

Therapeutic strategies for brachial plexus injury

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Abstract

Brachial plexus avulsion (BPA), a severe acute peripheral nerve injury in adults, results in total loss of the motor function in the upper limb. Although immediate re-implantation surgery is widely performed to repair this lesion, the motor function cannot be fully restored. The main cause is that the growth velocity of axon is extremely slow in order to re-innervate the target muscles before atrophy develops. Therefore, the survival of spinal motoneurons (MNs) is considered to be a prerequisite for the recovery of motor function. The introduction of survival-proactive agents with anti-oxidative stress and anti-inflammation properties has emerged as a new approach to the motor function recovery following BPA. In the current review, we summarized the treatments of BPA in both mouse and rat models following re-implantation surgery. Furthermore, the pain treatment options following BPA were discussed.

Key words: brachial plexus avulsion (BPA), motoneurons (MNs), pain.

Introduction

The number of patients suffering from brachial plexus injury (BPI) has been increasing steadily, mostly due to motorbike accidents [23,30,69]. Despite neurosurgical repair strategies to restore anatomical continuity between the injured motor axons and the distal nerves, function recovery of the distal musculature is often disappointing [50]. Functional loss is caused by the degeneration of nerve fibres, deficits of synapses and the nerve fibre growth inhibitory effect of glial scarring [10]. Significant motoneuron (MN) loss is reported following root avulsion lesions in adults [52,92,102] and most of the affected MNs ultimately die [39], causing the paralysis of the target muscle groups, as the brachial plexus is the unique nerve reserve to the upper limb. Very little axon regeneration occurred in the spinal

cord after acute or chronic injury, due to the stimulation of inhibitory molecules at the injury sites and the low intrinsic capacity for axon growth in neurons in the adult central nervous system (CNS). Multiple treatments have been performed on animal models to investigate the recovery of motor function following brachial plexus root avulsion (BPRA). Re-implantation of avulsed ventral roots temporarily delays MN degeneration and allows staggered regeneration of motor axons over the implantation site into the nerve root [26,73]. However, in patients with BPI, axons need to regenerate over distances of up to 80 cm before reaching their distal target muscles in the lower arm and hand. With an average axonal outgrowth velocity of 1-2 mm/day, axon regeneration is a protracted process, which requires several months, or even years [24]. To bridge this distance, an extended

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period of regeneration is required, resulting in limited distal regeneration and suboptimal recovery of voluntary function [28,84]. Re-implantation surgery, a widely performed approach, cannot entirely repair the motor function due to the slow velocity of axonal growth for the spinal MNs to re-innervate the target sites prior to the development of muscle atrophy [8,9]. The survival of MNs is necessary for the functional recovery. As a consequence, early and effective protection of neurons is necessary for lengthening the time window of the treatment and promoting the survival of lesioned MNs [65].

Maintaining the survival of affected MNs is extremely essential for axonal regeneration [40]. Eggers *et al.* discussed the clinical features and intervention strategies, including acute and delayed implantation, cell implantation, macromolecular intervention, neurotrophic factors and interference with neurite outgrowth inhibitors, presenting a general description of neurotrophic factor treatment and cell-based pharmacological approaches that have been applied in combination with surgical re-implantation [27]. Herein we reviewed the underlying mechanisms associated with oxidative stress and inflammation, and the genes with axonal growth and regeneration, brain changes and other treatments of BPA aimed at promoting MN survival and alleviating pain.

Inflammation and oxidative stress

Spinal root avulsion causes a multitude of pathophysiological events, including modified expression of genes and proteins associated with inflammation, oxidative stress, and apoptosis, which collectively cause substantial neuronal death [82]. After a primary mechanical injury, the secondary cascade produces reactive oxygen species (ROS) that cause cell damage and apoptosis [49]. Inflammatory cells and microglia accumulate at the injury site and cause neuronal death, aggravating oxidative damage and triggering inflammatory responses [58].

An experimental model of spinal root avulsion simulates the characteristics of human BPA injury [75]. In adult rodent models, ventral root avulsion injury triggers the excessive generation of reactive nitrogen species (RNS), including NO, and ONOO⁻ [81,91], and ROS as well as O₂⁻, H₂O₂ and [•]OH [59,64]. Accumulation of ROS/RNS can overwhelm the body's antioxidant capacity, induce lipid peroxi-

dation, protein oxidation and DNA modification [15], and cause oxidative damage at the injury site, leading to progressive MN loss [20]. In addition, another important hallmark of spinal root avulsion is the local neuroinflammatory response in the affected stage, characterized by excessive activated microglia/macrophages and astrocytes infiltrating the lesion sites [5,105], which produce pro-inflammatory cytokines and further inhibit axonal and dendrite regeneration [70], thereby resulting in aggravation of the oxidative insult [37]. Glial activation was observed in mice following BPRA [113]. Effective anti-oxidant and anti-inflammatory treatments can reduce neuronal death and lay the foundation for nerve regeneration.

Molecular changes

Significant changes of key molecules are associated with neuronal injury, which may be a powerful tool for ameliorating the inflammatory microenvironment and improve nerve regeneration. Activation of c-Jun was suggested to be associated with cell death in neonatal sympathetic neurons [6,29] and hippocampal neurons [77] due to a deprivation of neurotrophic factors. Early up-regulation of the neuronal NOS (nNOS) or inhibition of c-Jun phosphorylation in injured spinal cords may serve as the molecular targeted strategies for preventing the degeneration of MNs in BPRA in the future [24]. Elevated phosphorylated c-Jun level in neonatal spinal MNs after axonal injury has been associated with MN death and regeneration [104].

Previous studies have shown that c-Jun participates directly in regulating the growth-associated protein 43 (GAP-43) [43]. GAP-43 is a small acidic membrane protein associated with successful axonal growth and regeneration in the nervous system [43,80]. Both the mRNA and protein levels of GAP-43 elevate after BPI, and the GAP-43 protein is closely related to the axonal regeneration and functional recovery [11]. Yuan *et al.* reported that GAP-43 increased synchronously with the regeneration of spinal avulsed MNs after BPRA [103]. It was reported that, despite the colocalization of nNOS and GAP-43 in avulsed MNs, GAP-43 plays a more important role for MNs regeneration [101].

Several transcription factors and enzymes have been implicated in BPRA. Estrogen-related receptor γ (ERR γ) is a vital component in injured MNs and a common marker of γ MNs following BPRA [100]. Endog-

enous protein kinase C (PKC) and phospholipase-C γ (PLC γ) were activated in spinal MNs in the unilateral BPR model. Moreover, suppression of the PLC γ /PKC axis was shown to promote avulsion-induced MN death, while stimulation of the PLC γ /PKC axis remitted avulsion-induced MN death [111]. It was also reported that reducing apurinic/apyrimidinic endonuclease 1 (APE1), a ubiquitously expressed rate-limiting enzyme of DNA damage repairing, renders spinal MNs susceptible to oxidative stress [20]. However, further exploration using human systems is required to define other transcription factors mediating MN survival.

Brain changes

Several studies suggest that the neurons in the brain undergo fundamental changes after BPA injury. Elevated brain-derived neurotrophic factor (BDNF) and GAP-43 are beneficial for cerebral transhemispheric functional reconstruction after contralateral C7 root transfer following BPA injury [88]. Up to 12 months post operation, faster transhemispheric reorganization is observed after transfer of the contralateral C7 in young recipient nerves with total BPR [71]. The expression of major histocompatibility complex class I (MHC-I), paired-immunoglobulin-like receptor B (PirB) and cluster of differentiation 3 ζ (CD3 ζ) in motor cortex, neurons exhibited an initially decreasing trend both at the mRNA and protein levels on day 7, which was reversed at 3 months post-injury in BPR rats [107]. Factors participating in the network of motor cortical remodelling after BPR display dynamic changes. Major microRNAs (miRNAs/miRs) distributed in the motor cortex, such as miR-101-3p, miR-132, miR-134, miR-137-3p and miR-485, play vital roles in regulating neural plasticity and transhemispheric functional reorganization dendrite morphology, spontaneous synaptic responses and transmitter release after cervical spinal nerve root transfer following BPA injury [61,81,86]. Functional MRI studies revealed that the levels of proinflammatory cytokines, such as interleukin (IL)-1 β , IL-6, tumour necrosis factor α (TNF- α), are important mediators in the neural plasticity and transhemispheric functional reorganization [33,36,57,98]. A growing body of evidence offers novel insights into the mechanism through which altered expression of these factors in the brain can improve or impair the MN survival [108].

These results suggest that elucidating the molecular mechanisms underlying the brain changes accompanying by BPA injury may uncover new therapeutic targets for improving motor function recovery.

Interventions for motoneuron survival

Several combinatorial strategies have been adopted for nerve reimplantation in multiple animal models of root avulsion injury [4,19]. Exogenous glial cell-derived neurotrophic factor (GDNF) combined with foetal lumbar cells transfer resulted in improved MN survival, axonal sprouting and functional recovery after avulsion of spinal roots [74]. Besides, different sources of stem cells are ideal seed cells in peripheral nerve deficit models. Stem cells hold the merits of boosting tissue repair and regeneration by releasing considerable neurotrophic, angiogenic and anti-inflammatory factors which lead to structure remodelling, neovascularization and function restoration [46,47]. Interestingly, embryonic spinal cord neurons grafted to the injured distal nerve alleviated MN death, but also promoted axonal regeneration and generation of MNs with locomotive function [109]. Transplantation of human embryonic stem cells overexpressing fibroblast growth factor 2 (FGF-2) exerted a neuroprotective effect following spinal cord ventral root avulsion (VRA), retaining synaptic stability and reducing astroglial reactivity [3]. The injection of embryonic spinal cord-derived cells may be beneficial for preserving the muscle endplates and initiating earlier functional recovery through reducing muscle atrophy after peripheral nerve injury [76]. Contralateral C7 transfer combined with acellular nerve allografts loaded with differentiated adipose stem cells were beneficial for nerve restoration in BPI rats [60,97]. Though several studies have reported varied success using stem cell-based therapy to improve BPR outcomes, more pre-clinical and clinical experiments are needed to testify the constancy of the efficacy before consensus is reached. In general, stem cell-based therapy had increased the proportion of the viable MNs and regained the neurological function, thus indicating the expectant clinical benefits and potential translational value. Further, future explorations are required to lay emphasis on the implications of applying modified stem cells and the optimization of cell implantation protocols. Moreover, axotomized MN regeneration and reinnervation improved by ~2-fold after timed

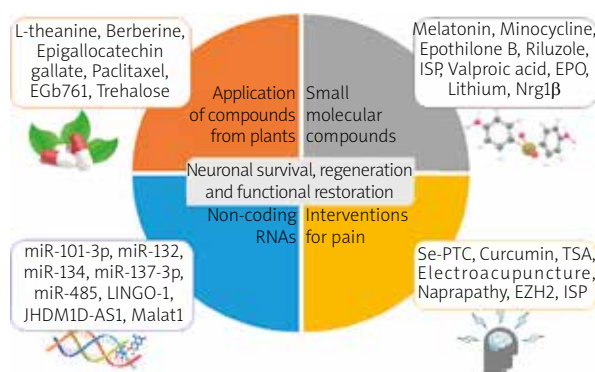


Fig. 1. Ways to promoting nerve survival, regeneration and functional restoration. Representative interventions and selected examples involved in nerve regeneration functional restoration mentioned in this review. ISP – intracellular sigma peptide, EPO – erythropoietin, LINGO-1 – immunoglobulin-like domain-containing NgR-interacting protein 1, Se-PTC – (R)-Se-phenyl thiazolidine-4-carboselenoate, TSA – trichostatin A, EZH2 – enhancer of zeste homolog 2.

GDNF gene delivery in a rat cervical VRA model [24,25]. These improvements were associated with a 2-fold increase in regeneration and enhanced reinnervation of the hand musculature. Elucidating the mechanisms involved in the interventions used to promote MN survival may provide new perspectives to recognize biomarkers or identify novel therapeutic targets for enhancing neuronal regeneration in spinal root avulsion injury (Fig. 1).

Application of compounds from plants

Treatment with plant-derived compounds may exert neuroprotective effects through enhancing nerve regeneration and functional restoration *via* suppressing neurological oxidative response, inflammation and apoptosis [66]. Tea-derived L-theanine combined with NEP1-40, a competitive antagonist of Nogo receptor (NgR), significantly promoted neuron regeneration after BPR, and the possible mechanisms included alleviation of oxidative damage and inflammatory responses at the injury sites and antagonism of myelin inhibition [42]. Berberine treatment can upregulate the L1 expression and axonal remyelination [12], markedly alleviated the avulsion-induced neuroinflammation *via* down-

regulating microglial and astroglial response, while increasing the expression of the antioxidative enzyme superoxide dismutase (SOD), and activating the PI3K/Akt pathway [110]. Intrathecal infusion of paclitaxel, a diterpene alkaloid, represses the expression of neuronal nitric oxide synthase (nNOS) and maintains mitochondrial function in addition to improving MN survival in the ventral horn after spinal root avulsion injury [79]. EGb761, which is a Ginkgo biloba extract containing crucial bioactive constituents, displays neurotherapeutic effects against neuronal apoptotic death and oxidative stress [2,17,63,90,106]. Its therapeutic effects partly rely on inhibiting the expression of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production in a dose-dependent manner [7,51]. Epigallocatechin gallate (EGCG), an active polyphenol isolated from green tea, enhances survival and functional restoration of MNs after BPR by regulating FIG4 [83]. Trehalose protects MNs in rats by enhancing autophagy and inhibiting apoptosis [53]. Artemisinin (ART), a famous antimalarial medicine, can facilitate the survival of MNs and axonal remyelination to promote the motor function recovery *via* inhibiting oxidative stress [14]. The aforementioned findings indicate that the application of plant-derived compounds may be a new treatment approach to neuronal damage, and efforts must be made to optimize the utilization of active plants components.

Small molecular compounds

As the application of small molecular compounds has been associated with gene regulation, elucidating the central factors that affect the occurrence and pathophysiological events in BPR may be of value. Small molecular compound therapy is likely to be a promising way to improve the outcome of BPR. Combined injection of melatonin and chondroitin sulfate ABC (ChABC), boosted axonal regeneration *via* decreasing inflammation, oxidative damage and glial scar formation after BPR [41]. Minocycline, both intraperitoneally and intrathecally improved MN survival by decreasing microglial proliferation following avulsion of nerve roots [18]. Administration of epothilone B, a microtubule-stabilizing drug, facilitated motor functional recovery after spinal root avulsion causing peripheral nerve injury [55]. In delayed spinal cord-brachial plexus reconnection after C7 ventral root avulsion, injured MNs were res-

cued by riluzole treatment [38]. System delivery of the intracellular sigma peptide (ISP) enhanced the number of axons by targeting the neuronal proteoglycan receptor protein tyrosine phosphatase σ (PTP σ) in a ventral root avulsion rat model [54]. c-Jun inhibition together with Bcl-2 overexpression promoted regeneration and functional restoration of MNs, whereas valproic acid reduced MN death induced by BPA [89]. Erythropoietin (EPO) reduced the apoptosis of neurons led by BPA *via* inhibiting JNK phosphorylation, c-Jun expression and PARP cleavage [56]. Lithium treatment following spinal root avulsion and reimplantation accelerated motor axon regeneration and remyelination, ameliorated denervated muscle atrophy and promoted earlier motor functional recovery in rats [32,35]. Nrg1 β improved the functional recovery of elbow flexion, promoted the survival of MNs, enhanced the re-innervation of biceps brachii and decreased muscle atrophy, providing a promising therapeutic approach to root avulsion [13]. Local administration of riluzole may also rescue injured MNs *via* promoting neuroprotection and increasing nerve regeneration [31].

Non-coding RNAs

Non-coding RNAs (ncRNAs), such as miRNAs and long non-coding RNAs (lncRNAs), act as post-transcriptional regulators to decrease their downstream target protein expression. Differential expression of the specific ncRNAs at different time points is important after unilateral BPA. The alterations of associated mRNAs participate in inflammation and regulate the calcium-signalling pathway in the early phase of BPA and MN death [99]. Tang *et al.* demonstrated that root avulsion resulted in up-regulation of miR-137-3p, which target calcium-activated neutral protease-2 (calpain-2) and further reduced nNOS expression in spinal MNs, exhibiting a protective effect against MN death [81]. Ding *et al.* reported that knockdown of leucine-rich repeat and immunoglobulin-like domain-containing NgR-interacting protein 1 (LINGO-1) by short hairpin (sh)RNA could promote axonal outgrowth and myelination, rehabilitate motor nerve endings, accelerate muscle reinnervation, enhance angiogenesis and promote avulsed forelimb recovery [22]. It was suggested that the increased number of motor endplates and improved angiogenesis was owing to lentiviral vectors-mediated overexpression of hypoxia-inducible

factor 1 α (HIF-1 α) into reimplanted C6 roots after BPA [85]. Intrathecally applied short interfering (si) RNA to silence the expression of c-Jun manifested that this gene may be responsible for the survival of MNs after root avulsion injury [16]. In addition, targeting miRNAs to indirectly regulate genes involved in inflammation initiated by injury and downstream signalling pathways contributing to tMN death may be a new route to prevent MN degeneration [82]. The lncRNA JHDM1D-AS1 was shown to exert anti-inflammatory and neuroprotective effects *via* regulating the miR-101-3p/dual-specificity phosphatase 1 (DUSP1) axis in rats following BPA [61]. Consequently, targeting the differentially expressed lncRNAs and miRNAs induced by BPA injury may uncover novel diagnostic and therapeutic options.

Interventions for pain

Neurogenic pain is a common and refractory complication after BPA injury [94]. The C-C motif chemokine ligand 2 (CCL2)/C-C motif chemokine receptor 2 (CCR2) axis can enhance NMDA receptor signalling to aggravate neuropathic pain induced by BPA [93]. In addition to motor and sensory deficits, pain can be equally debilitating. The main characteristics of BPA pain are its rapid onset (an effect which occurs immediately after the trauma) and the development of long-lasting neuropathy, which may be observed at sites distant from the lesion [62,72]. The neuropathic pain may lead to mechanical allodynia and cold allodynia. Approximately 80% of patients with BPA are left with long-term neuropathic pain [1]. Spinal astrocytes and microglia were shown to be quickly activated after BPA injury in a neuropathic pain rat model, which may partly explain the mechanism as well as indicate potential treatment options [44]. The antinociceptive organic selenium compound, (R)-Se-phenyl thiazolidine-4-carboxylate (Se-PTC), displayed superior mechanical and thermal anti-hyperalgesic effects *via* adjusting cannabinoid receptors CB1 and CB2 in a mouse model of BPA-induced neuropathic pain [21]. Cerebral ^{18}F -FDG metabolism alterations were also observed in a neuropathic pain model following BPA [78]. Treatment of pain post-BPI has been attempted using high-frequency spinal cord stimulation [34]. Administration of trichostatin A (TSA), a histone deacetylase inhibitor, was also shown to alleviate neuropathic pain through reducing neuroinflamma-

tion, AKT phosphorylation and mTOR signalling in a rat BPA model [112]. Enhancer of zeste homolog 2 (EZH2) was shown to modulate neuroinflammation and neuropathic pain *via* a novel mTOR-mediated autophagy signalling pathway [68]. However, the majority of the traditional treatments have proven to be ineffective for neuropathic pain relief after BPA injury. Accumulating evidence indicates that miRNAs and proteins implicated in nerve development and pathophysiology also play a critical role in BPA-induced neuropathic pain, which may be a potential method for pain relief [87,112]. Meng *et al.* demonstrated that the lncRNA Malat1 ameliorated neuropathic pain by decreasing neuronal excitability *via* regulation of calcium flux in the spinal cord [67]. The polyphenol curcumin may also alleviate BPA-induced pain by suppressing the levels of proinflammatory cytokines and neuropathic-associated proteins, and deactivating astrocytes [96]. Electroacupuncture and naprapathy have also been used to attenuate neuropathic pain following BPRA [45,48,95].

Conclusions

BPRA treatment demands various well-planned reconstructive procedures, including physiotherapy, surgery and medications, in addition to management of the intractable neuropathic pain. More clinical experiments are required to evaluate the safety, efficacy and adverse consequences of cell transfer. Other alternative treatments targeting the identified ncRNAs and related signalling pathways may hold promise as therapeutic methods for partial recovery of limb function.

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Disclosure

The authors report no conflict of interest.

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