INPLASY PROTOCOL

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None declared.

Impact of Endocannabinoid Mediated Glial Cells on Cognitive Function in Alzheimer's Disease: A Systematic Review and Meta-Analysis of Animal Studies

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Review question / Objective: This review aims to review systematically, and meta-analyse published pre-clinical research about the mechanism of endocannabinoid system modulation on glial cells and their effects on cognitive function in designated Alzheimer's Disease (AD) in the animal model.

Condition being studied: Its been acknowledged that the cure of Alzheimer's disease is still vague. Current medicine is working on symptoms only but never stop the disease progression due to neuronal loss. In recent years, researches have found that cannabinoid which is derived from cannabis sativa plant and its compounds exert neuroprotective effects in vitro and in vivo. In fact, cognitive improvement has been shown in some clinical studies. Therefore, the knowledge of cannabinoids and its interaction with living physiological environment like glial cells is crucial as immunomodulation to strategize the potential target of this substance. The original articles from related study relating endocannabinoid mediated glial cell were extracted to summarize and meta-analyze its impact and possible mechanism against cognitive decline in AD.

INTRODUCTION

Review question / Objective: This review aims to review systematically, and meta-analyse published pre-clinical research about the mechanism of endocannabinoid system modulation on glial cells and their effects on cognitive function in designated

Alzheimer's Disease (AD) in the animal model.

Rationale: To provide better understanding of mechanism of glial cells and its role in endocannabinoid modulation in Alzheimer's disease animal model.

Condition being studied: Its been acknowledged that the cure of Alzheimer's disease is still vague. Current medicine is working on symptoms only but never stop the disease progression due to neuronal loss. In recent years, researches have found that cannabinoid which is derived from cannabis sativa plant and its compounds exert neuroprotective effects in vitro and in vivo. In fact, cognitive improvement has been shown in some clinical studies. Therefore, the knowledge of cannabinoids and its interaction with living physiological environment like glial cells is crucial as immunomodulation to strategize the potential target of this substance. The original articles from related study relating endocannabinoid mediated glial cell were extracted to summarize and meta-analyze its impact and possible mechanism against cognitive decline in AD.

METHODS

Search strategy: "alzheimer* disease" OR "dementia" OR "mental disorder" OR "mental deterioration" OR "neurodegenerati*" OR "neuroinflammat*") AND TITLE-ABS-KEY ("endocannabinoid*" OR "endocannabinoid system*" OR "cannabinoid receptor*" OR "cannabinoid agonist*" OR "cannabinoid ligand*" OR "cannabinoid*" OR "cannabis" OR "cannabis sativa" OR "cannabidiol" OR "cbd" OR "tetrahydrocannabinol" OR "thc" OR "marijuana" OR "cannabivarin" OR "cannabigerol") AND TITLE-ABS-KEY ("microglia*" OR "autophag*" OR "microglia* activation" OR "microglia* stimulation" OR "microglia* function" OR "microglia* polarization" OR "microglia* propert*" OR "glia*" OR "gli*" OR "immune cell*" OR "immunomodulat*" OR "neuroprotect*" OR "astrocyte*" OR "astrogli*" OR "oligodendrocyte*" OR

"ependymal cell*") AND TITLE-ABS-KEY ("cogniti*" OR "intelligence*" OR "intellectual*" OR "executive function*" OR "think*" OR "learn*" OR "memor*" OR "judge*" OR "knowledge" OR "mind" OR "thought" OR "behavio*") AND TITLE-ABS-KEY ("animal" OR "rat*" OR "rodent*" OR "mice*".

Participant or population: Alzheimer's disease animal models.

Intervention: Intervention analyzed include cannabinoid agonist administration or inhibition of cannabinoid receptors.

Comparator: Alzheimer's disease model or control group treated with vehicle.

Study designs to be included: Animal studies characterized with four main identification components: Alzheimer's disease animal model, endocannabinoid system, glial cells and cognitive outcome. Controlled studies with a separate control group.

Eligibility criteria: Inclusion criteria: 1) Laboratory rodents of any species, age, sex, or weight-producing Alzheimer's disease (AD) models were covered. Besides, any kind of induction in which the design is dedicated for Alzheimer's disease model as a primary model will also be counted. 2) Any comparison between endocannabinoid modulation and the control group was taken into account. A placebo, such as physiological saline or some similar substance, has to be included in the control group. The drug's dosage, route of administration, and length of therapy were not constrained. 3) Primary outcomes include the measurement from cognitive tests. Secondary outcome of glial cell immunoreaction/glial cell mechanism changes by any mean of measurement. 4) Pathological changes were assessed and not restricted to Aβ. 5) Original experimental studies to measure the efficacy of endocannabinoid stimulation on AD animal models were included. Exclusion criteria: 1) Studies without AD models in animals. The induction that is not dedicated to Alzheimer's disease model as

a primary model or if the model seems to be non-specific/broad such as neurodegenerative/neuroinflammation. 2) No control group. 3) Studies with the outcome only have either cognition or glial cell results. 4) Duplication of references, review articles, lack of full text, and literature with incorrect or incomplete data.

Information sources: To find studies examining endocannabinoid's neuro-protective properties in rodent animal AD models, we conducted a thorough literature search. From four different databases, we gathered the pertinent publications: Ebscohos (CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, MEDLINE Complete, Psychology and Behavioral Sciences Collection), Scopus, PubMed, and Web of Science. We used "Alzheimer's disease" AND "Cannabinoid" AND "Glia" AND "cognition" as the keywords for the literature search.

Main outcome(s): Primary outcomes obtained in the selected articles describe the changes in the general cognitive function (memory, attention, language, orientation, and learning) as measured in escape latency and novel object recognition test from the modifications observed in endocannabinoid modulation method in AD animal models.

Additional outcome(s): Secondary outcomes related to the histological and biochemical characteristics of the animal were also observed, such as glial cell and inflammatory markers, amyloid burden, oxidative stress markers, synaptic plasticity, cellular apoptosis or enzymatic levels.

Quality assessment / Risk of bias analysis: The risk of bias for included studies was evaluated using a Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) checklist. Two reviewers are independently read the included literature and evaluate the risk of bias. For each item of the bias checklist, the results were graded as "Yes" (low risk), "No" (high risk) and "unclear" (lack of relevant information or uncertainty about bias). The arising discrepancies will be resolved through discussion, or by consulting a third reviewer.

Strategy of data synthesis: A meta-analysis was performed on the extracted data using RevMan 5.4 software. The standard mean difference (SMD) and 95 percent confidence intervals (CI) were calculated using a random-effects model for the possibility of heterogeneity. I2 values indicate measurement of heterogeneity which exist when $p < 0.05$.

Subgroup analysis: Subgroup analysis is conducted to assess the potential sources and give reasonable explanations for the heterogeneity. Subgroup analysis will be carried out according to the type of animal model (transgenic mice, non transgenic mice and rats).

Sensitivity analysis: When there was significant heterogeneity in the data, a sensitivity analysis was performed by omitting the included data one at a time to examine whether these alterations affected the cumulative result estimate which was successful.

Language restriction: English.

Country(ies) involved: Malaysia, India, Indonesia.

Keywords: Endocannabinoid, glial cell, microglia, astrocyte, cognition, Alzheimer's disease.

Contributions of each author:
Author 1 - Mohd Amir Kamaruzzaman - 1. Devised the project, the main conceptual ideas and proof outline; 2. Developed the systematic review protocol.
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