Mechanisms of nerve regeneration for drug-resistant epilepsy: scoping review protocol

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Authors' contributions

R.G.G. provided topic expertise, and contributed with the original idea, concept and design of the study, drafted the manuscript, revised, corrected and approved protocol’s methodology and final draft. H.S. provided methodological expertise and contributed in designing protocol’s methodology (including search strategy peer-review), corrected and approved the final draft. R.M., and A.M. contributed with topic expertise, designing protocol’s methodology (including search strategy), corrected and approved the final draft. C.A.A.R., and M.C.L. contributed with methodological expertise, corrected and approved the final draft. C.R.
provided topic expertise and contributed supervising the reviewer team, revised and approved protocol’s methodology and final draft. I.P.N. provided methodological expertise and contributed in designing protocol’s methodology (including the search strategy), coordinating co-author’s participation and activities, corrected and approved the final draft, will assure documenting and implementing of possible future protocol amendments, and is the guarantor of the review.

Conflicts of interest

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

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Abstract

Drug-resistant epilepsy, which affects 30 to 40 percent of epilepsy patients, is described as “the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules”. This condition lowers patients’ quality of life and raises their mortality risk. Patients with drug-resistant epilepsy might not be able to achieve seizure independence until progressive degeneration is stopped and the regulating function of interneurons is restored. Ongoing studies have developed techniques to maneuver signaling pathways for neural regeneration in the central nervous system, this is defined as “the regrowth or repair of nervous tissues, cells or cell products”. This scoping review protocol aims to evaluate the therapeutic potential of modulating 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, from database inception to present. Studies describing patients or experimental models of drug-resistant epilepsy receiving any treatment modulating nerve regeneration pathways will be included. Studies in languages different than Spanish or English that could not be appropriately translated or whose full-text files could not be retrieved after all efforts made will be excluded. Studies will be assessed for eligibility by two independent researchers. Results will be presented in tables. A narrative synthesis 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 the patients with epilepsy present this condition and besides have economical and psychological constraints, decreasing their quality-of-life and increasing the risk of mortality 3.

One of the theories that try to explain the causes and pathogenesis of DRE is the neural network hypothesis, which suggests that the influence of genes and microenvironment can induce neuronal degeneration and necrosis, gliosis, axonal sprouting, synaptic reorganization, and remodeling of neural network that leads to suppression of the brain’s seizure control and restriction to the drug access to targets 4, 5. Thus, a perspective regarding drug-resistant
epilepsy as a neurodegenerative process may be considered complementary, since the
dysfunction of connectivity among (inhibitory) interneurons and (excitatory) pyramidal
neurons, might maintain an excitatory state leading to seizure generation.\(^6\)

Current literature suggests therapeutic alternatives for drug-resistant epilepsy, such as
surgery or neurostimulation; surgical interventions require the localization of an epileptogenic
zone where neurons have been sprouting abnormally and may lead to multiple or diffuse
lesions seen on magnetic resonance imaging (MRI) as well as multifocal spikes seen on an
electroencephalogram (EEG)\(^7\). Despite these issues, epilepsy surgery is currently the most
effective strategy to achieve seizure freedom\(^8\).

Neurostimulation, in turn, is as invasive as surgery and needs re-interventions within a
range of 5-10 years to replace devices’ batteries and could 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 role of
interneurons is restored, patients with drug-resistant epilepsy may not reach seizure freedom.
For this purpose, ongoing studies have developed techniques to maneuver signaling pathways
for neural regeneration in the central nervous system (CNS), which is defined as “the regrowth
or repair of nervous tissues, cells or cell products”, involving mechanisms such as “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:

- **RhoA**: This pathway oversees bringing actin dynamics and microtubule polymerization and, despite its importance, no genetic mammalian model has been described, precluding therapeutic targeting.

- **PTEN**: when it is inhibited by genetic knock out, this well-studied tumor suppressor can promote axon regeneration by increasing mTOR expression. Indeed, studies have assessed with positive results its capacity to reduce seizures and normalize hippocampal neural hypertrophy; still, the mortality rate with this procedure is high.

- **GSK3**: Neurons lacking this component (involved in PI3K signaling) have increased microtubule dynamics leading to extensive axon growth. Targeting the β isoform can restore aberrant plasticity within neural circuits and have modulating implications that regulate inhibitory/excitatory balance, which includes GABAergic regulation. This is achieved by pharmacological phosphorylation with drugs like Tideglusib, but its impact on epilepsy has just been hypothesized.

- **JAK/STAT**: It 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 in the PNS.
Unfortunately, this signaling pathway is involved in inflammatory processes too\textsuperscript{16}.

- DLK: It operates as a sensor of neural cytoskeletal damage mediating a pathway that is crucial for the early phase of neural regeneration. Nevertheless, activation of this kinase also leads to neural degeneration and death in models of neurodegenerative diseases\textsuperscript{17}.

**The rationale for this study**

Thus, a scoping review of the mechanisms of nerve regeneration for drug-resistant epilepsy is consistent with Arskey and O’Malley\textsuperscript{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.

All these reasons together guide a new point of view for the investigation of nerve regeneration in epilepsy, in which well-defined therapeutic anatomical targets can be identified. This discussion would allow future dissertations around this subject evaluating its efficacy in the CNS.
Methods

Protocol development

This methodology is based on a previous protocol 19, but this study is not an update of any previous review. After elaborating the research questions, we used an online tool to define the appropriate type of review article as previously reported 20 resulting in scoping review (https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=6720&code=Ns4f0 BUi6r).

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

The protocol for this scoping review is compliant with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020 21), 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 as possible for a scoping review protocol.

Our protocol was drafted by the research team and revised as necessary. Supporting materials (checklists and forms) are made publicly available through the Open Science Framework (https://osf.io/ad67r/?view_only=ad1f76e460724570882be20218c15e64) as previously reported 26 (registration date Feb. 15th, 2022). Our research team is composed of clinical, preclinical, and socio-medical 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 are the following:

- To evaluate which modulation neural regeneration pathway — compared to other analogous ones — shows the most significant therapeutic potential for patients with drug-resistant epilepsy.
- To evaluate if modulation of neural regeneration pathways has a viable application in patients with drug-resistant epilepsy.
- To describe the possible side-effects of modulating neural regeneration pathways in patients with drug-resistant epilepsy.
- To evaluate which mechanisms of action, among the modulation of neural regeneration pathways, may benefit patients with drug-resistant epilepsy.
- To estimate if manipulating neural regeneration pathways could alter quality-of-life measures in patients with drug-resistant epilepsy.

Research questions \(^{27-30}\) for this review are described in Table 1.

Search strategy and screening

We report the search strategy for this protocol according to the PRISMA extension for searching (PRISMA-S \(^{31}\)). It was peer-reviewed using the PRESS Peer Review of Electronic Search...
**Strategies: 2015 Guideline Statement**. 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 present. In addition, the first 100 results from Google Scholar, sorted by relevance and without citations, will be retrieved using **Publish or Perish**. Gray literature will be consulted through the Encyclopedia of Science Citation Index- Science (Web of Science) and OpenDissertations (EBSCO).

The author’s collections will also be consulted. Researchers will be contacted if necessary, no additional sources will be considered. All 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, no other filters or limits will be applied. Search algorithms were elaborated 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 written in languages different than English and Spanish will be included if adequately translated using Google Translate, DeepL, or if English or Spanish translations be found.

Retrieved references will be de-duplicated using Zotero, Endnote, and Rayyan. Identified duplicates will be manually revised to confirm duplicated publications and will be eliminated. All references will be assessed for eligibility by two independent researchers using Sysrev, according to predefined criteria. A third researcher will solve possible
discrepancies. Agreement between 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 eliminate 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 described in a PRISMA flow diagram using an online template 40.

Eligibility criteria

Inclusion criteria

• Studies describing patients with drug-resistant epilepsy receiving any treatment
  modulating nerve regeneration pathways — independently 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 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 dissemination, language, or publication status will be considered.

Exclusion criteria

- Studies in languages different than Spanish or English that could not be appropriately translated using two software tools.
- Studies whose full-text files could not be retrieved after all efforts made.

Eligibility criteria may be adjusted during the screening process, as previously reported studies. At least 75% agreement among reviewer team members will be required to introduce changes in those criteria. Adjustments will be applied to all studies and reported accordingly.

Data charting

Either clinical or preclinical studies will be analyzed separately but might be discussed together. Studies will be analyzed by type of experimental model (cell cultures, rodents, or non-human primates). Data summaries will be presented in graphs, figures, and tables. The
narrative synthesis will include all studies. Primary outcomes will be treatment refractoriness, seizure frequency, and epileptogenic activity.

Variables to extract will be 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. Data will be extracted by two independent researchers using Sysrev. A third researcher will solve discrepancies. Unclear information will be discarded. This process will be pilot-tested using a random sample of 25-50 studies.

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, no conversions will be applied. No imputation method for missing data nor 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 try to include articles written in any language to reduce bias. Our multidisciplinary research group provides complementary perspectives. Only a narrative analysis of the evidence
will be provided. No risk-of-bias analysis or certainty of evidence assessment will be considered.

Legends

Table 1. Research questions for this systematic scoping review

Table 2. Databases to be consulted, their providers and dates of coverage

Table 1

<table>
<thead>
<tr>
<th>Question type</th>
<th>Framework</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Main research question</td>
<td><strong>P</strong>ICO framework (<strong>P</strong>opulation, <strong>I</strong>ntervention or <strong>P</strong>henomena of <strong>I</strong>nterest, <strong>C</strong>ontext)</td>
<td>In patients with drug-resistant epilepsy (<strong>P</strong>), what could be the therapeutic potential of modulating neural regeneration pathways (<strong>I</strong>) according to published studies (<strong>Co</strong>)?</td>
</tr>
<tr>
<td>Secondary research question 1</td>
<td><strong>P</strong>ICO framework (<strong>P</strong>atient/<strong>Population</strong>, <strong>I</strong>ntervention, <strong>C</strong>omparison, <strong>O</strong>utcome)</td>
<td>In patients with drug-resistant epilepsy (<strong>P</strong>), which modulation of neural regeneration pathway (<strong>I</strong>) — compared to other analogous ones — (<strong>C</strong>) shows the most significant therapeutic potential (<strong>O</strong>)?</td>
</tr>
<tr>
<td>Secondary research question 2</td>
<td><strong>MIP framework</strong> <em>(Methodology, Issues, Participants)</em></td>
<td>Does modulation of neural regeneration pathways <em>(M)</em> have a viable application <em>(I)</em> in patients with drug-resistant epilepsy <em>(P)</em>?</td>
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<tr>
<td>Secondary research question 3</td>
<td><strong>CoCoPop framework</strong> <em>(Condition, Context, Population)</em></td>
<td>What are the possible side-effects <em>(Co)</em> of modulating neural regeneration pathways <em>(Co)</em> in patients with drug-resistant epilepsy <em>(Pop)</em>?</td>
</tr>
<tr>
<td>Secondary research question 4</td>
<td><strong>CIMO framework</strong> <em>(Context, Intervention, Mechanisms, Outcomes)</em></td>
<td>According to published studies <em>(C)</em> regarding the modulation of neural regeneration pathways <em>(I)</em>, which mechanisms of action <em>(M)</em> may benefit patients with drug-resistant epilepsy <em>(O)</em>?</td>
</tr>
<tr>
<td>Secondary research question 5</td>
<td><strong>PIE framework</strong> <em>(Patient, Intervention, Evaluation)</em></td>
<td>In patients with drug-resistant epilepsy <em>(P)</em>, could manipulating neural regeneration pathways <em>(I)</em> alter their quality-of-life measures <em>(E)</em>?</td>
</tr>
</tbody>
</table>
References


33. editors. Improving efficiency and confidence in systematic literature searching. European Association for Health Information and Libraries (EAHIL).


