INPLASY

Neurotransmitter Analysis to Confirm the Diagnosis of Diabetic Cardiac Autonomic Neuropathy in Rodents: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 September 2024 and was last updated on 24 September 2024.

INTRODUCTION

Review question / Objective The objective of this study is to evaluate the effectiveness of neurotransmitter analysis in diagnosing diabetic cardiac autonomic neuropathy (DCAN) in rodent models, with a focus on identifying the most indicative neurotransmitters, such as norepinephrine and acetylcholine. This investigation aims to determine whether there is a correlation between neurotransmitter levels and the severity or progression of DCAN in diabetic rodents, as well as how these changes relate to other markers of cardiac autonomic dysfunction. Additionally, the study seeks to compare neurotransmitter analysis with other biochemical and physiological diagnostic methods, assessing the potential of neurotransmitter levels as early biomarkers for DCAN compared to traditional diagnostic approaches.

Rationale The rationale for your study is based on the need for improved diagnostic methods for diabetic cardiac autonomic neuropathy (DCAN), a severe complication of diabetes that is often underdiagnosed due to the lack of reliable and specific biomarkers. While physiological and biochemical approaches are commonly used, they often fail to detect early or subtle changes in autonomic dysfunction. Neurotransmitters, such as norepinephrine and acetylcholine, play a crucial role in regulating cardiac autonomic function, and their altered levels in diabetic conditions may offer a more direct and sensitive marker for DCAN. By systematically reviewing and analyzing studies on neurotransmitter levels in rodent models of DCAN, your research aims to clarify the diagnostic value of neurotransmitter analysis, assess its correlation with disease severity, and compare its effectiveness to traditional diagnostic methods. This study could establish neurotransmitter analysis as a potential early biomarker for DCAN, improving early detection and intervention strategies in diabetes management.

Condition being studied The condition being studied is diabetic cardiac autonomic neuropathy (DCAN), a complication of diabetes that affects the

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autonomic nervous system's control of the heart. It leads to impaired regulation of heart rate, blood pressure, and other autonomic functions, which can increase the risk of cardiovascular complications and mortality in diabetic patients. DCAN is characterized by a gradual degeneration of the nerves that control the heart and blood vessels, and its progression can be subtle, making early diagnosis challenging. Our study specifically focuses on rodent models of DCAN to explore the role of neurotransmitter imbalances as diagnostic indicators of this condition.

METHODS

Search strategy mice OR rat OR squirrels OR prairie dog OR porcupines OR beavers OR guinea pig OR hamster AND Noradrenaline OR norepinephrine OR adrenaline OR epinephrine OR acetylcholine AND diabetic cardiac autonomic neuropathy.

Participant or population None.

Intervention Our systematic review and meta-analysis study population consists of rodent models, specifically those with diabetic cardiac autonomic neuropathy (DCAN). These rodent models are commonly used in research to mimic the pathophysiological conditions of diabetes and its complications, allowing for the investigation of DCAN development, progression, and potential diagnostic markers such as neurotransmitter imbalances. By focusing on rodent models, the study aims to understand the effectiveness of neurotransmitter analysis in diagnosing DCAN and its correlation with disease severity, providing insights that may be translatable to human studies.

Comparator The comparator in your study is other biochemical and physiological diagnostic methods used for identifying diabetic cardiac autonomic neuropathy (DCAN) in rodent models. These may include traditional assessments such as heart rate variability (HRV), blood pressure monitoring, baroreflex sensitivity, and various biochemical markers related to autonomic dysfunction. By comparing neurotransmitter analysis with these established methods, your study aims to evaluate whether neurotransmitter levels can serve as more effective or earlier biomarkers for diagnosing DCAN, potentially offering a more sensitive or specific alternative to conventional techniques.

Study designs to be included To address the objective of the review, the included study designs will primarily consist of original experimental research articles that utilize rodent models of diabetic cardiac autonomic neuropathy (DCAN). This will encompass studies employing randomized controlled trials, cohort studies, and cross-sectional studies that focus on neurotransmitter analysis as a diagnostic tool for DCAN. Additionally, studies that involve comparative analyses between diabetic and non-diabetic rodent models will be included.

Eligibility criteria The inclusion criteria for this systematic review and meta-analysis focus on selecting original research articles, experimental studies, and peer-reviewed papers that specifically investigate diabetic cardiac autonomic neuropathy (DCAN) in rodent models. To be included, studies must utilize neurotransmitter analysis, such as norepinephrine, acetylcholine, or epinephrine measurements, to diagnose or assess DCAN. Eligible studies should involve rodent models (e.g., rats or mice) induced with either Type 1 or Type 2 diabetes, and must include a control group of non-diabetic rodents for comparison. Studies must measure neurotransmitter levels in cardiac or related tissues and correlate these levels with the presence or severity of DCAN. Additionally, studies should report quantitative data on the effectiveness, sensitivity, specificity, or accuracy of neurotransmitter analysis in diagnosing DCAN, along with comparative data on neurotransmitter levels between diabetic and non-diabetic rodents. Only articles published in English will be considered.

The exclusion criteria for this review are as follows: review articles, meta-analyses, editorials, letters, and conference abstracts without sufficient experimental data will be excluded. Studies focusing on non-rodent models or human clinical studies without relevant rodent-based experimental data, as well as those involving non-diabetic rodent models or models of diseases other than diabetes (unless used as a comparative group), will not be considered. Research that does not specifically address cardiac autonomic neuropathy or focuses on other diabetic complications will also be excluded. Additionally, studies that do not include neurotransmitter analysis as a primary diagnostic tool for DCAN, or those that rely primarily on other diagnostic methods (e.g., imaging, electrophysiology) without significant emphasis on neurotransmitter analysis, will be excluded. Studies that do not report clear outcomes related to the efficacy or accuracy of neurotransmitter analysis in diagnosing DCAN, or those with incomplete or ambiguous data that cannot be reliably extracted or analyzed, will not be included. Finally, articles published in languages other than English (unless translated versions are available), as well as studies that are not

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accessible through standard academic databases or do not provide full-text access, will also be excluded from the review.

Information sources The intended information sources for this systematic review and meta-analysis include several electronic databases and additional resources to ensure comprehensive coverage of the relevant literature. The primary databases will be Scopus, PubMed, EBSCOhost, and the Cochrane Library.
Scopus will be searched for articles related to diabetic cardiac autonomic neuropathy (DCAN) and neurotransmitter analysis, yielding 47 initial results. From these, 16 potentially relevant articles are anticipated for further evaluation. PubMed, a key resource for biomedical literature, will also be utilized to gather research articles on DCAN and neurotransmitter analysis, providing 40 results, with 27 relevant studies expected to meet the inclusion criteria. Additionally, EBSCOhost, which aggregates multiple databases, will be searched extensively, yielding a substantial 2,987 total results related to the topic, from which 19 studies are anticipated to be included in the review. While no relevant results were found in the Cochrane Library, it will still be monitored for any systematic reviews or clinical trials related to DCAN that may emerge.
In addition to these electronic databases, other information sources will include contacting authors of relevant studies. For pertinent studies that lack sufficient data, authors will be reached directly to request additional information or unpublished data that could aid in the review. Efforts will also be made to search for grey literature, including theses, dissertations, and conference proceedings, to capture unpublished or non-peer-reviewed studies that may provide valuable insights into the role of neurotransmitter analysis in diagnosing DCAN.

Main outcome(s) The outcomes of this systematic review and meta-analysis will focus on evaluating the diagnostic efficacy of neurotransmitter analysis in confirming diabetic cardiac autonomic neuropathy (DCAN) in rodent models. Key outcomes will include the levels of specific neurotransmitters, such as norepinephrine, acetylcholine, and epinephrine, measured in cardiac or related tissues. Effect measures will involve assessing the sensitivity, specificity, and accuracy of neurotransmitter analysis as diagnostic tools compared to traditional methods.
Timing will be categorized based on the duration of diabetes induction in rodent models, examining acute versus chronic diabetic conditions to understand how neurotransmitter levels correlate with disease progression. Additionally, outcomes will include correlations between neurotransmitter levels and clinical markers of DCAN severity, such as heart rate variability and blood pressure responses.
The review will synthesize quantitative data from included studies to calculate pooled effect sizes and conduct subgroup analyses, thereby providing insights into the reliability of neurotransmitter analysis in diagnosing DCAN and its potential as an early biomarker. This comprehensive evaluation aims to establish clear relationships between neurotransmitter changes and the severity of DCAN, ultimately contributing to improved diagnostic strategies for diabetic complications.

Quality assessment / Risk of bias analysis The risk of bias for the studies included in this review was assessed using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) checklist. Two reviewers independently examined the literature and evaluated the risk of bias. Each item on the checklist was rated as "Yes" (indicating low risk), "No" (indicating high risk), or "unclear" (due to insufficient information or uncertainty regarding the risk of bias). Any discrepancies that arose during the evaluation process were resolved through discussion or by consulting a third reviewer.

Strategy of data synthesis Data analysis for this systematic review and meta-analysis will follow a structured approach to ensure a comprehensive evaluation of the findings related to neurotransmitter analysis in diagnosing diabetic cardiac autonomic neuropathy (DCAN) in rodent models.
Initially, a systematic extraction of data from the included studies will be performed, capturing key variables such as study design, sample size, animal model details, neurotransmitter levels measured, and the corresponding outcomes related to DCAN severity. This information will be organized in a standardized data extraction form to facilitate consistent and accurate comparisons across studies.
Descriptive statistics will be used to summarize the characteristics of the included studies, including means, standard deviations, and ranges for neurotransmitter levels. In cases where studies report different units or scales, data will be converted to a common format to allow for valid comparisons.
For the meta-analysis, pooled effect sizes will be calculated using random-effects models to account for the variability between studies. The primary effect measures will include mean differences in neurotransmitter levels between

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diabetic and non-diabetic rodent models, as well as correlations between neurotransmitter levels and markers of DCAN severity.

Subgroup analysis Subgroup analyses will be performed to explore potential sources of heterogeneity, such as variations in diabetes type (Type 1 vs. Type 2), duration of diabetes, and different methods of neurotransmitter analysis. Funnel plots and Egger's test will be utilized to assess publication bias, and if significant bias is detected, further analyses will be conducted to explore its impact on the overall findings.

Sensitivity analysis All statistical analyses will be conducted using appropriate software, and a significance level of $p < 0.05$ will be adopted for all tests. The results of the meta-analysis will be presented using forest plots, highlighting the pooled estimates and confidence intervals for neurotransmitter levels associated with DCAN. This comprehensive analysis approach aims to provide valuable insights into the effectiveness of neurotransmitter analysis as a diagnostic tool for DCAN in rodent models.

Language restriction English.

Country(ies) involved Malaysia.

Keywords Diabetic Cardiac Autonomic Neuropathy (DCAN); Neurotransmitter; Diabetes; Rodent.

Contributions of each author

Author 1 - Mohd Amir Kamaruzzaman - Advised and coached on implementing systematic searching and meta-analysis.
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Author 2 - Shamala Devi Subramaniam - 1. Devised the project, the main conceptual ideas and proof outline; 2. Developed the systematic review protocol.
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Author 3 - Nurul Hayati Mohamad Zainal - Reviewed on animal intervention of the included studies based on the 'Syrcle' risk of bias tool for animal studies checklist.
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