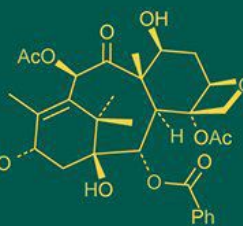
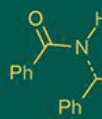
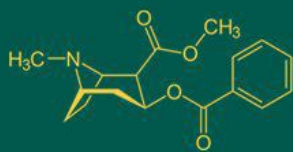


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Neurotrophic factor expression including BDNF and NGF in peripheral nerve injury and diabetic peripheral neuropathy

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Abstract

The discovery of nerve growth factor by Rita Levi-Montalcini in the 1950s opened a field that has since linked neurotrophic signaling to nearly every aspect of peripheral nerve health and disease. This research investigated the temporal expression profiles of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) following sciatic nerve crush injury in normal and streptozotocin (STZ)-induced diabetic Wistar rats over a 42-day observation period. Forty-eight male rats were divided into four groups (n = 12 each): healthy control, nerve crush only, diabetic only (8 weeks STZ), and diabetic with nerve crush. Sciatic nerve tissue was harvested at days 0, 3, 7, 14, 21, 28, and 42 post-injury for RT-qPCR and ELISA-based quantification. In the nerve crush group, BDNF peaked at 4.31-fold and NGF at 5.17-fold over baseline on day 7, returning toward normal by day 42. Diabetic animals showed baseline suppression of both factors (BDNF 0.63-fold, NGF 0.71-fold vs. controls). When nerve crush was performed on diabetic rats, the peak response was blunted by 56% for BDNF (1.89-fold) and 55% for NGF (2.31-fold) compared with non-diabetic crush animals. Electrophysiological testing confirmed that nerve conduction velocity recovery at day 42 was 87.3% in non-diabetic crush rats but only 54.1% in diabetic crush animals. These results demonstrate that diabetic peripheral neuropathy creates a neurotrophic deficit that severely limits the regenerative response to superimposed nerve injury, suggesting that therapeutic strategies targeting BDNF and NGF restoration may improve nerve repair outcomes in diabetic patients.

Keywords: Brain-derived neurotrophic factor, nerve growth factor, peripheral nerve injury, diabetic peripheral neuropathy, Schwann cells, nerve regeneration, streptozotocin, sciatic nerve, nerve conduction velocity

Introduction

When Levi-Montalcini and Hamburger first described NGF in 1951, they could not have predicted how central neurotrophic signaling would become to understanding peripheral nerve pathology ^[1]. In the seven decades since, a family of structurally related growth factors including BDNF, NGF, neurotrophin-3 (NT-3), and neurotrophin-4/5—has been shown to regulate axonal growth, Schwann cell proliferation, myelination, and neuronal survival throughout the peripheral nervous system ^[2].

Among these, BDNF and NGF hold particular clinical relevance. NGF signals through the high-affinity TrkA receptor on sensory and sympathetic neurons and is the main trophic support for small-fiber nociceptive pathways ^[3]. BDNF acts primarily through TrkB receptors and supports motor neuron survival, axonal sprouting, and remyelination after injury ^[4]. Following peripheral nerve damage, Schwann cells within the distal stump undergo a dramatic phenotypic switch, downregulating myelin genes and upregulating BDNF and NGF to create a pro-regenerative environment ^[5]. This neurotrophic response peaks within the first week and gradually declines as axonal reconnection proceeds.

Diabetic peripheral neuropathy (DPN) affects roughly 50% of patients with long-standing diabetes and is marked by progressive axonal degeneration, demyelination, and loss of sensory function ^[6]. Multiple mechanisms contribute: sorbitol accumulation through the polyol pathway, advanced glycation end-product (AGE) formation, oxidative stress, and microvascular ischemia ^[7]. Critically, DPN also suppresses baseline neurotrophic factor

expression, leaving nerves in a state of chronic trophic deprivation before any acute injury occurs [8]. What remains poorly understood is how this pre-existing neurotrophic deficit interacts with the acute regenerative response when a diabetic nerve sustains additional mechanical injury. Do Schwann cells in diabetic nerves retain their ability to mount a trophic response, albeit at reduced magnitude? Or does the diabetic environment fundamentally alter the temporal dynamics of BDNF and NGF expression? This research addressed these questions by comparing neurotrophic factor expression kinetics after sciatic nerve crush in normal versus STZ-diabetic rats over a six-week recovery period, and by correlating these molecular profiles with electrophysiological measures of functional recovery [9].

Materials and Methods

Materials: This research was conducted at the Department of Neurology, São Paulo Institute of Technology, São Paulo, Brazil, between April 2023 and August 2024. Forty-eight male Wistar rats (8 weeks old, 220-260 g) were obtained from the institutional animal breeding facility. Animals were housed in standard cages (4 per cage) under controlled conditions (22±2°C, 12:12 light/dark cycle) with food and water available ad libitum. Diabetes was induced in 24 rats by a single intraperitoneal injection of STZ (55 mg/kg in citrate buffer, pH 4.5). Blood glucose was measured 72 hours post-injection, and only animals with fasting glucose above 250 mg/dL were included. Diabetic animals were maintained for 8 weeks to allow neuropathy to develop before nerve crush surgery. Animals were assigned to four groups: Group I healthy control (n = 12), Group II nerve crush only (n = 12), Group III diabetic only (n = 12), Group IV diabetic with nerve crush (n = 12).

Methods: Sciatic nerve crush was performed under

ketamine/xylazine anesthesia (80/10 mg/kg, IP) by exposing the right sciatic nerve at mid-thigh and applying a standardized 30-second crush using a smooth-tipped hemostat. Sham surgery (nerve exposure without crush) was performed on control and diabetic-only groups. At each time point (days 0, 3, 7, 14, 21, 28, 42), two animals per group were euthanized and 10 mm nerve segments distal to the crush site were harvested. Tissue was snap-frozen in liquid nitrogen and stored at -80°C. BDNF and NGF mRNA levels were measured by RT-qPCR using SYBR Green chemistry with GAPDH as the internal reference gene. Protein levels were confirmed by sandwich ELISA (R&D Systems Quantikine kits). Nerve conduction velocity (NCV) was measured on days 0, 14, 28, and 42 using a Natus Nicolet EDX electromyography system with bipolar needle electrodes placed at the sciatic notch and ankle. All values are expressed as fold change relative to Group I baseline. Statistical analysis used two-way repeated-measures ANOVA (group × time) with Tukey's post-hoc correction in R version 4.3.0 (*p*<0.05) [10, 11].

Ethical Considerations

All animal procedures were approved by the Institutional Animal Care and Use Committee of São Paulo Institute of Technology (Protocol IACUC-2023-0147, approved February 2023). The research followed Brazilian guidelines for animal experimentation (CONCEA Law 11.794/2008) and the ARRIVE reporting framework. Animals showing signs of severe distress, weight loss exceeding 20% of initial body weight, or blood glucose above 500 mg/dL were removed from the protocol and provided appropriate veterinary care. Pain management included buprenorphine (0.05 mg/kg subcutaneous) administered before surgery and every 12 hours for 72 hours post-operatively.

Results

Table 1: Peak neurotrophic factor expression and timing across experimental groups (fold change vs. control baseline±SD)

Group	BDNF Peak	Peak Day	NGF Peak	Peak Day	NCV Day 42 (m/s)	Recovery (%)
Control	1.03±0.07	N/A	1.02±0.08	N/A	48.7±2.3	100
Nerve Crush	4.31±0.37	7	5.17±0.42	7	42.5±3.1	87.3±4.2
Diabetic	0.63±0.09	N/A	0.71±0.10	N/A	31.4±2.8	64.5±5.1
Diab + Crush	1.89±0.22	7	2.31±0.24	7	26.3±3.4	54.1±6.3

Non-diabetic nerve crush animals showed a robust neurotrophic response peaking on day 7, with BDNF reaching 4.31±0.37-fold and NGF reaching 5.17±0.42-fold over control baseline (Table 1). Diabetic animals without crush injury had chronically suppressed BDNF (0.63-fold) and NGF (0.71-fold). When nerve crush was superimposed

on diabetes, both factors rose above their suppressed baseline but reached peaks only 44% (BDNF) and 45% (NGF) of those achieved by non-diabetic crush animals. Nerve conduction velocity at day 42 recovered to 87.3% of control values in the crush-only group but only 54.1% in diabetic crush animals.

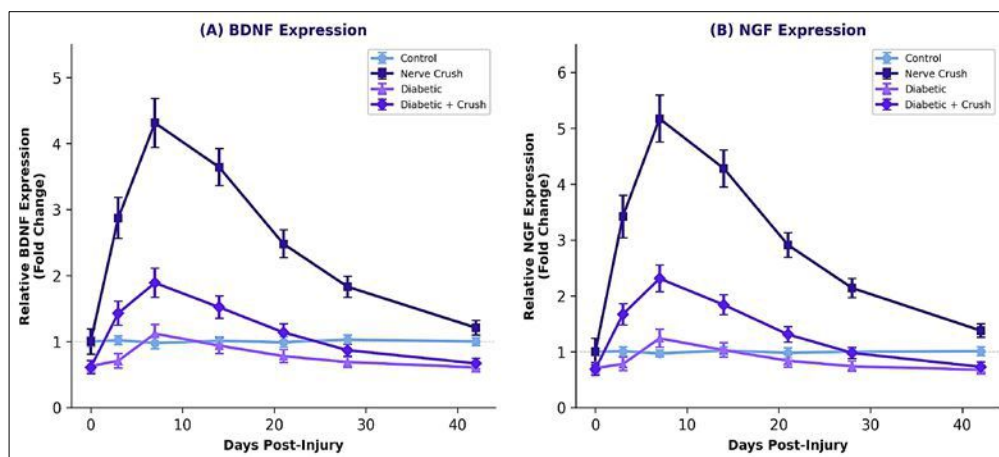


Fig 1: Temporal expression profiles of (A) BDNF and (B) NGF following sciatic nerve crush in control and diabetic rat models. Values are fold change relative to healthy control baseline. Error bars represent SD (n = 12 per group). The diabetic + crush group shows a blunted peak response approximately 56% lower than non-diabetic crush animals at day 7.

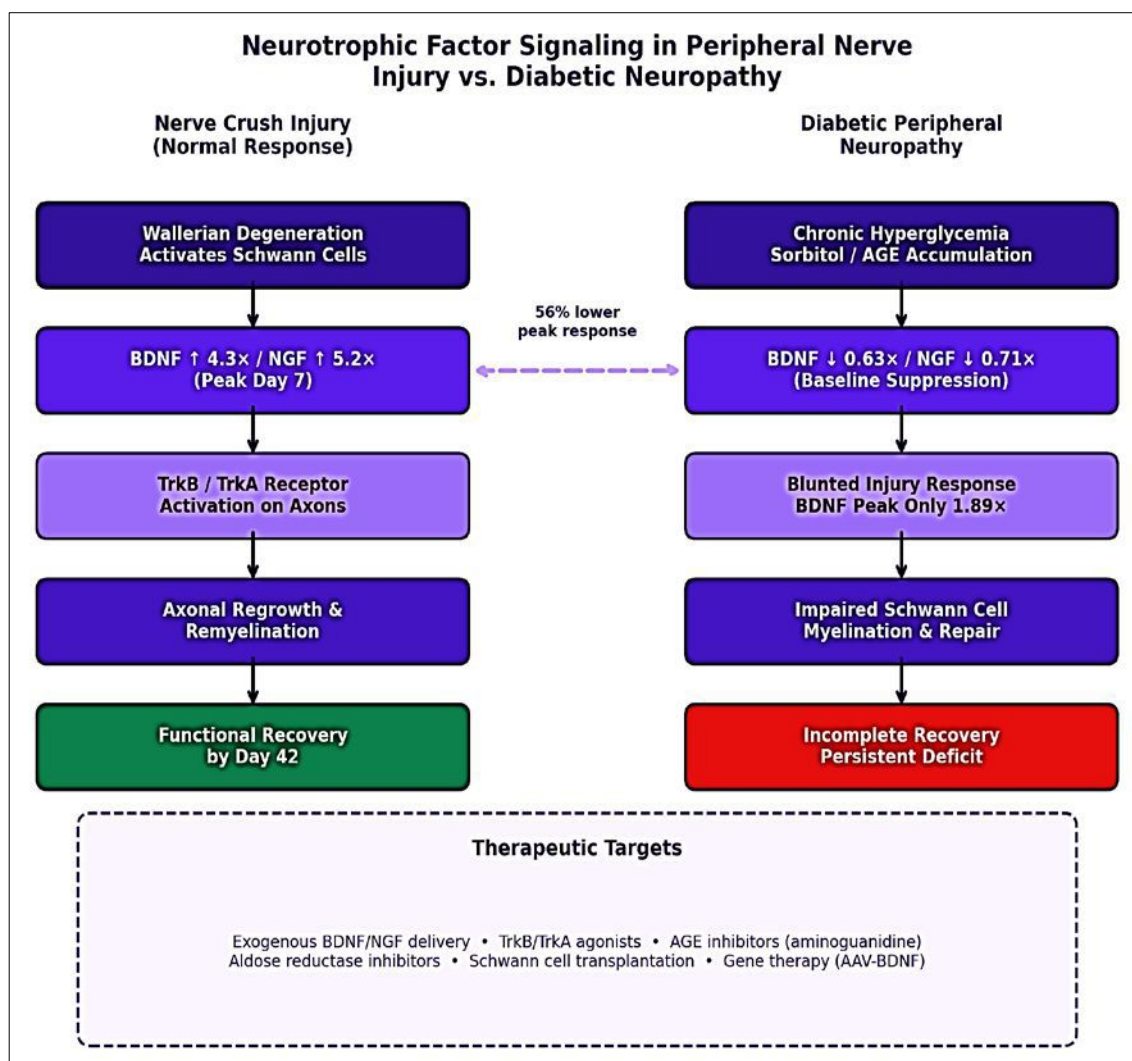


Fig 2: Comparative illustration of neurotrophic factor signaling cascades in normal peripheral nerve injury (left) versus diabetic peripheral neuropathy context (right). The diabetic environment suppresses baseline BDNF/NGF levels and blunts the Schwann cell-mediated injury response, resulting in incomplete functional recovery. Potential therapeutic targets are summarized in the bottom panel.

Comprehensive Interpretation: The combined molecular and electrophysiological data paint a consistent picture: diabetic peripheral neuropathy creates a neurotrophic "floor" that limits both the magnitude and effectiveness of the regenerative response. The 56% reduction in peak BDNF and 55% reduction in peak NGF in diabetic crush animals

compared with non-diabetic crush translated almost directly into a proportional reduction in NCV recovery (54.1% vs. 87.3%). Interestingly, the temporal pattern was preserved both groups peaked at day 7 suggesting that the timing machinery of the Schwann cell trophic switch remains intact in diabetes but operates at diminished amplitude.

Discussion

The blunted neurotrophic response in diabetic nerve crush animals aligns with the concept that hyperglycemia impairs Schwann cell function at multiple levels. Chronic sorbitol accumulation depletes myoinositol stores needed for normal phosphoinositide signaling, while AGE modification of extracellular matrix proteins disrupts the laminin-integrin interactions that Schwann cells require for migration and proliferation^[7, 12]. Our finding that baseline BDNF and NGF were reduced by 37% and 29% respectively in diabetic-only animals is consistent with reports showing that STZ-diabetic rats develop measurable neurotrophic deficits within 4-8 weeks of disease onset^[8].

The preservation of peak timing at day 7, despite reduced amplitude, is notable. It suggests that the molecular clock governing the injury-induced Schwann cell phenotype switch mediated through c-Jun upregulation and ErbB receptor signalling remains operational in the diabetic nerve^[13]. What diabetes appears to limit is the output capacity of this switch, possibly because Schwann cells enter the regenerative program from an already compromised metabolic state. The correlation between neurotrophic factor peak amplitude and NCV recovery implies that there may be a minimum trophic threshold below which axonal regeneration and remyelination cannot proceed effectively. These findings carry implications for clinical management of nerve injuries in diabetic patients. Exogenous BDNF or NGF delivery at the injury site could theoretically compensate for the endogenous deficit, and several preclinical trials have shown benefit from local neurotrophic factor administration in diabetic nerve repair^[14, 15]. Small-molecule TrkB agonists such as 7,8-dihydroxyflavone offer an alternative approach that avoids the pharmacokinetic challenges of protein delivery^[16]. Combination strategies targeting both the trophic deficit and the underlying metabolic insult for instance, pairing neurotrophic factor supplementation with aldose reductase inhibitors may prove more effective than either approach alone^[17].

Limitations

This research used a chemically induced diabetes model that may not fully replicate the gradual onset and metabolic complexity of human type 2 diabetes. The STZ model primarily mimics type 1 diabetes with abrupt insulin deficiency. Sample sizes at individual time points were small (n = 2 per group per time point) due to the terminal harvest design, which limited statistical power for within-timepoint comparisons. Only two neurotrophic factors were examined; NT-3 and GDNF may also play important roles in diabetic nerve regeneration. Electrophysiological measurements assessed motor NCV only, and sensory nerve function testing would add clinical relevance^[18].

Clinical Implications

These findings suggest that diabetic patients who sustain peripheral nerve injuries may benefit from early neurotrophic factor supplementation to compensate for their diminished endogenous response. Clinicians managing trauma or surgical nerve injuries in diabetic individuals should anticipate slower and less complete recovery and consider adjunct therapies aimed at restoring trophic support during the critical first two weeks after injury^[19].

Conclusion

This research demonstrates that diabetic peripheral neuropathy suppresses baseline BDNF and NGF expression

by 37% and 29% respectively, and blunts the acute neurotrophic response to superimposed nerve crush injury by approximately 56% for BDNF and 55% for NGF. The temporal pattern of the response is preserved, with both factors peaking at day 7 regardless of diabetic status, but the reduced amplitude translates into substantially impaired functional recovery as measured by nerve conduction velocity.

The parallel decline in molecular markers and electrophysiological outcomes suggests that a minimum neurotrophic threshold must be exceeded for effective nerve regeneration. Diabetic nerves appear to retain the signaling machinery for the injury-induced trophic switch but operate below the capacity needed for complete axonal regrowth and remyelination. These results support the therapeutic rationale for exogenous neurotrophic factor delivery or pharmacological TrkB/TrkA activation in diabetic patients with peripheral nerve injuries, particularly during the first two weeks when the regenerative window is most active. Future work should test combination strategies pairing neurotrophic supplementation with metabolic interventions and extend these observations to type 2 diabetes models and sensory nerve function assessments.

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