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REVIEW ARTICLE

THE ROLE OF CELECOXIB-MEDIATED COX-2 INHIBITION IN MODULATING NEUROINFLAMMATION IN HUMANS: A REVIEW

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Abstract

Peripheral nerve injury triggers a complex cascade of neuroinflammatory events that are essential for initiating regeneration but can become detrimental when prolonged. Cyclooxygenase-2 (COX-2) and its primary product prostaglandin E2 (PGE2) are rapidly upregulated at the injury site by Schwann cells, macrophages, and neurons. While early PGE2 signaling promotes Schwann cell dedifferentiation, cytokine release and axonal sprouting, sustained COX-2 activity contributes to chronic neuroinflammation, neuropathic pain, and glial scar formation that physically and chemically inhibit axonal regrowth. Celecoxib, a selective COX-2 inhibitor, has emerged as a pharmacological tool to modulate this dual role of neuroinflammation during peripheral nerve repair. This review synthesizes current evidence on the mechanisms by which celecoxib-mediated COX-2 inhibition influences the regenerative microenvironment. By blocking PGE2 synthesis, celecoxib shifts macrophage polarization from pro-inflammatory M1 to pro-regenerative M2 phenotype, reduces infiltration of neutrophils, and downregulates expression of TNF-α, IL-1β, and IL-6. Future research should prioritize dose-dependent studies, injury-stage-specific administration, and biomaterial-based delivery to maximize regenerative benefits while minimizing adverse effects on nerve repair. Understanding the precise interplay between COX-2, PGE2, and downstream regenerative pathways will be key to translating celecoxib-based therapies into clinical applications for peripheral neuropathies and traumatic nerve injuries.

Keywords: celecoxib, COX-2 inhibitor, macrophage, neuroinflammation, peripheral nerve regeneration, polarization, prostaglandin E2, Schwann cells.

INTRODUCTION

The clinical burden of peripheral nerve injuries

Peripheral nerve injuries account for 2-5% of all trauma cases and remain a major clinical challenge due to limited spontaneous recovery, especially in injuries with gaps >5 mm[1]. Functional outcomes are poor because regenerating axons must navigate a hostile microenvironment of chronic inflammation, oxidative stress, and fibrotic scarring[2]. Current gold standard, autologous nerve grafting, causes donor site morbidity and is limited by availability[3]. Pharmacological modulation of the injury microenvironment is therefore a critical strategy to improve axonal regrowth and functional recovery. Among pharmacological targets, the inflammatory cascade stands out because inflammation is both necessary for debris clearance and detrimental when excessive[4].

Neuroinflammation in the peripheral nerve microenvironment

Immediately after axotomy, Wallerian degeneration begins in the distal stump. Myelin and axonal fragments release damage associated molecular patterns (DAMPs) that activate resident Schwann cells and recruit hematogenous macrophages. This “acute neuroinflammation” is beneficial such as in Schwann cell response which consist of dedifferentiation into repair Schwann cells, upregulation of the c-Jun, and secretion of neurotrophins like NGF, GDNF, BDNF[5]. Macrophage response consists of M1 macrophages which infiltrate in days 1-3 to phagocytose myelin debris. M2 macrophages dominate after day 7 to

release IL-10, TGF-β for tissue repair[6]. Angiogenesis consist of VEGF release restores blood-nerve barrier. However, if pro-inflammatory signals persist >2 weeks, the environment shifts to "chronic neuro-inflammation". Sustained TNF-α, IL-1β, IL-6, and reactive oxygen species which causes neuronal apoptosis, demyelination, neuropathic pain via central sensitization, and fibroblast activation→ collagen scar formation. The scar plus myelin-associated inhibitors like MAG and Nogo-A create a biochemical wall that regenerating axons cannot cross. Thus, the therapeutic goal is not to abolish inflammation, but to modulate its duration and phenotype[7].

COX-2/PGE2 axis as a key regulator of post-injury inflammation

Cyclooxygenase exists in 2 isoforms which include the COX-1 which is constitutive and involved in homeostasis, while COX-2 is inducible by cytokines, LPS, and injury. In healthy peripheral nerve, COX-2 expression is minimal[8]. After injury, COX-2 mRNA and protein increase 10-50 folds within 6-24 h in Schwann cells, macrophages, fibroblasts, and DRG neurons. COX-2 converts arachidonic acid to prostaglandin H2→PGE2 via microsomal PGE synthase-1. PGE-2 acts through 4 G-protein coupled EP receptors known as EP1/EP3 increases Ca^{2+}, nociception, pain EP2/EP4 is known to increase cAMP to PKA activation. High cAMP early promotes Schwann cell migration and axon growth[9]. High cAMP chronically inhibits axon elongation and maintains M1 macrophage state. This creates a temporal paradox: Early PGE2 is "pro-regenerative" while late PGE2 is "anti-regenerative". Therefore, selective, timed inhibition of COX-2 is more rational than global non-steroidal anti-inflammatory drug (NSAID) use[10].

Celecoxib: pharmacology and rationale for nerve repair

Celecoxib is a sulfonamide, selective COX-2 inhibitor approved for arthritis and pain[11]. Selectivity ratio of COX-2/COX-1 ≈ 12:1, helps in reducing GI toxicity compared to non-selective NSAIDs like ibuprofen. Mechanisms relevant to PNI: Anti-inflammatory[11-12]: increase in PGE2 leads to decrease in vasodilation, edema, leukocyte recruitment. Shifts macrophage polarization M1 to M2.

Neuroprotective: There is decreased COX-2-mediated oxidative stress. COX-2 produces reactive oxygen species (ROS) as byproduct. This in turn leads to increase in neuronal apoptosis via Bcl-2/Bax pathway.

Analgesic: A decrease in PGE2-EP1 signaling in DRG neurons leads to reduction in mechanical allodynia and thermal hyperalgesia.

Anti-fibrotic: A decrease in PGE2 leads to a decrease in fibroblast activation which forms less scar tissue at repair site. Preclinical studies in rat sciatic nerve crush/transection models show celecoxib 5-20 mg/kg/day improves sciatic function index, increases myelinated axon count, and reduces pain behaviors. But high doses or early administration can delay regeneration, confirming the "Goldilocks zone" concept.

Delivery challenges and biomaterial solutions

Systemic celecoxib has 2 limitations: (1) Cardiovascular risk with chronic oral use, (2) Poor penetration to nerve injury site due to blood-nerve barrier. Local, controlled delivery is ideal[13]. Biodegradable biomaterials like chitosan hydrogels/ aerogels can provide sustained release 2-4 weeks to match regeneration timeline, act as physical conduit for axon growth and reduce systemic side effects[14]. Chitosan is cationic polysaccharide with inherent anti-inflammatory and antibacterial properties. Understanding celecoxib-mediated COX-2 inhibition provides a pharmacological lever to "tune" neuroinflammation. This is highly relevant for traumatic PNI, diabetic neuropathy, and post-surgical nerve repair where inflammation drives poor outcomes[15,16].

Interpretation of celecoxib's dual role in nerve repair

The literature review confirms that celecoxib mediated COX-2 inhibition does not have a simple excellent or detrimental effect on peripheral nerve regeneration[17]. Instead, it acts as a modulator of neuroinflammation whose outcome depends on three major factors such as timing, dose, and delivery method[18]. In the acute phase 0-72 h post-injury, PGE2 produced by COX-2 is required for Schwann cell dedifferentiation, upregulation of c-Jun, and recruitment of M1 macrophages for debris clearance. Complete suppression of COX-2 during this window delays Wallerian degeneration and axon sprouting, which explains why high-dose systemic celecoxib given immediately after injury sometimes shows reduced regeneration in animal models[19]. In contrast, during the subacute to chronic phase day 7-28, persistent COX-2 activity maintains M1 macrophage polarization, elevates TNF-α/IL-1β, and drives fibroblast-mediated scar formation[20]. This is when selective COX-2 inhibition by celecoxib becomes beneficial. By lowering PGE2-EP2/EP4 signaling, celecoxib shifts macrophages toward M2 phenotype, reduces pro-inflammatory cytokines, and creates a permissive environment for axon elongation and remyelination. This temporal switch supports the "inflammation tuning" concept rather than inflammation elimination.

Mechanisms on how celecoxib modulates key cellular players

The following mechanisms demonstrate the modulation effect of celecoxib on key cellular players.

1. Macrophages: Celecoxib decreases iNOS and TNF-α expression while increasing the Arg-1 and IL-10. This M1→M2 shift is critical because M2 macrophages secrete factors that promote Schwann cell migration and angiogenesis. PGE2-EP4 activation stabilizes HIF-1α to maintain M1 state, so celecoxib breaks this cycle.

2. Schwann cells: Repair Schwann cells require transient cAMP elevation to dedifferentiate, but sustained high cAMP via EP2/EP4 inhibits process extension. Celecoxib reduces chronic cAMP spikes, allowing Schwann cells to transition from clearance mode to myelination mode regulated by Egr 2-early growth response 2 (Krox-20)[21].

3. Neurons and pain: COX-2 is induced in DRG neurons after injury and contributes to central sensitization. Celecoxib decreases the PGE2-EP1 signaling, which explains the reduction in mechanical allodynia observed *in vivo*. This dual benefit improved regeneration + reduced neuropathic pain is a major advantage over therapies that only target one outcome[22].

4. Oxidative stress: COX-2 catalysis generates ROS as byproducts. Celecoxib's COX-2 blockade plus its direct antioxidant activity reduces oxidative damage to lipids and proteins in the nerve stump, protecting regenerating axons.

Importance of controlled-release delivery

Systemic oral celecoxib at 200-400 mg/day for humans achieves plasma levels that non-selectively inhibit COX-2 throughout the body, increasing cardiovascular risk[23]. Local delivery of the drug has two major problems: Sustained release 5-20 µg/day locally vs 100-200 mg/day systemically. This keeps PGE2 in the "pro-regenerative" range early, then suppresses it later.

Site specificity: Drug stays at injury site for 2-4 weeks, matching the time course of Schwann cell bands of Büngner formation[24]. *In vitro* release data showing 60-70% celecoxib release over 24-48 h followed by sustained release supports this rationale. This interaction prevents burst release that would cause complete COX-2 inhibition in the acute phase[23].

Comparison with other anti-inflammatory strategies

Compared to steroids like dexamethasone, celecoxib is more selective and has less impact on collagen synthesis and wound healing[24]. Compared to non-selective NSAIDs, celecoxib spares COX-1 which leads to less GI bleeding. Compared to biologics like anti-TNFα antibodies, celecoxib is cheaper and it is a small-molecule, making it feasible for biomaterial incorporation. However, unlike specialized pro-resolving mediators, celecoxib does not actively promote resolution; it only blocks synthesis. Future combination therapies of celecoxib and other NSAIDs could be explored[24].

Table 1: Summarized table of immune and inflammation markers.

Term	Meaning	Role in nerve regeneration
iNOS	Inducible Nitric Oxide Synthase	Enzyme that makes NO from L-arginine. Made by M1 macrophages. High iNOS = pro-inflammatory, oxidative stress, inhibits axon growth. You want it LOW during repair.
Arg-1	Arginase-1	Enzyme that also uses L-arginine but makes polyamines for repair. Marker of M2 macrophages. High Arg-1 = anti-inflammatory, promotes Schwann cell repair and axon growth.
IL-10	Interleukin-10	Anti-inflammatory cytokine. Secreted by M2 macrophages, Tregs. Suppresses iNOS, promotes myelin clearance and nerve repair. "Repair signal" cytokine.
LPS	Lipopolysaccharide	Bacterial toxin from E.coli cell wall. Used in lab to force macrophages into M1 / pro-inflammatory state. In nerve injury models it worsens damage if present.

Limitations and considerations

Timing window: The exact switch point from pro- to anti-regenerative COX-2 activity varies with injury type. Crush injuries may need celecoxib only after day 5, while transaction and gap may tolerate earlier administration due to higher baseline inflammation.

Cell type specificity: COX-2 in neurons vs Schwann cells vs macrophages may have different roles. Current data does not fully dissect cell-specific knockout effects.

Long-term safety: Even local celecoxib may affect prostacyclin/thromboxane balance. *In vitro* cytotoxicity data on Schwann cells and PC12 neurons is needed to define safe loading concentrations for gels.

Implications for biomaterial-based nerve repair

This review leads to 3 key design principles for celecoxib-loaded nerve conduits: Delayed release: Engineer gels to release <20% drug in first 72h, then sustained release. This can be achieved by increasing crosslinker density or adding hydrophobic coating.

Multifunctionality: Combine celecoxib for inflammation control with other plant extracts, bioactives for antioxidant and cell adhesion. This reduces drug dose needed. Table 1 summarizes the immune and inflammatory markers.

CONCLUSION

celecoxib-mediated COX-2 inhibition represents a rational pharmacological strategy to fine-tune neuro-inflammation during nerve regeneration. Celecoxib-mediated COX-2 inhibition is not a blunt anti-inflammatory tool but a precision modulator of the nerve regeneration microenvironment. When delivered in a controlled manner, it can suppress detrimental chronic neuroinflammation and neuropathic pain while preserving the early inflammatory signals needed for repair. This balance makes celecoxib-loaded biomaterials a promising adjuvant for peripheral nerve tissue engineering.

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AUTHOR'S CONTRIBUTIONS

Ezegbe CA: writing original draft, methodology. **Emeka-Obi OR:** conceptualization, writing original manuscript. **Okorafor EC:** writing original draft, conceptualization. **Chikaodi GO:** editing, methodology. **Nkesi AA:** methodology, investigation. **Ruhuoma GA:** writing original draft,

conceptualization. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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