MECHANISMS OF NERVE REGENERATION FOR DRUG-RESISTANT EPILEPSY: SCOPING REVIEW PROTOCOL

García-González Renato[1] | Sandoval Hugo[2] | Mishra Rakesh[3] | Malvaso Antonio[4]
Alarcon-Ruiz Christoper A.[5] | Ríos Camilo[6] | Pérez-Neri Iván[6]

1. Faculty of Medicine, Benemérita Universidad Autónoma de Puebla, Mexico

2. General Directorate, Luis Guillermo Ibarra Ibarra National Institute of Rehabilitation, Mexico City, Mexico

3. Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University, Vanarasi, India

4. School of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy

5. Research Unit for the Generation and Synthesis of Health Evidence, Universidad San Ignacio de Loyola, Lima, Peru

6. Department of Neurochemistry, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery, Mexico City, Mexico

Correspondence

Iván Pérez-Neri. Department of Neurochemistry, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery, Insurgentes Sur 3877, La Fama, 14269, Tlalpan, Mexico City, Mexico.

✉ ipneri03@gmail.com

Abstract

Drug-resistant epilepsy, affecting 30 to 40 percent of epilepsy patients, is described by the International League Against Epilepsy as "the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules". This condition affects patients' quality of life and increases their mortality risk. Individuals with drug-resistant epilepsy may remain unable to achieve seizure independence until progressive degeneration is halted, and the regulatory function of interneurons is restored. Recent studies have developed techniques for modulating signaling pathways related to neural regeneration in the central nervous system, encompassing the regrowth or repair of nervous tissues, cells, or cell products. This scoping review protocol aims to evaluate the therapeutic potential of interventions that modulate nerve regeneration pathways for patients with drug-resistant epilepsy. Published studies (all publication types) will be retrieved from Web of Science, PubMed, Scopus, EBSCOhost, Ovid, and Google Scholar, spanning from database inception to the present. Studies describing patients or experimental models of drug-resistant epilepsy receiving treatments that modulate nerve regeneration pathways will be included. Studies in languages other than Spanish or English that cannot be appropriately translated or whose full-text files cannot be retrieved despite exhaustive efforts will be excluded. Eligibility assessment will be performed independently by two researchers, and results will be presented in tables. A narrative synthesis of the findings will be provided.

Keywords: *epilepsy, neurotrophic factor, remyelination, axonal growth, regeneration*

Introduction

According to the International League Against Epilepsy (ILAE), epilepsy is a "disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. [...] defined by any of the following conditions: at least two unprovoked (or reflex) seizures occurring >24 h apart; one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; and/or diagnosis of an epilepsy syndrome".[1]

Drug-resistant epilepsy is defined as "the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom for 12 months, or 3 times the interseizure interval before treatment started".[2] It has been estimated that 30-40% of patients with epilepsy present this condition, which is accompanied by economical and psychological constraints, leading to a decrease in their quality-of-life and an increasing risk of mortality.[3]

One of the theories proposed to elucidate the causes and pathogenesis of drug-resistant epilepsy (DRE) is the neural network hypothesis, which suggests that a combination of genetic factors and microenvironmental influences can induce neuronal degeneration, necrosis, gliosis, axonal sprouting, synaptic reorganization, and remodeling of neural network. These alterations can lead to the suppression of the brain's seizure control mechanisms and hinder drug access to its targets.[4,5] Considering drug-resistant epilepsy as a neurodegenerative process provides a complementary

perspective, emphasizing that the dysfunction of connectivity between inhibitory interneurons and excitatory pyramidal neurons could sustain an excitatory state, leading to seizure generation.[6]

Current literature suggests therapeutic alternatives for drug-resistant epilepsy, with surgery and neurostimulation among them. Surgical interventions require the localization of an epileptogenic zone where neurons have abnormally sprouted, and may lead to multiple or diffuse lesions visible on magnetic resonance imaging (MRI) and multifocal spikes on electroencephalograms (EEGs).[7] Despite these complexities, epilepsy surgery is currently the most effective approach to achieve seizure freedom.[8]

Neurostimulation, in turn, is invasive and requires re-interventions within 5-10 years to replace device batteries. It could also cause complications (including bleeding, infection, mechanical complexities, and neuropsychiatric changes) that compromise the patients' quality-of-life.[9] However, its effect may be long-lasting and may also yield seizure freedom.[10]

Unless neurodegenerative progression is prevented, and the regulatory function of interneurons is restored, patients with drug-resistant epilepsy may not reach seizure freedom. To address this, ongoing research has developed techniques to manipulate signaling pathways for neural regeneration within the central nervous system (CNS). Neural regeneration is defined as the "regrowth or repair of nervous tissues, cells or cell products", and it involves mechanisms like the "generation of new tissues, neurons, glia, axons, myelin or synapses", that "may comprise endogenous neuroprotection leading to neuroplasticity and neurorestoration".[11] This differs from that of the peripheral nervous system (PNS) due to the neuron's limitations to accomplish the requirements of calcium influx (which is thought to play a central role in membrane resealing and local rearrangements of the cytoskeleton), mitochondrial transport (needed to satisfy energy supply) and stable microtubules for the establishment of a new growth cone and elongation. However, manipulating these signaling pathways could override this disadvantage as described below for some of them:[12]

- RhoA: This pathway governs actin dynamics and microtubule polymerization, but despite its importance, no genetic mammalian model has been described, hindering therapeutic targeting.

- PTEN: genetic knockout of PTEN, a well-studied tumor suppressor, can promote axon regeneration by increasing mTOR expression. Some studies have reported positive results in terms of reducing seizures and normalizing hippocampal neural hypertrophy with this approach. However, the mortality rate with this procedure is high.[13]

- GSK3: Neurons lacking this component, which is involved in PI3K signaling, exhibit increased microtubule dynamics, leading to extensive axon growth. Targeting the β isoform can restore aberrant plasticity within neural circuits and modulate inhibitory/excitatory balance, including GABAergic regulation.[14] This is achieved through pharmacological phosphorylation using drugs like Tideglusib, but its impact on epilepsy remains speculative.[15]

- JAK/STAT: This pathway is involved in transcription signals that promote the sprouting of neural connections. A study manipulating long non-coding RNA H19 was performed with an adeno-associated viral vector delivery system, demonstrating that it enhances glial cell activation and astrocytes proliferation, which could rise CNS regeneration to the level seen in the PNS. Unfortunately, this signaling pathway is also involved in inflammatory processes.[16]

- DLK: It operates as a sensor of neural cytoskeletal damage, mediating a pathway crucial for the early phase of neural regeneration. Nevertheless, activation of this kinase also has been linked to neural degeneration and death in models of neurodegenerative diseases.[17]

Study rationale

This scoping review on the mechanisms of nerve regeneration for drug-resistant epilepsy aligns with the framework proposed by Arskey and O'Malley:[18]

- To examine the extent of the advances that have been made in neural regeneration for developing the available therapeutic proposals in the epilepsy field.

- To summarize which of the findings on modulating nerve regeneration pathways could be more effective, relevant, and appropriate for clinical implementation.

- To identify research gaps that should be considered in future investigations which aim to bridge the knowledge gap between basic research and clinical application.

Together, these objectives provide a new perspective on investigating nerve regeneration in epilepsy, with a focus on identifying well-defined therapeutic anatomical targets. This discussion paves the way for future research to evaluate the efficacy of this approaches in the CNS.

Methods

Protocol development

This methodology is based on a previous protocol,[19] but it does not serve as an update to any previous review. Following the elaboration of the research questions, an online tool was used to determine the appropriate type of review article, as previously reported,[20] resulting in a scoping review (https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=6720&code=Ns4f0BUi6r).

We conducted searches in the International Prospective Register of Systematic Reviews (PROSPERO), the JBI Database of Systematic Reviews, and the Open Science Framework to identify ongoing protocols for systematic or scoping reviews related to our primary research questions. However, no relevant records were found (July 1-9th, 2021; updated on March 15th, 2022).

This scoping review protocol adheres the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020[21]) guidelines, complemented with the PRISMA extensions for abstracts (PRISMA-A[22]), protocols (PRISMA-P[23]), scoping reviews (PRISMA-Scr[24]), and the JBI Manual for Evidence Synthesis.[25] Those guidelines were applied to the best extent possible for a scoping review protocol.

This protocol was collaboratively developed by the research team and revised as needed. Supporting materials (checklists and forms), have been made publicly available through the Open Science Framework (https://osf.io/ad67r/?view_only=ad1f76e460724570882be20218c15e64) as previously reported[26] (registration date: February 15th, 2022). The research team is composed of clinical, preclinical, and sociomedical researchers.

Objectives

The primary objective of this review is to evaluate the therapeutic potential of modulating nerve regeneration pathways for patients with drug-resistant epilepsy. Secondary objectives include the following:

- To evaluate which neural regeneration pathway modulation, when compared to analogous pathways, exhibits the most significant therapeutic potential for drug-resistant epilepsy patients.
- To evaluate if the modulation of neural regeneration pathways has a viable application in drug-resistant epilepsy patients.
- To describe potential side-effects associated with the modulation of neural regeneration pathways in drug-resistant epilepsy patients.
- To evaluate which mechanisms of action, within the scope of neural regeneration pathways modulation, may benefit drug-resistant epilepsy patients.
- To estimate the impact of manipulating neural regeneration pathways on quality-of-life measures in drug-resistant epilepsy patients.

Research questions[27–30] for this review are detailed in Table 1.

Table 1. Research questions for this systematic scoping review

Question type	Framework	Description
Main research question	**PICo** framework (Population, Intervention or Phenomena of Interest, Context)	In patients with drug-resistant epilepsy (**P**), what is the therapeutic potential of modulating neural regeneration pathways (**I**) according to published studies (**Co**)?
Secondary research question 1	**PICO** framework (Patient/Population, Intervention, Comparison, Outcome)	In patients with drug-resistant epilepsy (**P**), which modulation of neural regeneration pathway (**I**) — compared to other analogous ones— (**C**) shows the most significant therapeutic potential (**O**)?
Secondary research question 2	**MIP** framework (Methodology, Issues, Participants)	Does the modulation of neural regeneration pathways (**M**) have a viable application (**I**) in patients with drug-resistant epilepsy (**P**)?
Secondary research question 3	**CoCoPop** framework (Condition, Context, Population)	What are the possible side-effects (**Co**) of modulating neural regeneration pathways (**Co**) in patients with drug-resistant epilepsy (**Pop**)?
Secondary research question 4	**CIMO** framework (Context, Intervention, Mechanisms, Outcomes)	According to published studies (**C**) regarding the modulation of neural regeneration pathways (**I**), what mechanisms of action (**M**) may benefit patients with drug-resistant epilepsy (**O**)?
Secondary research question 5	**PIE** framework (Patient, Intervention, Evaluation)	In patients with drug-resistant epilepsy (**P**), could the manipulation of neural regeneration pathways (**I**) alter their quality-of-life measures (**E**)?

Search strategy and screening

The search strategy for this protocol adheres to the PRISMA extension for searching (PRISMA-S[31]). It was peer-reviewed following the *PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement*.[32] Published studies (all publication types) will be retrieved from Web of Science (Clarivate), PubMed, Scopus, EBSCOhost (Academic Search Ultimate), Ovid, and Google Scholar, from database inception to the present. In addition, the first 100 results from Google Scholar,[26] sorted by relevance and without citations, will be obtained using Publish or Perish.[33] Gray literature will be consulted through the Conference Proceedings Citation Index- Science (Web of Science) and OpenDissertations (EBSCO). The author's collections will also be considered. Researchers will be contacted if necessary, no additional sources will be considered.

All the included databases, their providers, and dates of coverage (if available) are listed in Appendix A (registered at https://osf.io/ad67r/?view_only=ad1f76e460724570882be20218c15e64). Default EBSCOhost configuration (Limiters - Hidden NetLibrary Holdings; Expanders - Apply equivalent subjects; Search modes - Boolean/Phrase) will be used, and no other filters or limits will be applied. Search algorithms were developed using an online tool and are publicly available (https://app.2dsearch.com/new-query/6127cc615508d60004ba6a40). Their line-by-line evaluation is described in Appendix B (available at https://osf.io/ad67r/?view_only=ad1f76e460724570882be20218c15e64). Articles in languages other than English and Spanish will be included if adequately translated using Google Translate,[34] DeepL,[35] or if English or Spanish translations are available.[36]

Retrieved references will undergo deduplication using Zotero, Endnote, and Rayyan.[37] Any identified duplicates will be manually reviewed to confirm their status and will be removed.[37] All references will be assessed for eligibility by two independent researchers using Sysrev,[38] according to predefined criteria. A third researcher will solve possible discrepancies. Agreement between the reviewers will be assessed using Sysrev's concordance tool.[38] Two screening stages — Title/Abstract, and Full-text — will be performed. The screening process will be pilot-tested using a random sample of 25-50 studies.[25,39]

References selected for inclusion will be retrieved using the Retraction Watch database (https://retractiondatabase.org/) to identify and exclude retracted studies. The search strategy will be rerun after twelve months and/or before completing the final analysis to identify recent studies for possible inclusion in future updates of this review.

Results from the search strategy will be outlined in a PRISMA flow diagram using an online template.[40]

Eligibility criteria

Inclusion criteria
- Studies describing patients with drug-resistant epilepsy receiving any treatment aimed at modulating nerve regeneration pathways — regardless of their age, race, sex/gender, current treatment, or any other PROGRESS-Plus equity characteristics[41] —reporting an outcome on disease course, severity, adverse effects or financial cost, compared to either placebo, an inactive treatment or standard treatment.
- No specific diagnostic criteria for drug-resistant epilepsy will be considered if the studies describe their population as presenting the condition, as previously reported.[42] The analysis will not be limited to any specific clinical setting. All quantitative, qualitative, or mixed-method studies will be considered.
- Any experimental model of epilepsy reporting and effect of any treatment for modulating nerve regeneration pathways.
- No restrictions regarding follow-up time, year of publication, language, or publication status will be considered.

Exclusion criteria
- Studies in languages other than Spanish or English that cannot be appropriately translated using two software tools.
- Studies for which full-text files cannot be retrieved despite all efforts made.

Eligibility criteria may be modified during the screening process, as has been done in previous studies.[26] A minimum of 75% agreement among team members reviewing the studies will be required to introduce changes to these criteria.[25] Any adjustments will be applied to all studies and reported accordingly.

Data charting

Clinical and preclinical studies will be analyzed separately, although they may be discussed together. Studies will be analyzed based on the type of experimental model used (cell cultures, rodents, or non-human primates). Data summaries will be presented using graphs, figures, and tables. The narrative synthesis will include all studies. The primary outcomes of interest will be treatment refractoriness, seizure frequency, and epileptogenic activity.

The following variables will be extracted: epileptogenic foci/brain region/neuronal circuit, seizure type, invasiveness of

the intervention, time to outcome after treatment, side effects, interactions with conventional treatments, modulation of cell neurophysiological properties, and epilepsy type. Two independent researchers will conduct the data extraction using Sysrev,[38] with any discrepancies resolved by a third researcher. Unclear information will be discarded. This process will be pilot-tested using a random sample of 25-50 studies.[25,39]

Data synthesis

All studies selected for inclusion will be considered for narrative synthesis. Only studies reporting original results will be charted. Units of measurement will be presented as originally reported, with no conversions applied. No imputation method for missing data or statistical synthesis will be applied.

Strengths and limitations of the present protocol

This scoping review provides an integrative perspective of the therapeutic potential and possible side-effects of neural regeneration pathways for drug-resistant epilepsy based on both clinical and preclinical studies. Our search strategy is comprehensive and was peer-reviewed. We will attempt to include articles written in any language to reduce bias. Our multidisciplinary research group provides complementary perspectives. However, only a narrative analysis of the evidence will be provided. No risk-of-bias analysis or certainty of evidence assessment will be considered.

Authors' contributions

R.G.G. provided topic expertise, contributed to the original idea, concept and study design, drafted the manuscript, and reviewed, corrected and approved the methodology and final draft of the protocol. H.S. provided methodological expertise, contributed to the design of the protocol's methodology (including the search strategy and peer-review), corrected, and approved the final draft. R.M. and A.M. contributed topic expertise, participated in designing the protocol's methodology (including search strategy), corrected, and approved the final draft. C.A.A.R. contributed methodological expertise, corrected and approved the final draft. C.R. provided topic expertise, supervised the reviewer team, reviewed, and approved the protocol's methodology and final draft. I.P.N. provided methodological expertise, contributed to designing the protocol's methodology (including the search strategy), coordinated co-author's participation and activities, corrected, and approved the final draft. He will ensure documentation and implementation of possible future protocol amendments, and serves as the guarantor of the review.

Conflicts of interest

There was no conflict of interest in the preparation of this manuscript.

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