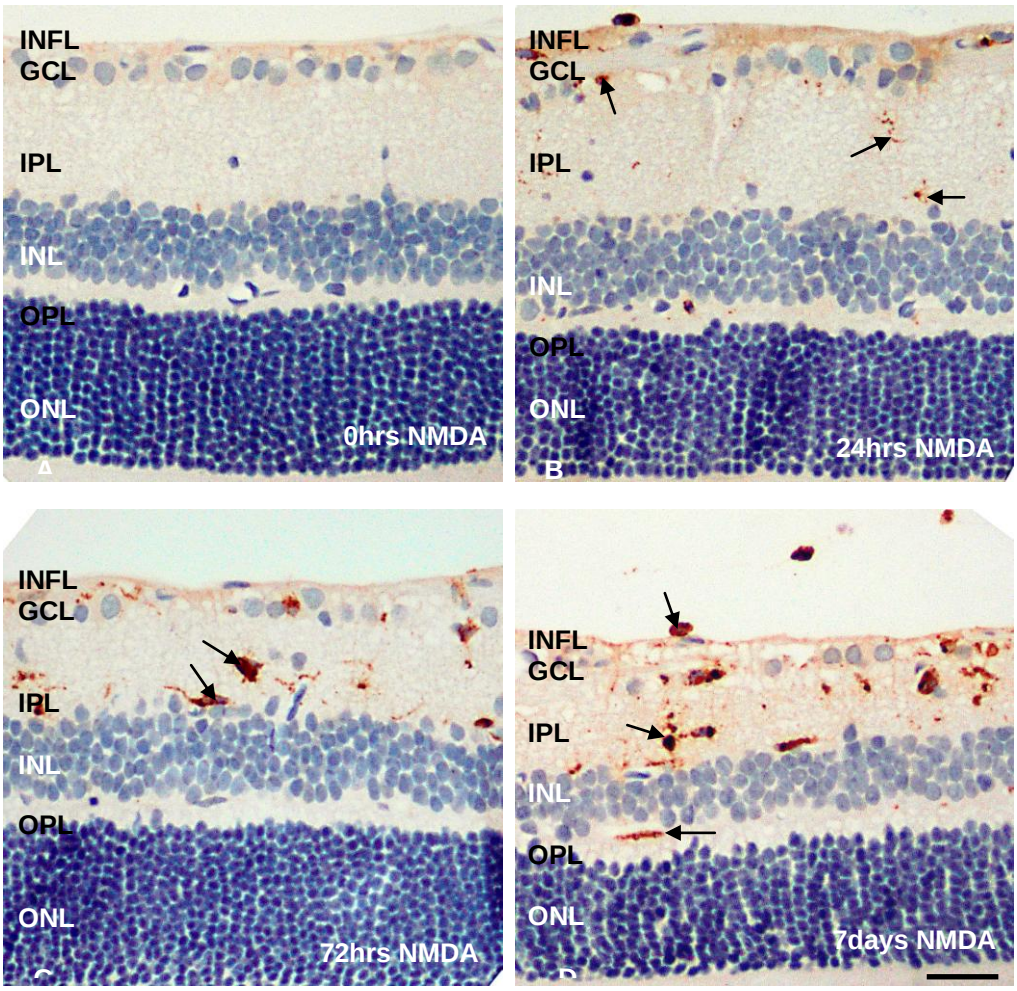

Figure 53. ED-1 immunoreactivity in the retinas of NMDA-injected rats. Soon after injection no immunoreactivity was detected (A). Punctate ED-1 expression is seen 24hrs post-injection (B, arrows). Pleomorphic microglia sending thin processes are seen in INFL, GCL and IPL 72hrs after NMDA injection (C, arrows). ED-1 expression is more pronounced at 7days with labelled (D, arrows) microglial processes seen in INFL, GCL, IPL as well as OPL. X200 magnification. Bar= 50μm

10.2.2 ED-1 immunostaining in the optic nerve

Saline control optic nerves did not show immunoreactivity in proximal as well as distal segments at any time points examined. [See Figure 54] Negative and positive controls showed no damage at any time point.

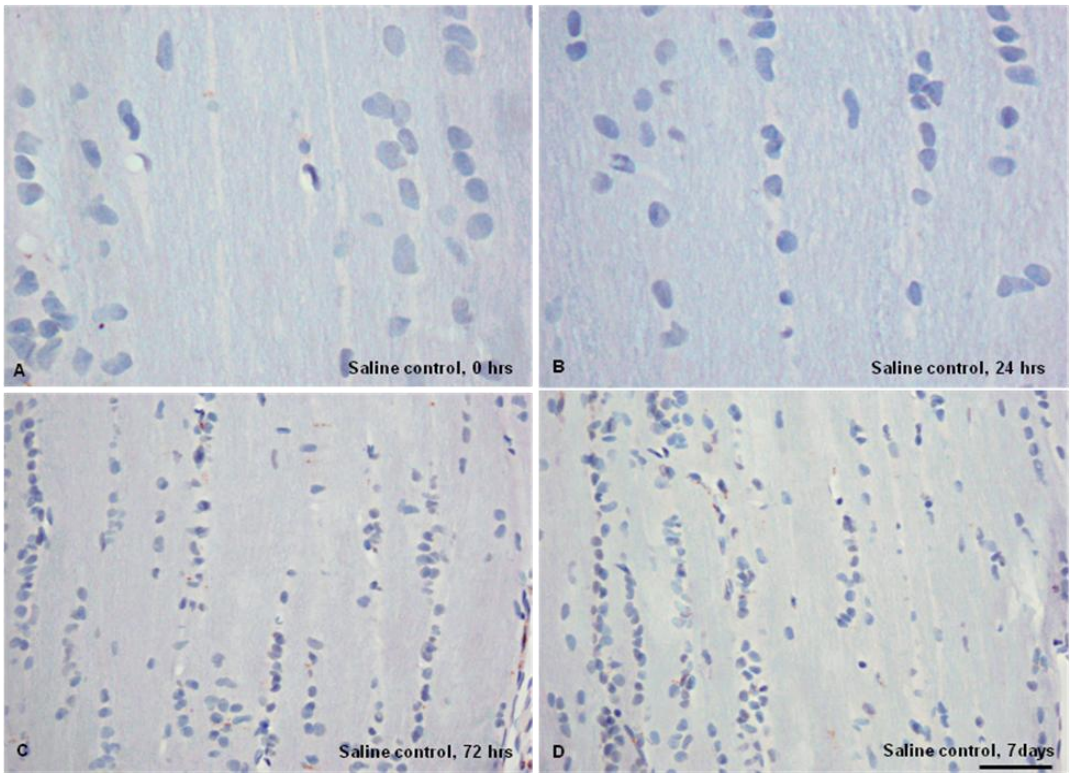

Figure 54. ED-1 immunoreactivity in the longitudinal sections of saline-injected optic nerves. No immunoreactivity is seen at any time points. X200 magnification. Bar=50μm

No ED-1 immunostaining was seen upto 24hrs in the NMDA-injected nerves. Occasional punctate staining appeared at 72hrs. The ED-1 immunostaining increased enormously at 7 days where large number of cells showed ED-1 immunoreactivity. At this stage, punctate immunoreactive material was clearly evident in the thin processes of microglial cells. Careful

observation of the optic nerve sections did not reveal any difference in the ED-1 immunostaining between the proximal and distal optic nerve segments. [See Figure 55]

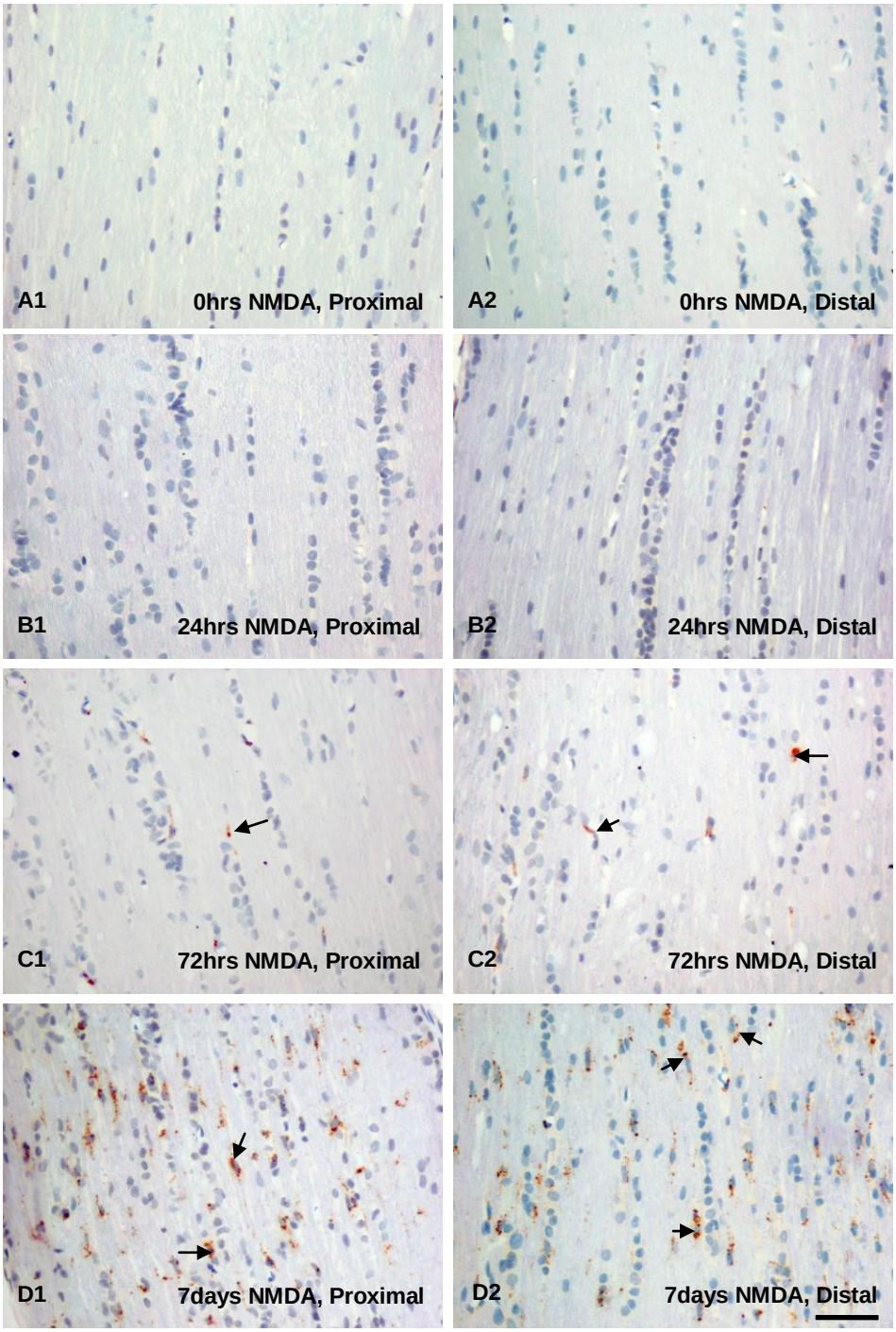

Figure 55. ED-1 immunoreactivity in the longitudinal sections of NMDA-injected optic nerves. No ED-1 immunoreactivity is seen in NMDA injected optic nerves at 0hrs (A1, A2) and 24hrs (B1, B2) after injection. Slight immunostaining in seen at 72hrs (C1, C2, arrows), which becomes very intense at 7days (D1, D2 arrows). Note- no difference is observed in ED-1 immunostaining between the proximal and distal optic nerve segments at each time point. X200 magnification. Bar=50μm

10.2.3 GFAP immunostaining in the retina

Negative controls showed no damage at any time point. In the control saline-injected retinas, astrocytes and Müller glial cells showed a moderate level of GFAP immunoreactivity. Thin GFAP-labelled processes of the Müller cells ran perpendicular to the surface extending into the outer part of the IPL. No change was observed in the saline-treated animals at any time point. [See Figure 56]

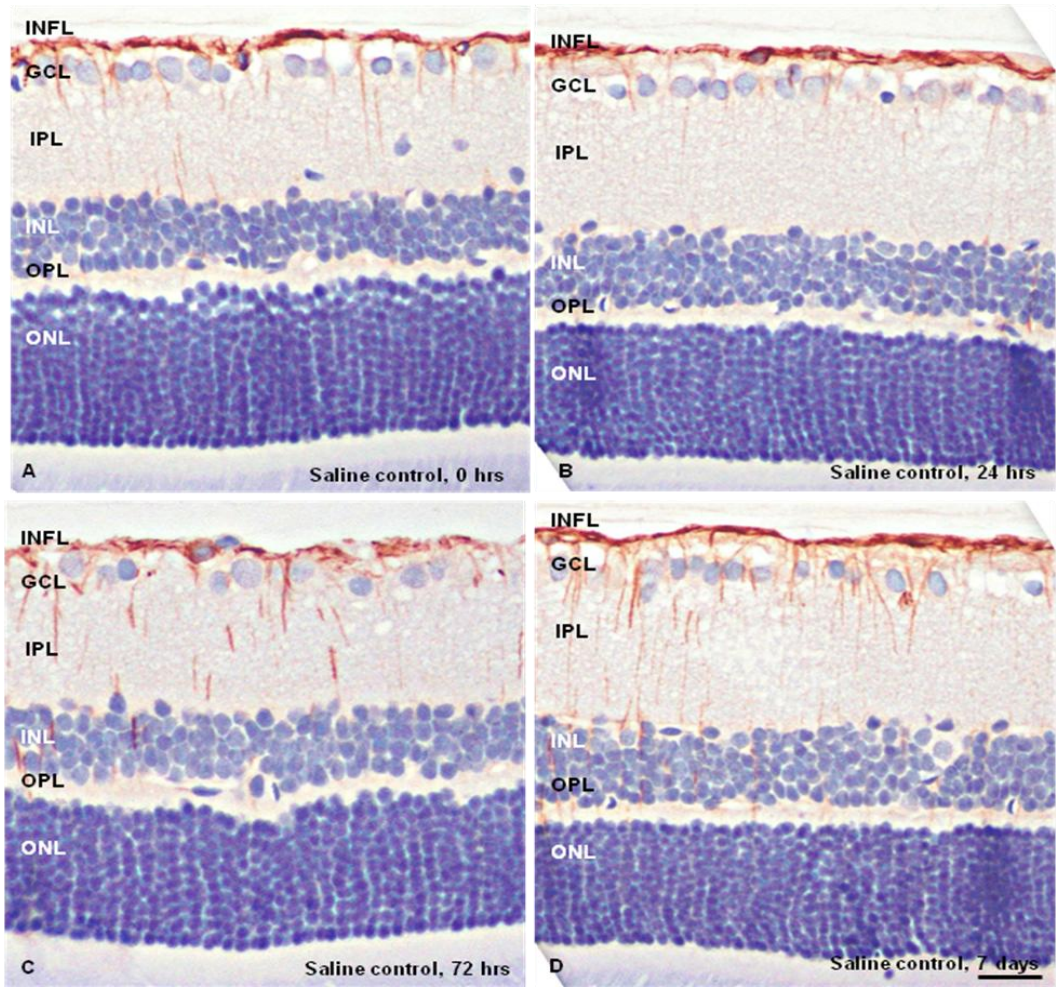

Figure 56. GFAP immunoreactivity in the saline-injected rat retinas. In the saline-injected retinas, GFAP immunoreactivity was restricted primarily to the INFL and GCL (arrowhead). X200 magnification. Bar= 50μm

Although, the intensity of GFAP immunostaining remained unaffected at 1 day after NMDA injection, the pattern of staining was affected mildly. Thin GFAP-labelled processes extended deeper into the IPL, INL and OPL. At day 3 post-NMDA exposure, GFAP immunoreactivity increased further. The number of GFAP-labelled processes in the INFL increased. The intensely labelled processes of the Müller cells became thick and were seen extending into the IPL, INL and OPL. GFAP immunostaining increased markedly at day 7 after NMDA injection, when the intensely stained cells and processes increased further in the INFL. The thickness of the retina reduced and the heavily labelled thick Müller cell processes were seen in parallel arrays now extending across the entire width of the retina. Throughout the process of analysis, the somata of the Müller glial cells within the INL did not show a well-defined GFAP staining at any of the time points studied. [See Figure 57]

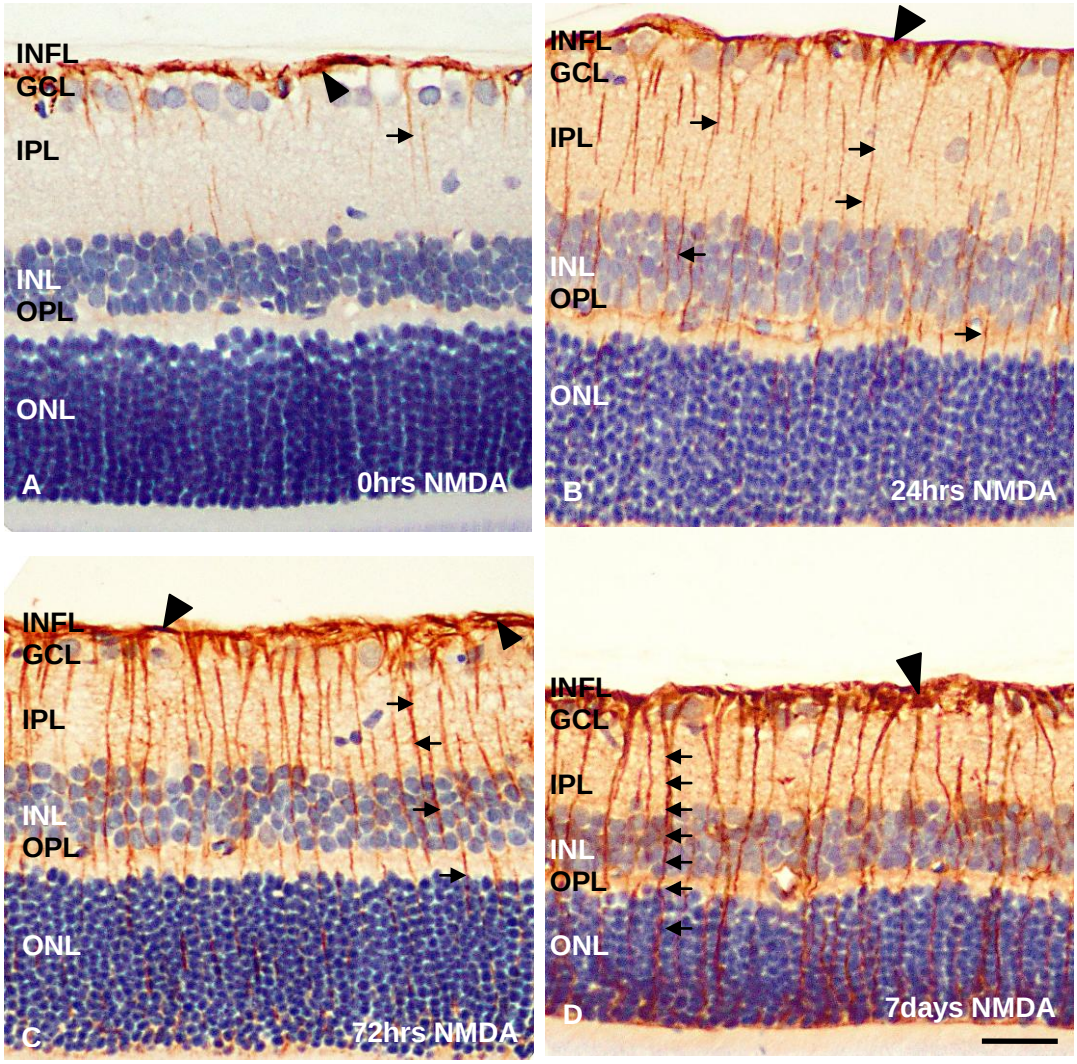

Figure 57. GFAP immunoreactivity in NMDA injected rat retinas. GFAP expression is mildly increased 24hrs post NMDA injection where thin Müller cell processes are seen extending into the IPL, INL and OPL (B, arrows). The expression is noticeably enhanced at 72hrs after NMDA injection during which increased GFAP immunoreactivity is seen in the INFL (C, arrowhead) and thick Müller cell processes are seen extending into the IPL, INL and OPL (C, arrows). GFAP expression is more pronounced in INFL at 7days (D, arrowhead) and heavily labelled processes extend across the entire width of retina (D, arrows). X200 magnification. Bar= 50μm

10.2.4 GFAP immunostaining in the optic nerve

Transverse sections of the paraffin-embedded saline-injected control optic nerves stained with GFAP showed numerous immunopositive star-shaped astrocytes spreading their immunostained processes uniformly across the whole section of the optic nerve to form an

astrocytic web in the optic nerve. The saline-injected retinas showed similar level and pattern of GFAP immunostaining at all time points observed. [See Figure 58] Negative controls also showed no damage at any time point.

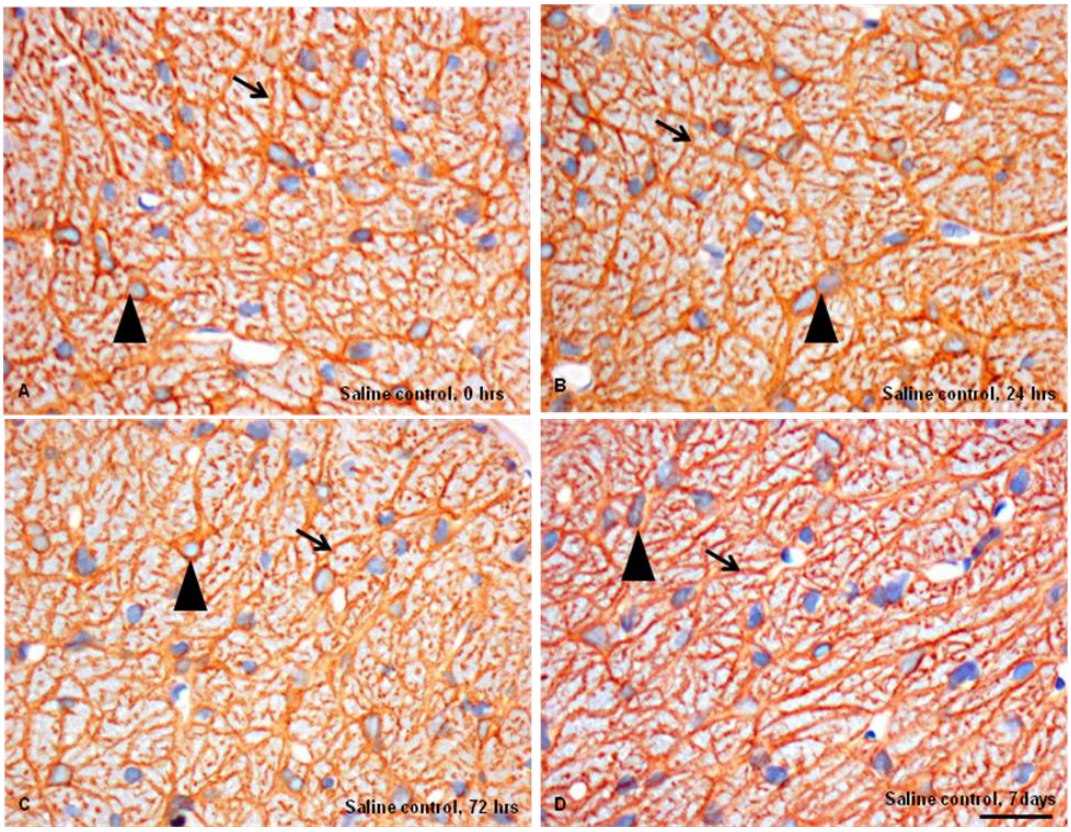

Figure 58. GFAP immunoreactivity in the transverse sections of saline-injected rat optic nerve. GFAP immunoreactivity is observed in star-shaped astrocytes (arrowhead) which send out multiple thin immunoreactive processes (arrows) to form an astrocytic web in the optic nerve. No difference in immunostaining is seen at any time points after saline injection. X400 magnification. Bar= 25μm

No change in immunoreactivity was seen at 0 and 24 hrs of NMDA exposure. Although a similar distribution pattern was observed in all experimental (NMDA-injected) and control optic nerves, some of the GFAP-immunoreactive astrocytes were characterized by hypertrophy of the cell bodies, with a few showing thick and intensely labelled processes after 72hrs of NMDA injection. GFAP immunostaining at 7 days showed more numerous GFAP

immunoreactive processes from enlarged reactive astrocytes, which seemed to nearly fill the whole optic nerve specimen. No apparent difference was observed in the GFAP immunoreactivity between the proximal and distal segments of the saline or the NMDA-injected optic nerve segements. [See Figure 59]

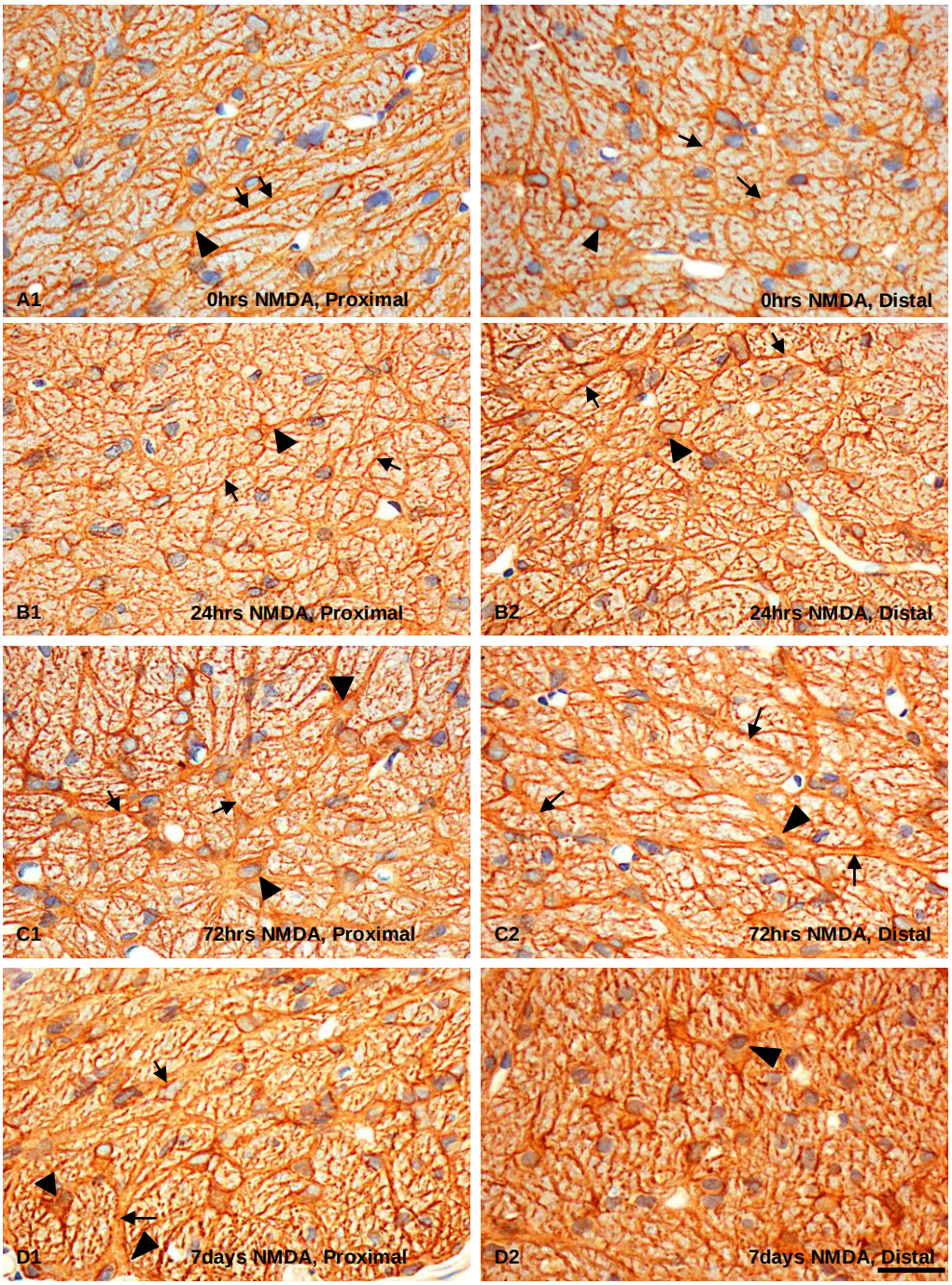

Figure 59. GFAP immunoreactivity in the transverse sections of NMDA-injected rat optic nerve. Normal profile and GFAP staining is seen immediately (A1, A2) and 24hrs (B1, B2) after NMDA injection. GFAP reactive astrocyte distribution is same at 72hs (C1, C2) post-injection but note the thick fibrillary process (C1, C2, arrows) with hypertrophied cell bodies (C1, C2, arrowheads), typical of reactive astrocytes. At 7days, increased number of astrocytic process form a dense network through the nerve cross-section (D1, D2). Large-sized astrocytic cell bodies (D1, D2, arrowheads) with thick processes (D1, arrow) are still clearly seen. No difference in immunoreactivity is seen between the proximal (A1, B1, C1, D1) and distal optic nerve segments (A2, B2, C2, D2) at any time points. X400 magnification. Bar= 25μm

10.3 Discussion

This section of the study recorded the temporal sequence of microglial and astroglial changes in the retina and optic nerve of the eyes exposed to 20nM NMDA for up to7 days. Microglial response in the form of increased ED-1 immunoreactivity and macroglial response in the form of enhanced GFAP expression in astrocytes and Müller cell end feet processes was detected in the retina as early as 24hrs followed by a steady increase in the expression of both at 3 and 7 days after NMDA injection. Optic nerve showed a late response with a moderate but gradual increase in the GFAP and ED-1 immunoreactivity beginning after 72hrs of NMDA injection. No observable difference was seen in the GFAP and ED-1 immunostaining between the proximal and distal optic nerve segments. Further studies need to be conducted, where minor differences in the astroglial and microglial response between these two segments, if present, can be quantified by quantitative immunoblot using an image analyser.

NMDA induced excitotoxic RGC death is a very useful model to study the role of glial cells in neuronal degeneration and protection. Inward Ca^{2+} current due to NMDA receptor stimulation releases intracellular glutamate, which in turns stimulate glutamate transporters and establish a positive feedback loop to maintain chronic or delayed excitotoxicity.[264, 265] Studies have shown that the localization of the glutamate transporter, GLAST, determines the glutamate clearance ablility of astrocytes and the expression of this glutamate transport protein is modulated by the GFAP distribution in the cytoskeleton of astrocytes.[691] The current study showing increased expression of GFAP indicates that the astrocytes become proactive in the uptake of extracellular glutamate when exposed to NMDA. Also, increasingly accumulated glutamate in the extracellular milieu, activates the surrounding microglia via direct or indirect T-cell mediated protective immune response in an attempt to limit further excitotoxic damage .[692, 693] Astrocytes have a limited clearance ability in comparison to microglial cells due to

the arachidonic acid and ROS released by the injured cells via incompletely defined molecular mechanisms,[694] Progressive microglial and astrocytic activation as is seen in the current study represent the CNS immune response against neuronal degeneration and play a major role in the defence against excitotoxic nerve damage.

Microglial cells, the sensors of even minor pathological changes in the nervous system, are the key cells in the T-cell mediated immune response against the antigens of injured cells. Cytokines and growth factors released from the activated T cells regulate the sentinel microglia and recruited macrophages.[692] Once activated, microglial cells prevent excitotoxin-mediated neurodegeneration by phagocytosis and removal of neuronal debris and reuptake of the excessive glutamate.[695] Also, the release of interferon-gamma from activated microglial cells improves glutamate uptake by astrocytes and other microglial cells and as antigen presenting cells, activated microglia expressing Major Histocompatibility Complex II (MHC-II) and B7.2 proteins bind to T cell receptors to activate them further.[692, 696] Although, the neuroprotective role of microglial cells is under surveillance, evidences are emerging for its controversial role in neurodegeneration. It is believed that the activated microglial cells, which do not express MHC-II proteins, secrete neurotoxins such as PGE_2, NO and TNF-α.[692] NO and TNF-α are directly neurotoxic and prevent glutamate reuptake,[697] whereas, PGE_2 stimulate glial cells to release more glutamate which results in further neurotoxicity.[698]

Following axotomy-induced cell death of retinal ganglion cells, intact blood-retinal barrier prevents recruitment of new ED-1+ wandering macrophages into the retina, whereas proliferation and activation of the resident microglia (OX42+ and 5D4+ cells) causes increased immunological expression of lysosomal ED-1 protein in the retina.[699, 700] Increasing

recruitment of large, round ED-1+ cells derived from circulating monocytes/ macrophages due to disruption of the blood-retinal barrier causes increased ED-1 immunolabelling seen with ischemic retinal injury.[701] Results are available to show steadily increasing ED-1 expression following kainite-induced retinal excitotoxicity.[702] NMDA induced retinal injury produced in this experiment produces progressively increasing ED-1 immunoreactivity at day 1, 3 and 7 post-injection. The study suggests increased microglial activation in response to excitotoxic retinal injury, however, it is difficult to say whether the increased ED-1 immunolabelling is due to activation of resident microglia or appearance of blood-derived macrophages or both, especially when evidence is available that NMDA can cause disruption of blood-brain barrier.[703]

Microglial cells derived from the precursor cells prior to the development of retinal vasculature lack macrophage specific markers.[687] However, microglia originating from blood-derived monocytes after establishment of the retinal vascularity, express markers for macrophage/monocyte lineage such as OX41, OX42, OX3, OX6, OX18, ED-1, Mac-1, F4/80, 5D4 anti-keratan sulfate, and lectins.[687] Most commonly used markers to study retinal microglia are OX42, 5D4, ED-1 and OX6. OX42 recognizes the complement receptor;[704] 5D4, a cell surface keratan sulphate;[705] ED-1, a lysosomal protein [686] and OX6 binds to the major histocompatibilty complex II. Three major types of resident microglial cells seen in the normal rat retina are OX42+/5D4-, OX42-/5D4+ and OX42+/5D4+.[701] Studies have shown that during post-natal phase of development, OX42+ and ED-1+ large, round amoeboid microglia derived from blood monocytes appear transiently in the retina, to be transformed later into small, ramified OX42+ and ED-1- resting microglial cells.[704] However, few weekly staining ED-1+ microglial cells encountered in the normal adult rat retina,[700, 701] may represent blood-borne macrophages recently infiltrating the retina as a part of normal turnover

process.[704] However, the present study found no ED-1 immunoreactivity in the saline-injected control retinas.

Increase in the GFAP immunoreactivity in the astroglial cells could indicate the increased synthesis of new protein or enhanced expression of this protein due to conformational changes. After retinal photocoagulation, Humphrey et al detected a prolonged increase in retinal GFAP immmunorectivity upto 45 days following a transient rise in retinal GFAP mRNA which returned back to normal within 7 days.[706] The study suggested the increased synthesis of GFAP as the cause of enhanced expression of this protein. Following intravitreal injection of NMDA, increased production of CNTF in the retinal Müller cells [469] via the Jak-STAT (Signal transducers and activators of transcription) pathway [707] increases the transcription of GFAP protein in these cells resulting in increased retinal GFAP expression as is observed in this study.

As already explained that this is the first study to focus on nerve degeneration following isolated somal injury, astroglial and microglial changes observed in the optic nerve are discussed in comparison to glial reaction following direct axonal injury. Axonal damage produced striking changes in the astrocytic and microglial cells seen as increased GFAP and ED-1 immunoreactivity in the optic nerve, respectively. Similar to axotomy or crush injury,[708] optic nerve degeneration secondary to excitotoxic perikaryal death provided no evidence of astrocytic proliferation. Although, the number of astrocytes remained same after injury, astroglial cells developed filament rich processes which became markedly hypertrophic and stained intensely with antibodies to GFAP.[605, 709, 710] Valat J et al also observed a stable astrocytic population after enucleation, which, according to them, was due to equilibrium between increased differentiation of glioblasts and increased death.[711]

Generally, glial cell in the CNS respond much slower to injury than in PNS.[369] Macrophage response and clearance of myelin occur more slowly than astrocytic activation.[605, 711] In the optic nerve post NMDA intravitreal injection, astrocytic reaction was observed at 72hrs and intense ED-1 labelling of microglial cells appeared at day 7. Delayed mononuclear macrophage response, as observed in the present and previous studies,[711, 712] suggests the intactness of the blood-nerve barrier for a long time after axonal damage preventing the recruitment of circulating macrophages.[349] Before any damage to the blood-nerve barrier, the activated microglia may originate either from resident microglia [349] or transformed from glioblasts and oligodendrocytes.[711] However, once the protective barrier formed by astrocytic end feet processes is damaged, increased number of circulating macrophages enter into the CNS at the site of damage.

Astrocytic and microglial activation, besides playing role in neurodegeneration, play a role in nerve regeneration. [713] Various growth factors released from these cells may cause neuronal regrowth. A study by Barouch et al has shown that the major source of neurotrophic factors in excitotoxin injured retina are macrophages/microglia, expressing NGF and NT-3 and astrocytes which secrete NT-3 and T-cells releasing BDNF and NT-3.[714]

In conlusion, an increase in the retinal and optic nerve GFAP and ED-1 reactivity was detected after intravitreal NMDA injection in rats. Delayed immunolabelling of GFAP and ED-1 in the optic nerve indicates that the optic nerve degeneration is secondary to the retinal response to NMDA. This immunohistochemistry study using GFAP and ED-1 markers may be useful for understanding the optic nerve damage in other acquired causes of optic neuropathies including glaucoma.

Chapter 11: CONCLUSION AND FUTURE DIRECTIONS

Animal models have been widely used in neuropathologic and ophthalmic research to advance the knowledge of pathophysiology of many chronic neurodegenerative and blinding conditions. The current study is aimed to explore various aspects of optic nerve pathology after NMDA-induced excitotoxic injury to the rat retina. In this study, the spatiotemporal pattern of light microscopic and ultrastructural changes, impairment of axon transport system and glial cell response are examined in the retina and optic nerve following intravitreal injection of 20nM NMDA in the rat eyeball. Retinal exposure to NMDA induces progressive thinning of the inner retina, RGC loss, Wallerian-like dying-back optic nerve degeneration, slow and fast axon transport impairment, and astrocytic and microglial activation in the inner retina and optic nerve.

As early as 24hrs after NMDA injection, RGCs show reversible pathological changes in the form of somatodendritic swellings without nuclear damage. Immunoperoxidase staining at the same time for GFAP and ED-1 demonstrate trivial macroglial and microglial cell activation concomitant with inner retinal stress. While the RGCs undergo reversible injury, the optic nerve axons and glial cells remain virtually unaffected. This indicates that early sublethal pathological events in RGCs preceed the axonopathy in somagenic degeneration. Although these retinal changes remain unidentified under a light microscope, they can be detected using other methods such as EM, histochemistry and genetic studies. This study provides grounds for the development of more accurate and sensitive diagnostic techniques to identify early subtle retinal damage. Such methods can also serve as good screening tools for recognizing glaucoma and possibly other neurodegenerative conditions in high-risk populations.

Retina at 72 hrs show severe necrotic RGC death with significant loss of approximately half of the cells. Retinal injury is associated with progressive increase in inflammatory response of microglial, Müller and astroglial cells in the form of enhanced GFAP and ED-1 immunoreactivity. Optic nerve at this stage start to show pathological changes which are more prominent distally (optic tract > distal optic nerve > proximal optic nerve) suggesting 'dying-back' nature of pathology. Nerve fibres are seen in various stages of degeneration. Fibres in the early stages show exclusive nodal changes in the absence of disturbed paranodal axo-glial relationships. Nerve fibres in the late stages of degeneration, which express features of watery degeneration, dark degeneration and demyelination, reflect that the final pathway of cytoskeletal breakdown is similar to classical Wallerian degeneration. The most prominent finding at this stage is'watery' degeneration', where the axonal swellings show features of cytoskeletal disintegration, complete loss of cytoskeletal elements or abnormal accumulation of organelles and neurofilaments. Only a few fibres undergoing 'dark degeneration' show features of demyelination. Excitotoxic retinal injury causes impairment of slow axonal transport resulting in decrease anterograde transport of NF-L to the axon terminal and hence their accumulation in proximal neuron (seen as NF-L rich spheroids). Absence of β-APP immunoreactivity in the axons suggests that fast axon transport is still functional. These optic nerve changes are associated with mild microglial and astrocytic activation reflecting the inflammatory reaction in response to the axonal injury seen as increased ED-1 and GFAP immunoreactivity. Activation of these cells results in their enhanced interaxonal β-APP immunouptake. The current study provides evidence in support of the theory that the impaired axonal transport play an important role in the structural damage to axons in dying-back degeneration of somagenic aetiology.

At day 7 of NMDA injection, necrotic cell death in GCL reduces the RGC population to 30%. Optic nerve degeneration progresses further with additional axonal loss. Impairment of slow axonal transport causes more shrinkage of remaining optic nerve axons. At this stage, impaired fast axonal transport results in increased axonal β-APP accumulation. These degenerative changes enhance the microglial and macroglial inflammatory response in the retina and optic nerve seen as more pronounced ED-1 and GFAP immunostaining. The inner retina now shows features of dendritic sprouting with the dendrites occupying the empty spaces created by the dead RGCs. This astonishing finding challenges the view that the neurons have limited ability to regenerate with necrotic type of cell death. Though it may be difficult to achieve control over the process of necrosis, this study provides a hope in the field of nerve regeneration after acute neuronal loss. Although the study does not intend to identify the source of origin of the regenerating dendrites, it opens the doors for future studies in which the growth potential of various retinal cells can be assessed, in order to replace the damaged neurons. This may keep our hopes alive in the field of optic nerve regeneration.

Future Directions

This unique non-traumatic optic neuropathy model provides details of the major pathological events in somagenic nerve degeneration, where axonal changes indirectly result from somal injury. This pathological study explains the sequential changes in neurons and glial cells after excitotoxic perikaryal death and also suggests the role of axonal transport system in somagenic degeneration.

This fundamental research revealed a pathological picture of Wallerian-like degeneration after perikaryal excitotoxic injury in the CNS. This novel finding is consistent with recent evidence of a labile axonal "survival" factor, nicotinamide mononucleotide adenylyltransferase 2,(Nmnat2)

produced by the neuronal cell body. Further study is required to test the hypothesis that a lack of Nmnat2 is the mechanism by which axons degenerate after excitotoxic perikaryal injury.

Chapter 12 APPENDICES

12.1 Appendix 1: Ethics Approval

IMVS

INSTITUTE OF MEDICAL AND VETERINARY SCIENCE

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Veterinary Services Division
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13th June, 2006

Dr R Casson
Ophthalmology and Visual Sciences
ROYAL ADELAIDE HOSPITAL

Dear Dr Casson,

Re: Project No. 53/06
'Retina and axon-myelin relationships in the optic nerve in normal and pathological conditions'

Thank you for forwarding the additional information as requested by the IMVS Animal Ethics Committee. The information was considered at the meeting held on 1st June, 2006 and accepted.

Yours sincerely,

Carol Hewitt
Secretary
IMVS/Central Northern Adelaide Health Service
Animal Ethics Committee

IMVS

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28th April, 2006

Dr R Casson
Ophthalmology and Visual Sciences
ROYAL ADELAIDE HOSPITAL

APPLICATION FOR ANIMAL ETHICS APPROVAL

I am pleased to advise that your Project entitled 'Retina and axon-myelin relationships in the optic nerve in normal and pathological conditions' has been given approval by the I.M.V.S./Central Northern Adelaide Health Service, Animal Ethics Committee for the period 20/04/06 to 30/04/09 subject to you providing the Secretary with the following details:-

1) In Q13 you refer to 5-6 rats. If you really do mean 5-6 rats, how are you going to decide? It is preferable to nominate a number with appropriate justification. Clarification is required as to the exact number of rats to be used.
2) CO_2 or cardiac perfusion? The committee understands that you may kill rats with cardiac perfusion of the anaesthetised rat, or by CO_2 inhalation if perfusion is not needed. The description of your project did not make it clear which groups were likely to get what method of killing and tissue collection. Future applications will be easier to understand and make decisions about if they are more self explanatory.
3) Q11 – "Use of sterile equipment will be considered". What is meant by this statement and how do you decide on how to implement an aseptic technique?
4) The AEC understood and accepts your comment about the lack of need for analgesia after small volume intraoccular injections, but reference to your personal experience of what you do for human patients for similar procedures or processes would have been helpful.

Project number 53/06 has been assigned to this application and should be used on all correspondence, animal orders and cage identification associated with this Project. Your animal user's permit number should also be quoted when ordering animals for this study.

It will be necessary for you to complete annually a brief progress report form for the purpose of review by the Committee and collation of statistical data for the responsible Minister.

I am obliged to point out that if it becomes apparent that the Project will continue for a longer period than is covered by this approval it will be necessary for you to seek a time extension from the AEC. Furthermore, if experience gained by yourself or others during your project demonstrates that the pain category or any other aspect of animal welfare is in fact different from that anticipated in your application form, the AEC must be informed at the earliest possible time.

I have enclosed a copy of the application, signed by the Chairman of the Animal Ethics Committee for your records.

Yours sincerely,

Carol Hewitt
Secretary
IMVS/CNAHS Animal Ethics Committee

Government of South Australia
Central Northern Adelaide
Health Service

5.2

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Chairman
Prof Dinesh Selva
Clinical Director
Dr Henry Newland
Unit Directors
A/Prof R Casson
Dr M Goggin

5th May, 2006

Carol Hewitt
Secretary
IMVS/CNAHS Animal Ethics Committee

Dear Carol,

I would like to thank the committee for their careful consideration of project 53/06.
In answer to the queries;

1) 6 rats will be used in each group. (5 rats achieve borderline significance; hence 6 will be used to try and obtain definitive results.)
2) rats that undergo histological analysis will be killed by cardiac perfusion under deep anaesthesia. Rats that undergo other forms of analysis are not perfused and are killed by CO2 overdose.
3) sterile equipment for intraocular surgery will be used.
4) humans undergoing intravitreal injection have topical local anaesthetic only and do not generally need any subsequent analgesia. Retinal ischaemia is painless and eye socket surgery either requires no post operative analgesia or mild oral pain killers only.

Sincerely,

Robert Casson
Associate Professor
Ophthalmology & Visual Sciences
Royal Adelaide Hospital

12.2 Appendix 2: Publication 1

Saggu, S.K., Chotaliya, H.P., Cai, Z., Blumbergs, P., Casson, R.J. (2008) The spatiotemporal pattern of somal and axonal pathology after perikaryal excitotoxic injury to retinal ganglion cells: A histological and morphometric study.
Experimental Neurology, v. 211 (1), pp. 52-58

12.3 Appendix 3: Publication 2

Saggu *et al. BMC Neuroscience* 2010, **11**:97
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BMC Neuroscience

RESEARCH ARTICLE Open Access

Wallerian-like axonal degeneration in the optic nerve after excitotoxic retinal insult: an ultrastructural study

Sarabjit K Saggu[1], Hiren P Chotaliya[1], Peter C Blumbergs[2], Robert J Casson[1*]

Abstract

Background: Excitotoxicity is involved in the pathogenesis of a number neurodegenerative diseases, and axonopathy is an early feature in several of these disorders. In models of excitotoxicity-associated neurological disease, an excitotoxin delivered to the central nervous system (CNS), could trigger neuronal death not only in the somatodendritic region, but also in the axonal region, via oligodendrocyte N-methyl-D-aspartate (NMDA) receptors. The retina and optic nerve, as approachable regions of the brain, provide a unique anatomical substrate to investigate the "downstream" effect of isolated excitotoxic perikaryal injury on central nervous system (CNS) axons, potentially providing information about the pathogenesis of the axonopathy in clinical neurological disorders. Herein, we provide ultrastructural information about the retinal ganglion cell (RGC) somata and their axons, both unmyelinated and myelinated, after NMDA-induced retinal injury. Male Sprague-Dawley rats were killed at 0 h, 24 h, 72 h and 7 days after injecting 20 nM NMDA into the vitreous chamber of the left eye (n = 8 in each group). Saline-injected right eyes served as controls. After perfusion fixation, dissection, resin-embedding and staining, ultrathin sections of eyes and proximal (intraorbital) and distal (intracranial) optic nerve segments were evaluated by transmission electron tomography (TEM).

Results: TEM demonstrated features of necrosis in RGCs: mitochondrial and endoplasmic reticulum swelling, disintegration of polyribosomes, rupture of membranous organelle and formation of myelin bodies. Ultrastructural damage in the optic nerve mimicked the changes of Wallerian degeneration; early nodal/paranodal disturbances were followed by the appearance of three major morphological variants: dark degeneration, watery degeneration and demyelination.

Conclusion: NMDA-induced excitotoxic retinal injury causes mainly necrotic RGC somal death with Wallerian-like degeneration of the optic nerve. Since axonal degeneration associated with perikaryal excitotoxic injury is an active, regulated process, it may be amenable to therapeutic intervention.

Background

Excitotoxicity, the mechanism involved in the pathogenesis of neurological diseases, including stroke, motor neuron disease (MND), Alzheimer's disease (AD), retinal ischemia and glaucoma [1-12], is classically considered as a somatodendritic insult due to prolonged or excessive activation of excitatory amino acid receptors. Studies have also indicated axonopathy as an early feature in neurodegenerative diseases associated with excitotoxicity [13-16]. It is unclear whether the nerve degeneration associated with excitotoxicity is due to primary insult at the perikaryal level in the grey matter or a primary excitotoxic injury in the white matter.

An excitotoxin delivered to the central nervous system (CNS), could trigger injury not only in the somatodendritic region, but simultaneously, in the axonal region. As retinal ganglion cells (RGCs) axons have a relatively long projection within the eye before reaching the optic nerve, intravitreal excitotoxic injury, which is physically isolated from the retro-orbital axons, may be the result of toxic insult to RGCs and/or intraocular axonal compartment. Studies have confirmed perisynaptic localisation of

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N-methyl-D-aspartate (NMDA) receptors in RGCs [17]. Although there is evidence for the presence of non-NMDA glutaminergic receptors for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite in the postsynaptic myelinated axons in the central neurons [18] and the expression of NMDA receptors on oligodendrocyte processes in white matter [19], there is no direct evidence of presence of functional NMDA receptors on axons [20]. Therefore, retro-orbital optic nerve axonal degeneration observed in NMDA-induced retinal insult is logically a consequence of primary damage to RGCs; however, damage to intraorbital axons can also be considered a primary site of insult, if future studies provide direct evidence for the presence of functional NMDA receptors over axons.

The retina and optic nerve, as approachable regions of the CNS, provide a unique substrate to investigate the effect of NMDA induced excitotoxic RGC injury on the optic nerve axons. We previously noted that NMDA induced retinal injury produced an axonopathy which was synchronous with the somal degeneration of RGCs and which was most prominent in the more distal portions (closer to the midbrain) of the axon [21]. To our knowledge, despite numerous reports about excitotoxic neuronal death in the retina, the "downstream" ultrastructural changes in the optic nerve (the RGC myelinated axons) have never been reported. In the current study, we provide ultrastructural information about the RGC somata and their axons, after NMDA-induced retinal injury.

Methods

Experimental model

Male Sprague-Dawley rats (n = 8) weighing 300-350 g [Institute of Medical and Veterinary Sciences (IMVS), Adelaide, South Australia] were kept at room temperature, with food and water available ad libitum. Adequate care was taken to minimise pain and discomfort for the animals used in this study and the experiments were conducted in accordance with the Australian and international standards on animal welfare. All experiments were approved and monitored by the IMVS, Animal Ethics Committee (Approval No. 53/06).

The excitotoxic RGC injury model was prepared in a manner similar to that previously described [22,23]. After anaesthetising the rats with isoflurane (2.5 L/min isoflurane in 2.5 L/min oxygen), instilling topical 0.4% benoxinate drops in both eyes and applying a sterile loop around the globes, a single dose of 5 μl of 4 mM NMDA (20 nmol, source- Sigma Aldrich, USA) was injected slowly over 30 seconds into the vitreous space of the left eye using a microsyringe fitted with a 30-gauge needle. Right eyes received 5 μl of the NMDA vehicle (sterile 0.9% saline) to serve as controls.

Sets of animals (n = 8 per group) were killed humanely by cardiac perfusion at various time intervals: immediately, 24 hrs, 72 hrs and 7 days after injection. Under deep anaesthesia, animals were killed by intracardiac perfusion with a solution of 2.5% glutaraldehyde with 4% paraformaldehyde in 0.1 M phosphate buffer pH 7.4. To minimise stretch injury to the optic nerve caused by direct enucleation of the globe, the eye, optic nerves and tracts were dissected via a craniotomy. Eyes were separated by cutting the optic nerve 1 mm behind the globe. The optic nerve was divided into proximal (nearer to the globe) and the distal segment (nearer to the midbrain).

Tissue preparation

Tissues perfused with 2.5% glutaraldehyde were transferred into polypropylene vials and post-fixed in the same fixative overnight at room temperature. The specimens were then rotator-rinsed in sodium cacodylate buffer (with sucrose, pH 7.4) for 30 minutes, and post-fixed in 1% osmium tetroxide (OsO_4) overnight at room temperature. The specimens were the re-rinsed in sodium cacodylate buffer three times for 30 minutes each, and then dehydrated in a graded alcohol series (70%, 95% and 100%). Dehydrated tissues were then infiltrated and later embedded in fresh TAAB-Epoxy resin with propylene oxide (2-epoxypropane) used as a clearing agent.

Sectioning and staining

Polymerised resin blocks containing tissue specimens were trimmed and semi-thin sections (0.5 μm) were cut on a mechanical ultramicrotome using a glass knife. Floating each section onto a water bath, sections were collected on labelled polysine slides, dried on the hot plate for 1 hour and stained with toluidine blue. Finally, sections were mounted and cover-slipped. Ultrathin sections (60-80 nm) were cut in the same manner as semi-thin sections, but using a diamond knife. Sections picked on 150 mesh acetone-washed copper grids and dried overnight were stained with Uranyl acetate and Lead citrate stains.

Results

RGCs in control retinas

The ultrastructure of retina was interpreted in conjunction with the light microscopy (LM) by an experienced neuropathologist (PCB). In the ganglion cell layer (GCL) of saline injected control eyes, most numerous large-sized cells containing pale nuclei with one or two nucleoli were identified as RGCs, in comparison to amacrine cells, which were smaller and had dark staining nuclei [24,25]. Microglial cells were identified as occasional small-sized cells, with short processes and elongated nuclei. The inner

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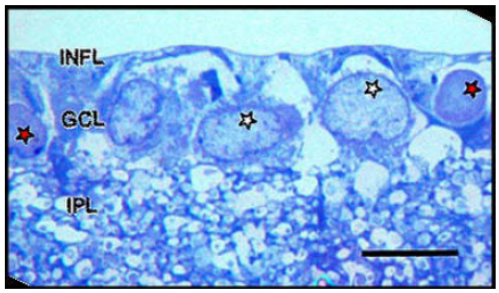

Figure 1 LM appearance of resin-embedded semi-thin section of saline control normal inner retina stained with Toluidine blue stain. INFL: inner nerve fibre layer, GCL: ganglion cell layer, IPL: inner plexiform layer. Ganglion cell layer shows prominent nuclei of RGCs (white stars) and amacrine cell (red stars). Bar = 10 μm.

plexiform layer (IPL) showed sections of dendritic processes of RGCs. (Figure 1)

Under transmission electron microscopy (TEM), control RGCs had a well-defined continuous plasma membrane, and a non-uniform distribution of organelles in the cytoplasm, with maximum concentration in the perinuclear region. RGCs contained tubular sacs of rough endoplasmic reticulum (rER) surrounded by large numbers of ribosomes (Nissl bodies). Mitochondria were identified as round or oval double- membrane structures with characteristic cristae. In addition, the cytoplasm contained elements of Golgi apparatus (GA), free ribosomes and microtubules sectioned at various angles. A large round nucleus, surrounded by a double layered nuclear membrane, contained homogeneously dispersed karyoplasm (chromatin material) and one or two electron dense nucleoli. RGCs from the control saline-injected eyes showed a similar normal profile at all time points. (Figure 2)

Ultrastructural changes in RGCs

Intravitreal administration of NMDA resulted in excitotoxic damage to RGCs which began as early as 24 hrs. At 24 hrs, 10-20% RGCs showed cytoplasmic engorgement with swelling of numerous dendritic processes giving a spongiform appearance to the IPL. Cytoplasm of swollen RGCs appeared dense and uniformly granular due to scattered ribosomes. Some mitochondria appeared swollen and the rER appeared slightly vacuolated. The cell membrane appeared intact and no nuclear changes were seen at this stage. (Figure 3)

At 72 hrs, the dendritic swelling persisted and the ganglion cell density decreased. RGCs displayed a necrotic form of cell death with features of degeneration seen in a continuum of changes. Most abnormal RGCs had an intact cell membrane with their cytoplasmic matrix containing free monomeric ribosomes, vesicles and dilated cisterns of ER as well as GA. In conjunction with the disaggregation of polyribosomes and disintegration of vacuolated ER, most mitochondria were irregularly oedematous. Some morphologically normal mitochondria were still evident in affected cells. Some cells showed early features of nuclear damage, such as hyperconvoluted nuclei and chromatin condensation into small clumps abutting the nuclear envelope. Nucleoli, however, were morphologically normal. Some RGCs displayed extreme cytolysis and loss of architecture in the form of disrupted cytoplasmic organelles. Their nuclear envelope and organelle membranes were fragmented. Damage was so severe that demarcation between nucleus and cytoplasm was impossible in some cells. Electron-dense clumped nuclear remnants were dispersed into the cytoplasm, which contained vacuolated and rupturing organelles and onion-like multilaminated 'myelin figures'. (Figure 4)

At 7 days, the IPL appeared markedly thinned, with dendrites becoming shrunken and dense. As the purpose of this study was to explore ultrastructural changes, no quantification of IPL thickness was attempted here. However, statistical analysis of retinal thinning was done using light microscopy and results published previously [21]. The GCL showed sparse distribution of RGCs, but preservation of most amacrine cells. At this time point, damaged RGCs showed electron-dense neuronal debris remaining in contact with clusters of reactive microglial cells and astrocytic processes. Numerous dendritic processes, recognised by their higher microtubule composition in comparison to axons, were seen distributed in the GCL. These dendrites were packed in the form of clusters, which occupied the empty spaces created by necrotic RGCs. Compared to the dendrites in the IPL, these processes appeared normal in terms of filamentous and organelle composition, with many displaying mitochondria of normal morphology. (Figure 5)

Ultrastructure of normal optic nerve

The parallel-cut intraocular portion of optic nerve axons seen in retinal sections from saline injected control eyes showed 0.25 to 1 μm thick unmyelinated axons running longitudinally in the INFL with axoplasm showing uniformly distributed longitudinal cytoskeletal filaments and organelles. In some axons with a substantial length of axon visible, mitochondria-rich varicosities were separated by narrowed portion of filament rich axons. (Figure 6)

The retro-orbital optic nerve from saline injected animals at all time points displayed ultrastructural features similar to those previously described in the normal adult rat [26-29]. In transverse sections, well-fixed myelinated axons of various diameters maintained round to ovoid sectional profiles (Figure 7a) with numerous microtubules and neurofilaments dispersed evenly in the axoplasm. Microtubules

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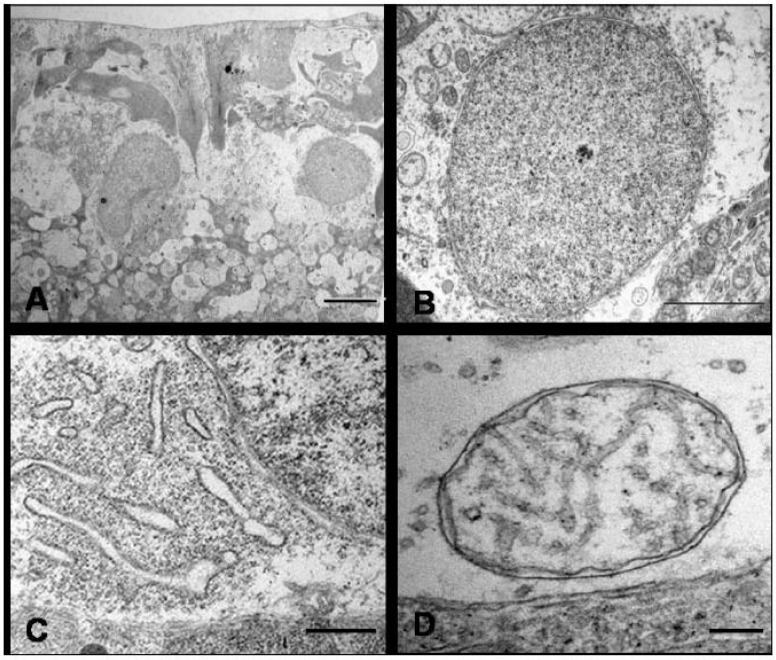

Figure 2 Ultrastructural appearances of normal RGCs from saline injected eye. Typical RGCs are seen (A, Bar = 5 μm) with normal nuclei (B, Bar = 2 μm), endoplasmic reticulum (C, Bar = 1.7 μm) and mitochondrion (D, Bar = 20 nm).

were seen as hollow round cross-sections and neurofilaments as small electron-dense dots with no central clearing. Also seen in the axoplasm were mitochondria with normal morphology and intact cristae. Surrounding the axons, myelin remained compact with a normal periodicity with no intramyelinic lacunae or vacuoles. In longitudinal sections (Figure 7b), axons ensheathed by darkly stained myelin contained filamentous structures (neurofilaments and microtubules) which showed linear orientation, parallel to the length of the axons. The nodes of Ranvier displayed a normal morphology with well preserved paranodal terminal loops contacting axolemma and a non-myelinated nodal gap measuring less than or approximately equal to 1 μm. Various glial cells surrounded the axons. Oligodendroglial cells had an electron-dense cytoplasm and heterochromatic nuclei. Astrocytes were identified by the electron-lucent cytoplasm and processes which contained bundles of intermediate filaments. Microglia had heterochromatic nuclei similar to oligodendroglia, but their cytoplasm appeared less dense.

Ultrastructural changes in NMDA-injected optic nerve axons

Optic nerves from NMDA-injected eyes, examined immediately and 24 hrs after injection were similar to the optic nerve of saline-injected eyes. At 72 hrs post-NMDA insult, unmyelinated fibres running in the INFL maintained normal morphology; however, pathology was identified in the retro-orbital optic nerve. After careful observation of cross sections of proximal and distal segments, three distinct abnormalities were identified with changes appearing more pronounced in the distal as compared to the proximal optic nerve (data not quantified). These ultrastructural changes had similar spatiotemporal and pathological features to that described in classical Wallerian degeneration [30,31].

1) Axonal swellings

Swollen axons appeared pale and enlarged with axolemmal expansion and cytoskeletal disintegration, characterizing 'watery degeneration'. The axoplasm was partially or completely devoid of organelles and cytoskeletal elements. Loss of microtubules with relative preservation of neurofilaments was observed in some axons. Many fibres contained dense accumulations of neurofilaments, altered tubulo-vesicular membranous organelles, mitochondria and multilayered whorled masses, which appeared to be arising from the inner layers of myelin. The myelin sheath surrounding these axons remained compact and unaltered at most places. (Figure 8)

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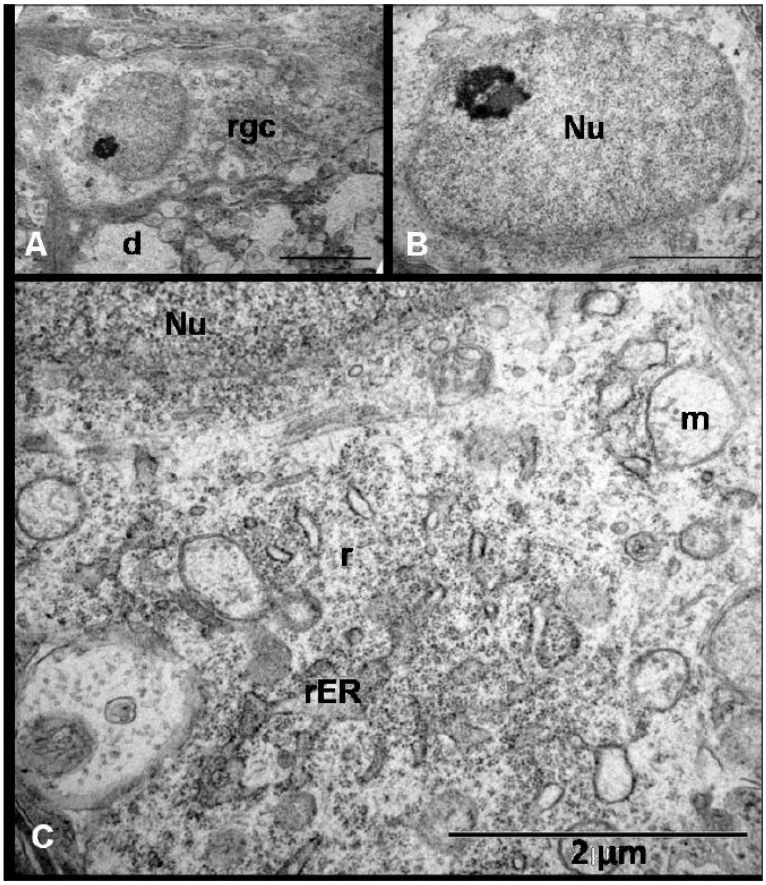

Figure 3 Ultrastructural appearance of RGCs 24 hrs after NMDA injection shows (A, Bar = 5 µm) early dense appearance of the cell (rgc) cytoplasm with dendritic swelling (d) and normal euchromatic nucleus with a prominent nucleolus (B, Bar = 2 µm). Notice the dilatation of mitochondrion (m) and endoplasmic reticulum (ER) as well as some scattered ribosomes (r) in the cytoplasm (C, Bar = 2 µm).

2) Dense axons

Some small to medium sized axons, which appeared dark under lower magnification, had their axoplasm filled with an amorphous, granular and dark material, thus portraying what is described as 'dark degeneration'. Although, organelles were visible in some fibres, it was difficult to define the composition of dense axoplasmic material even at very high magnifications. The myelin of dark axons did not show significant alterations. (Figure 9)

3) Demyelination

Occasional fibres showed features of demyelination which included vacuolation and splitting of the myelin sheath. These demyelinating changes were mainly seen around abnormally dense/dark axons. Partial or complete loss of axon transformed the myelin into collapsed structures which appeared as 'myelin bodies' in the extracellular space. Few normal axons also showed myelin changes such as lamellar separation or widening which made the myelin look abnormally thick and dark. (Figure 10A &10B)

Longitudinal sections displayed abnormal focal swellings and dense axons scattered between numerous normal fibres. Magnified images revealed some pathological changes even in fibres which appeared healthy under lower magnifications. The main abnormal features were abnormal accumulation of tubulo-vesicular structures including organelles in the nodal and paranodal region, formation of nodal blebs, and intermittent myelin proliferation where the fibres showed splitting and proliferation of inner layers of myelin in the internode. The myelin proliferations formed whorls and loops, which protruded into the axon carrying the axolemmal

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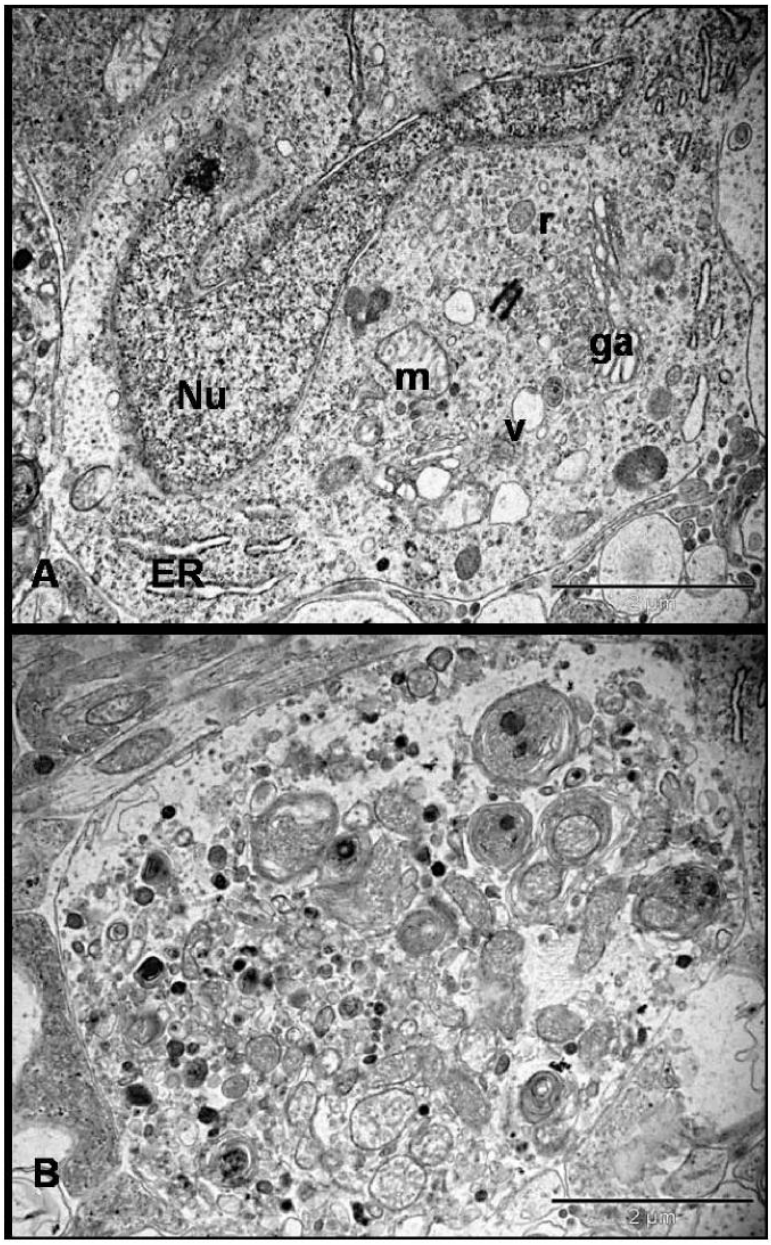

Figure 4 Ultrastructure appearance of RGCs 72 hrs after NMDA injection. Neurons are found at different stages of degeneration and the neuronal death is morphologically 'necrotic'. Figure A shows the hyperconvoluted nucleus and cytoplasm filled with multiple vacuoles, ribosomes and swollen organelle. Figure B shows severe necrotic cell death where the cell has lost its architecture and converted into debris. There is no demarcation between cytoplasm and electron-dense bodies. The cytoplasm is studded with the multi-laminated myelin figures and damaged organelles (Bars = 2 μm); Nu = nucleus, ER = endoplasmic reticulum, ga = golgi apparatus, m = mitochondria, v = vesicles, r = ribosomes.

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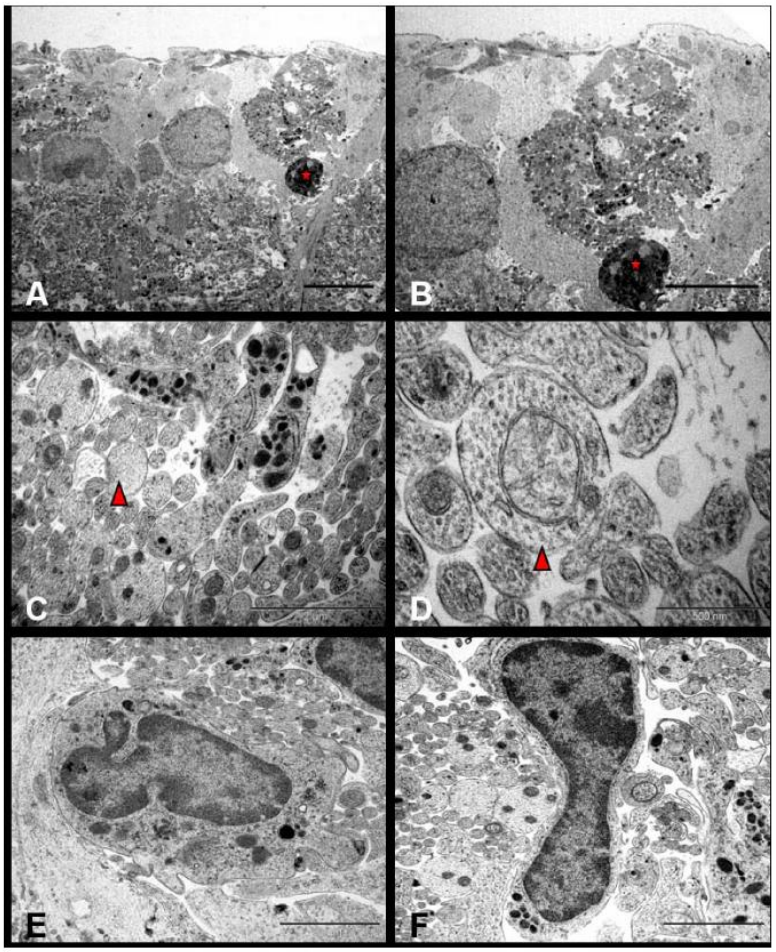

Figure 5 NMDA-induced ultrastructural changes in RGCs at 7 days where necrotic cell in the form of highly electron-dense neuronal debris (Red star, A & B, Bar = 2 μm) is seen lying adjacent to numerous membrane-bound microtubule-rich neuritic processes (C, red triangle, Bar = 2 μm) identified as dendrites under high power (D, red triangle, Bar = 500 nm); Figure E and F show reactive microglia surrounding the dendritic sprouts. (Bars = 2 μm).

covering around them. In some places, the proliferation was so pronounced that the mesaxonal loops occupied the entire diameter of axon. The axoplasm around the myelin whorls looked normal. The later finding was strictly restricted to the distal segments. No disturbance in the axon-myelin relationship was observed in the paranodal regions and the myelin terminal loops maintained normal relationships to the axons. No myelin debris was seen inside the astrocytic and microglial cells. (Figure 10)

The degenerative changes at 7 days were clearly more intense than the previous stage. Extensive invasion by the filamentous astrocytic processes completely disorganized the nerve structure. Almost all fibres were altered and only a few scattered fibres showed a normal appearance. A remarkable feature at this stage was the predominance of dark fibres, as compared to watery fibres. These dark axons appeared shrunken on longitudinal sections to create a gap between the atrophic axon and the inner layers of myelin. Moreover, demyelinating changes such as myelin breakdown, detached and vacuolated lamellae and formation of myelin bodies were frequently seen. Phagocytosing cells including microglia, astrocytes and oligodendroglial cells were present throughout, and myelin debris was mostly an extracellular feature. The most striking finding on

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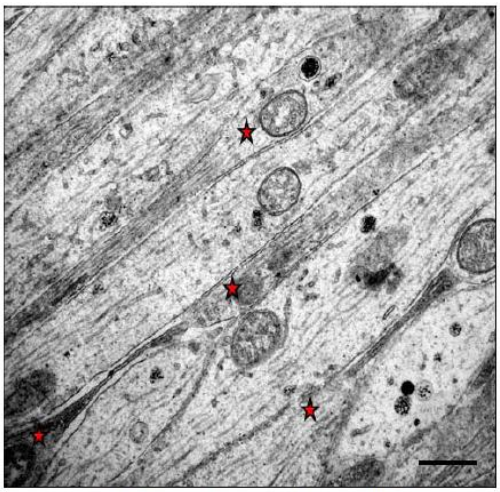

Figure 6 TEM of the parallel running longitudinal sections of the intraorbital axons in saline injected control retina immediately after the injection. A few fibres cut to a substantial length showed varicosities (red star) and intervaricosity regions simultaneously (Bar = 1 μm).

longitudinal sections, where a substantial length of axon was seen, was that the same axon showed features of watery degeneration (axonal swelling) and dark degeneration (hyperdense axoplasm). (Figure 11)

Discussion

Most of the information about the pathology of axonal degeneration is derived from the experimental nerve transection model which causes classic Wallerian degeneration of axons [32] and a reactive gliosis [30,31]. Under the light microscope, NMDA induced excitotoxic injury to the retina causes significant reduction in thickness of inner retina at 72 hrs (posterior retina, $p = 0.002$ and peripheral retina, $p = 0.012$) with thickness reducing further to 68% and 76% in both regions compared to the control eyes at 7 days ($p < 0.05$) [21]. This implies loss of RGCs and their dendrites. Damage to RGC somata is characterized by a well-ordered sequence of organelle changes along with a dying-back-like degeneration of the axons (the optic nerve fibres) [21].

There is paucity of literature regarding degenerative changes in the optic nerve at the ultrastructural level. To our knowledge, this is the first study to report the pathological changes in the optic nerve at ultrastructural

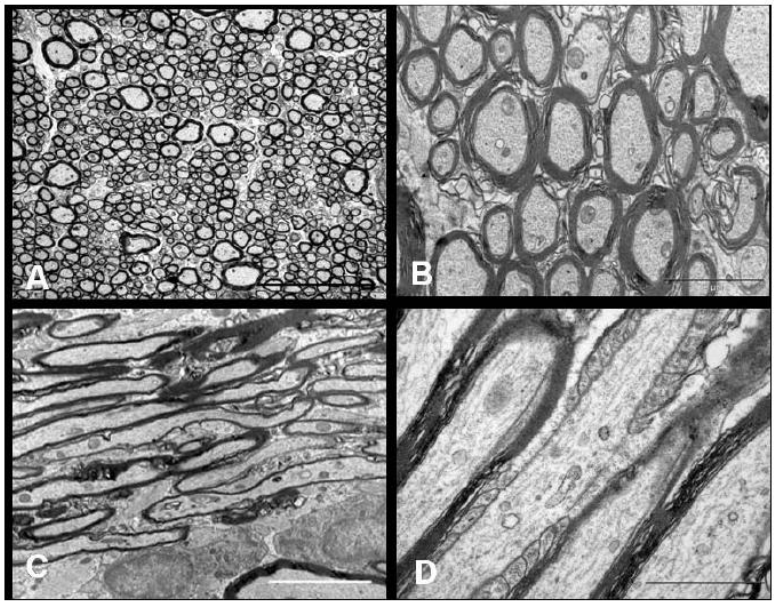

Figure 7 EM of the retro-orbital distal segment of rat optic nerve of the saline injected control animal immediately after the injection. Axoplasm of the myelinated axons contain numerous neurofilaments, microtubules, mitochondria and various other organelles. The transverse sections (A, Bar = 5 μm and B, Bar = 2 μm) show compact arrangement of the myelin lamellae around the axons in the internodal regions. The longitudinal sections show parallel running myelinated axons (C, Bar = 5 μm). Axon-myelin relationship in the nodal-paranodal region is better appreciated at very high magnification (D, Bar = 1 μm) Here, myelin terminal loops are seen attached to the paranodal axolemma on either side of the node.

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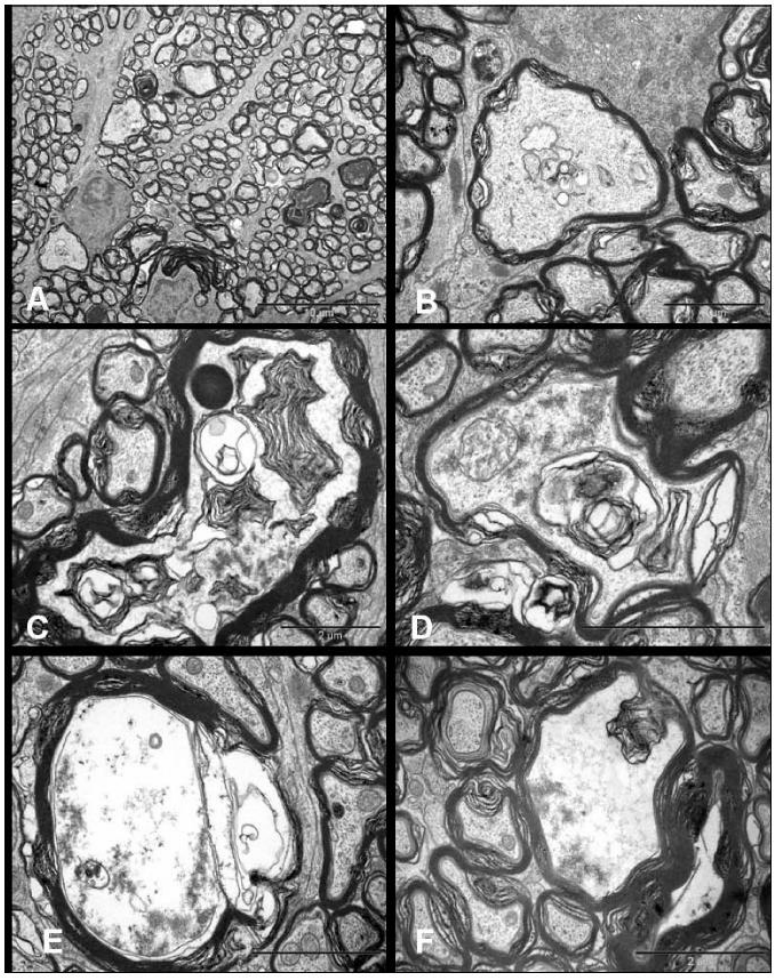

Figure 8 Ultrastructural appearances of axonal swellings in the transverse sections of distal segment of rat optic nerve after 72 hrs of NMDA injection. The major change observed is the appearance of swollen axons (A, Bar = 10 μm). The axoplasm of these axonal swellings show abnormal collection of altered tubulovesicular structures (B-D, Bars = 2 μm), cytoskeletal disintegration (C-F, Bars = 2 μm), and multilayered whorled masses (C & F, Bars = 2 μm), which are seen to be arising from the inner layers of the myelin (F, Bar = 2 μm).

level after excitototxic retinal damage. To characterize the events leading to neuronal cell death after isolated injury to the perikaryon, this morphologic study in rats describes the time-dependent pathological sequelae in the RGCs and optic nerve after NMDA-induced retinal damage. TEM analysis showed that the effects of excitotoxic stimuli begin in the retina within 24 hrs where RGCs undergo progressive necrosis, and the optic nerve degeneration mimics classic Wallerian degeneration. Studies have shown that Wallerian degeneration mutation rescues axons but not cell bodies in a rat model of glaucoma and that axonal degeneration can be delayed for weeks in the presence of the slow Wallerian degeneration gene (WldS), suggesting that Wallerian degeneration is an active, regulated process [33]. Recent research suggests that the more long-lived, functionally related WldS protein, a variant of Nmnat1, substitutes for endogenous Nmnat2 loss after axon injury, which is actually considered to prevent spontaneous degeneration of healthy axon [34].

NMDA-induced retinal changes

Previous studies have shown that the excitotoxic injury could lead to apoptotic, autophagic or necrotic cell

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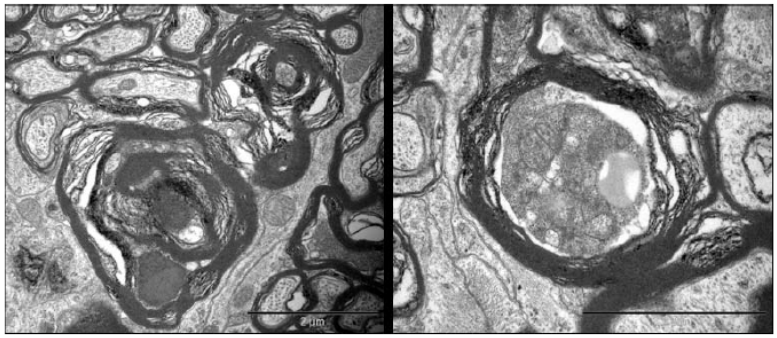

Figure 9 Ultrastructural appearance of hyperdense axons in distal optic nerves seen 72 hrs after NMDA injection (Bars = 2 μm). Note that despite the extent of the changes, some adjacent axons still appear normal.

death [35-42]. Evidence is also available that the excitotoxic injury can produce hybrid forms of cell death, existing on a continuum between the classically defined apoptosis and necrosis [38,39,43], and is likely to depend on the degree of insult and the sensitivity of the exposed neurones. Time-dependent studies of glutamate exposure to cultured neuronal populations showed that the excitotoxins induce early necrosis and delayed apoptosis [36,44]. There is also evidence that the necrotic neurons may completely recover to undergo apoptotic transformation later [44]. The current study is consistent with previously reported pathology [45,46].

Cell death, seen 72 hrs after excitotoxic insult, exhibited the essential features of necrosis characterized by progressive organelle swelling, cytolysis and karyolysis. RGCs showed mitochondrial swelling, dilated ER, dissolution of ribosomes in early stages and disintegration of cytoplasmic organelles, change in nuclear morphology and mild chromatin aggregation in advanced stages [43,47-50]. Because apoptosis requires functional mitochondria [51], the presence of swollen and disrupting mitochondria suggested that the event was non-apoptotic. In the presence of whorl-like multi-laminated 'myelin figures' or 'myelin-like bodies' [52] in severely damaged RGCs, and in the absence of highly specific features of apoptosis (heterochromatin segregation, nucleolar disintegration or apoptotic bodies) as well as autophagocytosis (presence of typical autophagosomes) [52-55], cellular events were labelled as necrotic.

NMDA-induced optic nerve changes

In comparison to the popular models of immediate (axotomy) or delayed (stretch) disruptive injuries, where the axons and myelin are simultaneously and directly damaged at the site of lesion, optic nerve fibres in the current model do not suffer any form of direct injury. Because the optic nerve is physically isolated from the eyeball, retro-orbital axonal changes seen in the present study are most likely the result of direct injury to RGCs or indirect damage to the intraretinal axons. Several physiological studies suggest that the axons lack excitatory amino acid receptors and they respond to excitatory amino acids indirectly by the change in extracellular ion composition associated with neuronal depolarization [56-58].

The initial sequence of events resulting in axonal degeneration depends upon the type of injury. During early Wallerian degeneration, asymmetric paranodal myelin retraction was seen as the initial event after axotomy in frog optic nerve followed by the formation of nodal blebs and accumulation of abnormal organelles in nodal axolemma [59]. In response to excitotoxic perikaryal injury, this study found nodal changes in the form of bleb formation and abnormal accumulation of organelles in the paranodal region with no obvious myelin terminal loop retraction as early changes. These changes resembled the response observed after non-disruptive stretch injury, where accumulation of membranous organelles in the paranodal and internodal regions preceeded the nodal bleb formation related with loss of axolemmal undercoating [60].

Nodal changes seen in the present study indicate the role of disrupted ionic equilibrium in initiating axonal damage following excitotoxic perikaryal injury. It has been proposed that the decreased ATP and mitochondrial formation, usually seen with necrotic cell death, results in energy-dependent pump failure at active nodal sites causing ionic imbalance, focal cytoskeletal dissolution and neurofilament compaction; loss of membranous Ca^{2+}-ATPase pump causing Ca^{2+} influx induce calpain-mediated proteolysis of the subaxolemmal proteins which results in the formation of nodal blebs [61,62]. This proteolytic activity spreads to involve the entire nodal axoplasm [63] results in focal axonal swellings with variable amount of

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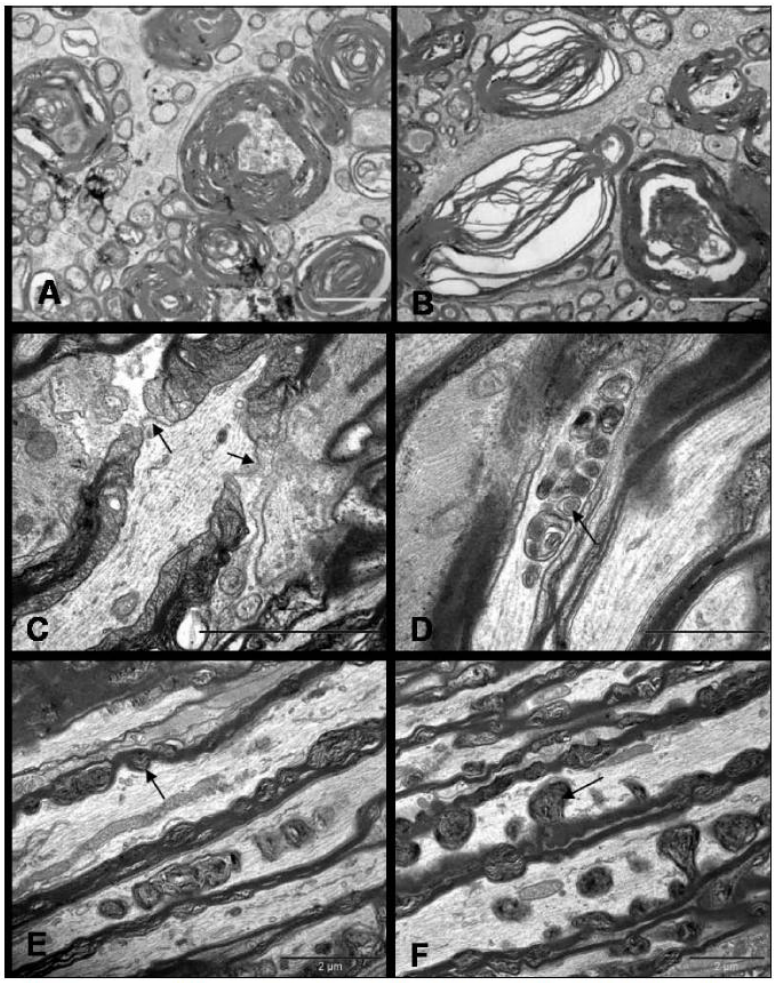

Figure 10 Ultrastructure appearances of distal segment of rat optic nerve after 72 hrs of NMDA injection. Transverse sections show separation and vacuolation of myelin sheath (A & B). Longitudinal sections display nodal blebs (C, arrows), abnormal accumulation of altered organelles (D, arrow), myelin whorls (E, arrow) arising from the inner myelin and forming mesaxon (F, arrow). The cytoskeleton surrounding the myelin whorls appears normal at this stage (E & F). Bars = 2 µm.

cytoskeletal disruption. Studies have also shown that proteolyic degradation of sidearms of neurofilaments results in their axoplasmic aggregation [64]. These cytoskeletal changes are likely to affect the axonal transport system leading to the accumulation of transport material including vesicles, organelles, proteins and enzymes in the paranodal and internodal regions [65].

Similar to the study using optic nerve crush injury, the current study also identified watery and dark degeneration in the axons [66]. Both patterns were observed at 72 hrs and 7 days of injury. Although there was no apparent predominant form at 72 hrs, there was a clear increment of fibres undergoing dark degeneration and demyelination at 7 days. It is unclear whether the same axon displays different type of axoplasmic degeneration at variable distance from RGC at the same time or individual axons undergoes a specific type of degeneration throughout its length. It is possible there is a cause and effect relationship between both types of degeneration, but evidence is circumstantial. Unlike the stretch injury model, axons form the only link between the myelin and the cell body in the current study. It was presumed

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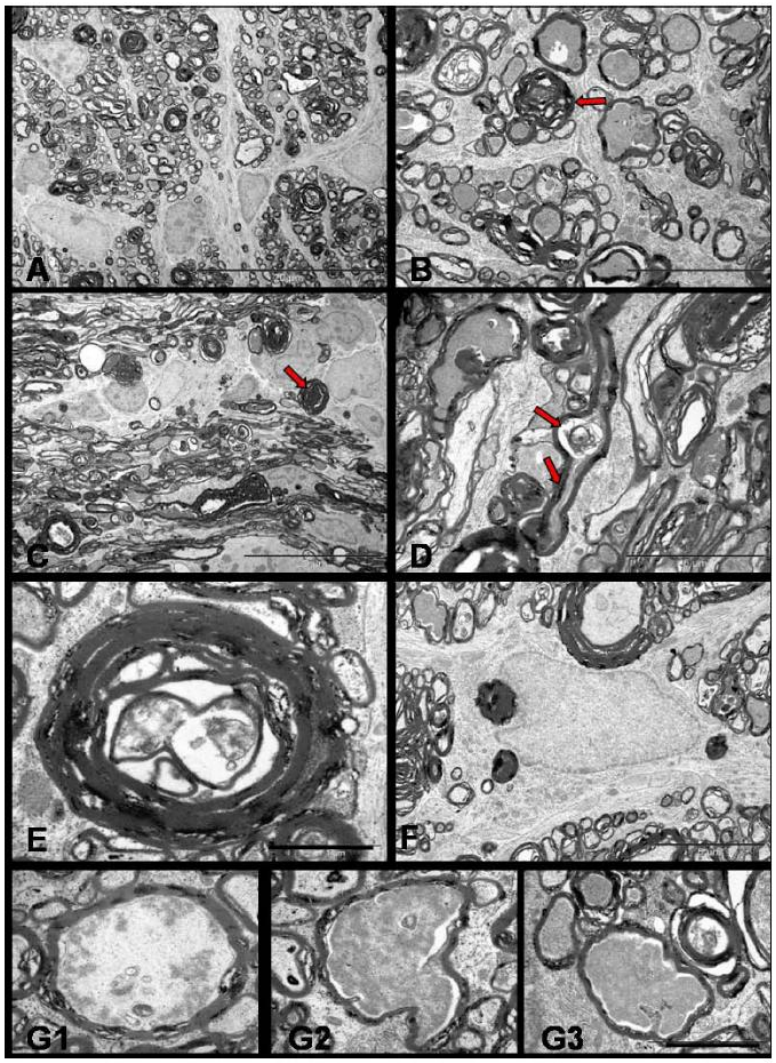

Figure 11 TEM of distal segment of rat optic nerve after 7 days of NMDA injection. Transverse (A, Bar = 20 μm & B, Bar = 5 μm) and longitudinal sections (C, Bar = 20 μm & D = Bar = 5 μm) show the fibres undergoing dark degeneration with most axons showing hyperdense axoplasm (red arrows). Longitudinal profile show the focal axonal swelling and hyperdense axoplasm in the same axon (D, arrows). Axon towards the end stage of degeneration (E, Bar = 1 μm) show nearly collapsed axon structure and the myelin debris phagocytosed by the astrocytes (F, Bar = 5 μm). Last series of photographs (G1, G2, G3, Bar = 2 μm) represent axoplasm in various stages of dissolution.

that perikaryal insult is unlikely to damage myelin without producing axonal changes. However, myelin showed proliferation and intermittent separation at internodes in the absence of cytoskeletal damage.

Glial cells in the optic nerve also reacted to excitotoxic-induced axonal degeneration in a manner similar to that seen during Wallerian degeneration [67]. Although, there are evidences for the expression of NMDA receptors on oligodendrocyte processes in white matter [19], oligodendrocytes in retro-orbital optic nerve axons remained normal. But astrocytes underwent reactive changes with the development of extensive filament-rich processes. Studies have shown that astrocytes and microglial cells invade the myelin sheath at the intraperiod line and phagocytose the peeled off outer lamellae [68]. No such glial invasion was seen in this

study. Myelin debris was seen scattered in the extracellular space. Phagocytosed myelin which is initially in the form of the paired electron-dense curvilinear lines decompose and form a homogeneous or heterogeneous osmophilic layered structure, the myelin body, which, in the final stages, disintegrate and transform into globoid lipid droplets and needle shaped cholesterol crystal [68].

Conclusion

In conclusion, selective perikaryal excitotoxic injury causes a predominantly necrotic form of somal death with simultaneous nodal-paranodal changes in axons culminating later to Wallerian-like degeneration in the form of dark and watery degeneration with demyelination. The Wallerian-like degeneration noted in this model, after primary perikaryal injury, raises the possibility that excitotoxicity-induced axonopathy is an active, regulated event. This hypothesis could be tested by using the current model and comparing the axonal degeneration in slow Wallerian degeneration (WldS) rats with the degeneration in control rats.

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Authors' contributions

SS, the main author, prepared the study design after extensive literature review, collected the tissue samples, carried out electron microscopy and photography, analysed and interpreted the data. She also drafted the manuscript, made the changes as per supervisors and reviewers suggestions with the help of HC, who also assisted in collecting tissue samples, and made important intellectual contributions in the analysis of data. RC, being the principle supervisor, participated in study design, supervised each step of the study, made important suggestions on the recent updates on the research topic with contribution in reviewing the manuscript. PB, being an experienced neuropathologist, helped in thorough analysis of ultrastructure of optic nerve. All authors read and approved the final manuscript.

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