ROLE OF MANGANESE IN THE PATHOPHYSIOLOGY OF HEPATIC ENCEPHALOPATHY: SCOPING REVIEW PROTOCOL

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Abstract

Introduction: Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver disease and/or portosystemic blood shunting, characterized by alterations in alertness, personality, cognition, and motor functions. Its severity can be classified into four grades from mild to coma. This disease may affect several brain regions, including the cingulate gyrus, insular cortex, and globus pallidus. The pathophysiology of HE is thought to be multifactorial, involving manganese accumulation in the brain, the damaging effect of ammonia on glial cells, etc. Previous studies describe the pathophysiology of HE or the effect of manganese on the central nervous system. However, there is no review addressing both topics from an integrative perspective through a systematic methodology. This scoping review aims to evaluate the role of manganese in HE. **Methods**: Published studies (all publication types) will be retrieved from Web of Science, Medline, Scopus, EBSCOhost, Ovid, and Google Scholar. Inclusion criteria: studies reporting manganese levels in any biological sample sample of patients with HE, any experimental model reporting the effect of manganese administration on neuroprotection in models of liver damage, or showing an effect on manganese levels in the liver and/or the brain. Exclusion criteria: studies reporting subjects exposed occupationally or environmentally to manganese, or written in languages different than Spanish or English that could not be appropriately translated, or whose full-text files could not be retrieved. Either clinical or preclinical studies will be analyzed separately but might be discussed together. Data summaries will be presented in graphs, figures, and tables. A narrative synthesis will be presented. This protocol complies with PRISMA-P.

Keywords: *manganese, ammonia, oxidative stress, neurotransmitter, neuronal death*

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver disease and/or portosystemic blood shunting, characterized by transient or persistent alterations of alertness, personality, cognition, and motor functions,[1] that mainly occurs in alcoholic cirrhosis.[1] HE can be triggered by several stress factors such as gastrointestinal bleeding, hypokalemia, infections, dehydration, constipation, hypotension, oral protein load, deteriorating liver function, anesthesia, and surgery.[2] It may also occur in non-human species.[3]

HE is classified into three main types: type A, due to acute liver failure; type B, resulting from portosystemic bypass or shunting, and type C, associated with cirrhosis.[2] Furthermore, its severity is categorized into four grades (I, II, III, and IV) from mild symptoms to coma.[2] This disease can affect several brain regions, including the cingulate gyrus, insular cortex, and globus pallidus.[4] Minimal HE (MHE) is a mild form of the disease which shows no cognitive or motor alterations but affects patients' quality of life.[1] This latter presentation occurs in 70% of cirrhotic patients.[2]

Repeated HE episodes might lead to acquired hepatocerebral degeneration, causing neuronal loss and astrocytosis in several brain regions such as the basal ganglia, cerebral cortex, and cerebellum.[1,4] The pathophysiology of HE is thought to be multifactorial. The proposed pathogenic mechanisms include manganese (Mn) accumulation in the brain, ammonia toxicity, gut dysbiosis, etc.[4,5] Injury to the basal ganglia can lead to extrapyramidal symptoms similar to those observed in Parkinson's disease.[1,2] This is different from cirrhosis-related parkinsonism, which is unresponsive to HE treatment and is also associated with brain Mn accumulation.[4]

HE pathophysiology mostly involves ammonia-mediated mechanisms.[1] This occurs since the liver is the primary organ responsible for ammonia metabolism through the urea cycle and glutamine synthesis.[1] In HE, ammonia is accumulated in the brain — even in mild cases[1] — and damages glial cells (astrocytes and microglia) to a greater extent than neurons, leading to neuroinflammation.[1] Hyperammonemia may cause brain edema, especially in type A HE.[2] This leads to astrocyte swelling, blood-brain barrier disruption, and increased intracranial pressure,[2] which may lead to brain herniation and death.[2] HE patients can be candidates for liver transplantation, following which HE significantly improves, even though some patients show signs of persistent cognitive impairment.[2] However, this intervention is limited by organ availability.

Alzheimer's type II astrocytosis is a common neuropathological feature of this disorder. These changes may differ histologically across brain regions: spherical forms of astrocytes are observed in the cerebral cortex, while an irregular shape is present in the basal ganglia.[1] Nonetheless, this type of astrocytosis is associated with several hyperammonemic syndromes, but not limited to liver damage.[1]

In the central nervous system, astrocytes contribute to ammonia clearance through glutamine synthesis.[3] Astrocyte dysfunction results in an increased glutamine level and a decreased glutamate availability.[3] In turn, glutamine is released from astrocytes and taken up by neurons, which convert it back to glutamate through glutaminase activity.[3] High extracellular glutamine concentrations inhibit further release of this amino acid, leading to its intracellular accumulation and swelling.[3] In addition, ammonia can impair chloride channel function, increasing cell excitability[1] and stimulating glutamine synthesis, enhancing brain edema.[2] Moreover, ammonia may alter the Krebs cycle,[1] affecting energy metabolism.

Affected neurotransmitter systems and modulators in HE include GABA, serotonin, histamine, dopamine, and neurosteroids,[1] also, the glutamate-nitric oxide (NO) pathway may be altered[2] due to glutamine-mediated regulation of NO synthesis.[6] This can also cause oxidative stress.[2]

Despite the role of ammonia in HE pathophysiology, its serum levels do not correlate with HE severity,[2] and normal blood concentrations do not exclude HE diagnosis.[3] This suggests the involvement of additional mechanisms, like neuroinflammation and Mn accumulation.[3] Liver damage may disturb the clearance of all substances using this route for their primary excretion, including Mn.[1] Thus, serum Mn levels are increased up to 7-fold in patients with cirrhosis; within the brain, Mn accumulates mainly in the globus pallidus.[1] Astrocytes are the main cell type accumulating Mn, and they may reach a 50-fold higher intracellular concentration compared to surrounding cells.[3] This causes Alzheimer's type II astrocytosis,[3] as ammonia does. Also, Mn may stimulate an inflammatory response and oxidative stress mediated by microglia.[3]

Mn is an essential trace element that serves as a cofactor for several enzymes such as arginase, glutamine synthetase, and Mn superoxide dismutase.[7] It is a micronutrient usually present in parenteral nutrition admixtures.[7] Accordingly, it is considered that large intravenous Mn doses during parenteral nutrition may cause oxidative stress, liver damage, and neurologic and psychiatric symptoms[7] — some authors

consider that Mn can generate oxidative stress under those conditions.[7] Mn can also alter glutamine uptake by astrocytes, impairing the glutamine/glutamate cycle.[7]

It has been suggested that lowering ammonia levels might be beneficial for HE patients.[1] Additionally, benzodiazepine receptor antagonists, histamine antagonists, or dopaminergic agonists have shown limited efficacy in clinical trials.[1] Non-pharmacological interventions include artificial liver support systems and liver transplantation,[1] but they are not available for every patient, especially in veterinary medicine;[3] extrapyramidal symptoms may not be reverted by transplantation.[1] For these reasons, modulating Mn levels or its downstream mechanisms might benefit HE patients. However, reducing oral intake is not an efficient strategy for this purpose,[7] so additional therapeutic strategies await development.

Rationale for the study
Previous narrative reviews describe the pathophysiology of HE or the effect of Mn in the central nervous system[8] but, to the best of our knowledge, there is no evidence synthesis addressing both topics from an integrative perspective, and using a systematic methodology.

For those reasons, performing a scoping review may be the next step required to elucidate the actual role of Mn in HE, the mechanisms underlying this relationship, and the therapeutic alternatives that could arise from its analysis.

Methods

Protocol development
This methodology is based on a previous protocol.[9] After elaborating on preliminary research questions, we used an online tool to define the appropriate type of review article for our study, as previously reported;[10] the result was: scoping review (https://whatreviewsisrightforyou.knowledgetranslation.net/map/results?id=6448&code=hna8lHck7j).

The International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/), JBI Clinical On-line Network of Evidence for Care and Therapeutics (JBI COnNECT+, https://connect.jbiconnectplus.org/), and the Open Science Framework (https://osf.io/), were consulted to identify ongoing protocols for systematic or scoping reviews related to our research questions, but no relevant records were found (July 28th, 2021; updated in March 14th, 2022).

Our protocol was drafted by the research team and

revised as necessary. Supporting materials (checklists and forms) are publicly available through the Open Science Framework (https://osf.io/p7gdm/?view_only=123a09c13cd44ad3a6587e922f44c36e) as previously reported[11] (registration date Oct. 9th, 2021; last update Feb. 11th, 2022). Our research team comprises researchers with different stakeholder profiles: preclinical, clinical, and socio-medical, recruited with the aid of Cochrane TaskExchange (https://taskexchange.cochrane.org/).

This protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA 2020[12]), complemented with the PRISMA extensions for abstracts (PRISMA-A[13]), protocols (PRISMA-P[14]), scoping reviews (PRISMA-Scr[15]), and the JBI Manual for Evidence Synthesis.[16] Those guidelines were applied as much as suitable for a scoping review protocol. PRISMA 2020 and PRISMA-A checklists were elaborated using online templates (https://prisma.shinyapps.io/checklist/).

Objectives
The primary objective of this scoping review is to evaluate the pathophysiological role of Mn accumulation in HE. Secondary objectives are:
- To evaluate the role of Mn accumulation in modulating oxidative stress.
- To evaluate the possible interaction between Mn accumulation and brain ammonia metabolism.
- To evaluate the effect of Mn accumulation on neurotransmitter systems relevant to HE.
- To evaluate the possible effect of sex on Mn-induced neurotoxicity.
- To evaluate the therapeutic potential of modulating Mn levels for HE.

Research questions for this review are described in Table 1.[16–18]

Search strategy
This search strategy is reported according to PRISMA-S.[19] It was elaborated by a trained researcher, and it has been peer-reviewed using the PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement.[20] Published studies (all publication types) will be retrieved from Web of Science (Clarivate), Medline (PubMed), Scopus, EBSCOhost (Academic Search Ultimate), and Ovid, from database inception to the present. Also, the first 100 results from Google Scholar (https://scholar.google.com/), sorted by relevance and without citations, will be retrieved[11] using the software program Publish or Perish.[21] The author's collections will also be considered.

Table 1. Research questions for this systematic scoping review

Question type	Framework	Description
Primary research question	PCC (Population, Concept, and Context)	In hepatic encephalopathy (P), what is the pathophysiological role (C) of manganese accumulation (C)?
Secondary research question 1	CIMO (Context, Intervention, Mechanisms, Outcomes)	In hepatic encephalopathy (C), what is the role of manganese accumulation (I) on modulating oxidative stress (M) for neurotoxic effects (O)?
Secondary research question 2	CIMO (Context, Intervention, Mechanisms, Outcomes)	In hepatic encephalopathy (C), does manganese accumulation (I) interact with other pathogenic mechanisms (M) causing neurotoxicity (O)?
Secondary research question 3	CIMO (Context, Intervention, Mechanisms, Outcomes)	In hepatic encephalopathy (C), what is the effect of manganese accumulation (I) on the neurotransmitter systems (M) involved in its pathophysiology (O)?
Secondary research question 4	PCC (Population, Concept, and Context)	In hepatic encephalopathy (P), what is the influence of sex/gender (C) on manganese neurotoxicity (C)?
Secondary research question 5	MIP framework (Methodology, Issues, Participants)	Does modulating manganese levels (M) has a therapeutic potential (I) for hepatic encephalopathy (P)?

No other sources will be consulted. 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.

Databases to be consulted, their providers, and coverage dates (if available) are listed in Appendix A (available at https://osf.io/p7gdm/?view_only=123a09c13cd44ad3a6587e922f44c36e). Search algorithms were elaborated using an online tool (except that for EBSCOhost, which was adapted from other algorithms) and are publicly available (https://app.2dsearch.com/new-query/611956d77e2b2d00042239a8). Those algorithms were adjusted if necessary during the line-by-line analysis, which is described in Appendix B (available at https://osf.io/p7gdm/?view_only=123a09c13cd44ad3a6587e922f44c36e).

Articles written in languages other than English and Spanish will be included if adequately translated using Google Translate[22] or if English or Spanish translations be found.[23] Gray literature will be consulted through the Conference Proceedings Citation Index - Science (Web of Science Core Collection) and OpenDissertations (EBSCOhost). Retrieved references will be de-duplicated using Rayyan QCRI default algorithm, complemented with Zotero and Bookends;[24] Ovid deduplication tool will be used within

that platform. Identified duplicates will be manually revised to confirm duplicated publications and will be eliminated.[24]

Selection of studies
Two independent researchers will assess all references for eligibility using Sysrev[25] according to predefined criteria. A third researcher will solve discrepancies. Agreement between reviewers will be assessed using Sysrev concordance tool.[25] Two screening stages will be performed: Title/Abstract, and Full-Text.[16] Both stages will be pilot-tested with a random sample of 25-50 studies.[16, 26]

Studies selected for inclusion will be retrieved using the Retraction Watch database (http://retractiondatabase.org/) to identify retracted studies, which will be eliminated. The search strategy will be rerun six months after initial searches to identify more recent studies for possible inclusion. Results from the search strategy will be described in a PRISMA flow diagram.[27]

Eligibility criteria
Inclusion criteria
- Original, experimental, or theoretical studies reporting Mn levels in any biological or tissue sample, assessed by any imaging or biochemical method, in patients with HE. Any study design will be considered.

- No specific diagnostic criteria for HE will be considered if the studies describe their population as presenting this specific condition, as previously reported.[28]
- The analysis will not be limited to any clinical setting or article type. All quantitative, qualitative, or mixed-method studies will be considered.
- Original, experimental, or theoretical studies that describe experimental models reporting the effect of Mn administration (any pharmacological regime) on measures of neuroprotection (cell death, oxidative stress, excitotoxicity) in models of liver damage. Any study design will be considered.
- Experimental models of liver damage showing an effect on Mn levels in the liver and/or the brain.

Exclusion criteria
- Studies reporting subjects exposed occupationally or environmentally to Mn.
- Studies written in languages other than Spanish or English that could not be appropriately translated.
- Studies whose full-text files could not be retrieved.

As previously reported,[11] these criteria may be adjusted during the screening process. Adjustments will be applied to all studies and reported accordingly.

Data charting
Variables to be charted include age (years for humans, body weight or months for experimental animals), gender, HE type (A, B, or C), HE severity (MHE, grades I, II, III, or IV), Mn levels (any units of measure), biological sample (any tissue or fluid), brain region or cell type (neurons or glial cells), cell/tissue damage mechanism (cell death, edema, excitotoxicity, oxidative stress, astrocytosis), quality-of-life measures, pharmacological or surgical treatment, intra-hospital stay, patients' outcome, substance use, affected neurotransmitter system, experimental model (cell culture, rodents, non-human primates). Data charting will be pilot-tested with a random sample of 25-50 studies.[16] Also, some variables recommended by the JBI Manual of Evidence Synthesis[16] (authors, publication year, aims/purpose, study population, sample size, study design/methodology, interventions type/duration, comparator, outcome measures, key findings) will be charted. Only original studies are eligible for these charting methods.

Data synthesis
Either clinical or preclinical studies will be analyzed separately but might be discussed together. Data summaries will be presented in graphs, figures, and tables. Results will be presented in the units they were reported, and no conversions will be applied. Studies will be analyzed separately by type of experimental model (cell cultures, rodents, or non-human primates). A narrative synthesis will be performed for all studies. Only original research studies are eligible for data charting. A scientific paper will be submitted to a leading journal in this field.

Strengths and limitations of the present protocol
This scoping review will provide an integrative perspective of the role of Mn for HE based on a comprehensive search of both clinical and preclinical studies. In contrast to other protocols,[11] our research questions were elaborated according to systematic frameworks supporting our search strategy, which was also peer-reviewed. An effort will be made to include articles written in any language. The multidisciplinary research group provides complementary perspectives from several profiles.

This protocol complies with several methodological guidelines, including some for systematic reviews (PRISMA 2020, PRISMA-P, PRISMA-S, PRESS) and not only those for scoping reviews (PRISMA-Scr, and the JBI Manual for Evidence Synthesis). However, only a narrative analysis of the evidence will be presented. No risk-of-bias analysis or certainty of evidence assessment is included. The heterogeneity of the included studies may be a strength of this review since it allows an exhaustive analysis of the research topic. However, it is also a limitation as this precludes performing a systematic review of intervention or a meta-analysis.

Author's contributions

I.P.N. provided topic and methodological expertise, contributed to the design of the protocol's methodology (including the development of the search strategy), coordinated the reviewer team, drafted and approved the manuscript. H.S. provided methodological expertise, contributed to the design of the protocol's methodology (including peer-review of the search strategy), corrected and approved the final draft. A.M., and N.L.R.I. provided topic expertise, contributed to the design of the protocol's methodology (including the search strategy), corrected and approved the final draft. C.A.A.R., M.E., and C.R. provided methodological expertise, corrected and approved the final draft.

Conflicts of interest

I.P.N. is an editor for Archivos de Neurociencias.

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