FOOD FOR THOUGHT

CALORIC RESTRICTION AS A THERAPEUTIC STRATEGY FOR ALZHEIMER'S DISEASE

Júlia Turner Cabeza | Bachelor thesis | BSc in Microbiology

Universitat Autònoma de Barcelona

Facultat Biociències UAB

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition affecting millions worldwide, characterized by cognitive decline and dementia. The rising incidence of the disease and the lack of effective current treatments point to the need for alternative therapeutic strategies. Gut microbiota has emerged as a promising research avenue due to its association with AD pathology. **Caloric restriction (CR)**, a dietary intervention involving controlled calorie reduction, has shown promising effects in extending lifespan and modulating gut microbiota.

OBJECTIVES

This review will explore the potential of CR as an adjuvant therapeutic strategy for AD by:

- Investigating the **microbiota-gut-brain (MGB)** axis in **AD**.
- Assessing the **effects of CR** on the **gut microbiome (GM)** in relation to AD.

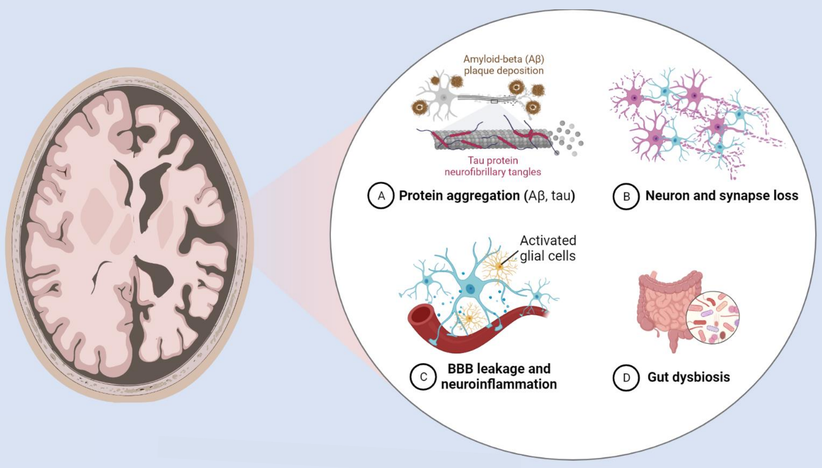


Figure 1: Neuropathologic hallmarks of AD.

THE MGB AXIS IN ALZHEIMER'S DISEASE

The MGB is a network of neural, immune and metabolic signaling pathways through which the **gut microbiota (GM)** and the **brain** interact.

AGING

As the primary risk factor for AD, aging contributes to AD pathogenesis via the MGB, through:

- Age-related changes in GM.
- A **dysfunction** of anatomic and immune pathways.

METABOLIC PATHWAYS

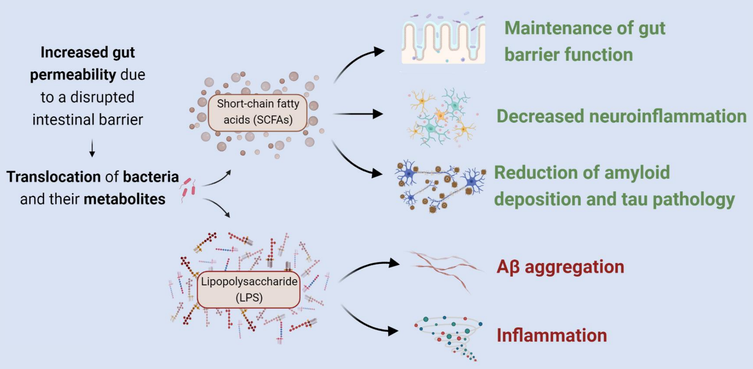


Figure 2: Effect of bacterial metabolites on the MGB, in relation to AD.

IMMUNE PATHWAYS

Age-related changes lead to an **increased translocation** of **metabolites** to the central nervous system (CNS).

↑ **Proinflammatory genera**
Escherichia/Shigella

↓ **Anti-inflammatory genera**
E. rectale

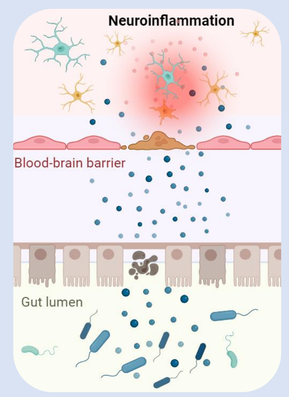


Figure 3: Translocation of gut metabolites causing neuroinflammation of glial cells.

CALORIC RESTRICTION

CR is a dietary intervention, involving a reduction of 20-40% in total calorie intake without causing malnutrition. It **positively affects lifespan** in animal models, by **delaying** the onset of **age-related diseases**.

- Disrupts the normal succession of aging microbiota.
- Restores ***Firmicutes/Bacteroidetes* ratio**.

↑ bacteria abundance **positively** associated with lifespan.
↓ bacteria decrease **negatively** associated with lifespan.

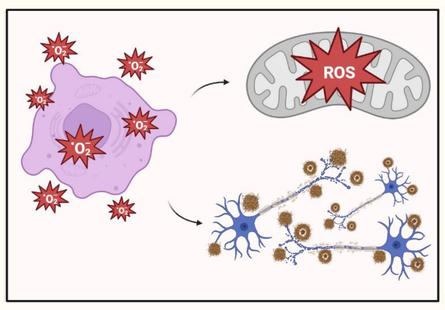
Table 1: Impact of caloric restriction on microbial groups.

MICROORGANISMS	INCREASE ↑ DECREASE ↓	EFFECT
Allobaculum	↑	SCFA production
Lactobacillus	↑	Anti-inflammatory and maintenance of gut barrier function
Faecalibaculum	↑	SCFA production and anti-inflammatory
Akkermansia	↑	Improvement of intestinal barrier function, reduced inflammation, alleviation of Aβ plaque deposition
Lachnospiraceae	↑	SCFA production
Bacteroides	↓	Increased bacterial translocation and elevated pathogenic Aβ levels
Saccharimonadia	↓	Inflammatory intestinal disease

1. REDUCTION OF OXIDATIVE STRESS

Reactive oxigen species (ROS) are associated with **mitochondrial dysfunction** and **Aβ** and **tau protein aggregation**.

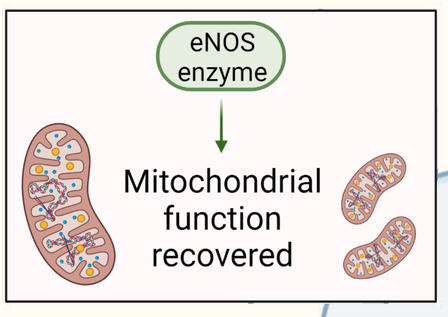
CR reduces oxidative stress → **neuroprotective**



2. IMPROVED MITOCHONDRIAL FUNCTION

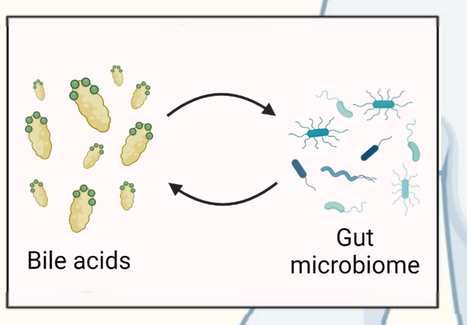
Mitochondrial dysfunction is a **key hallmark of AD**. CR improves mitochondrial function by activating the **eNOS enzyme**:

- Activates biogenesis
- **Reduction** of **neurotoxicity**



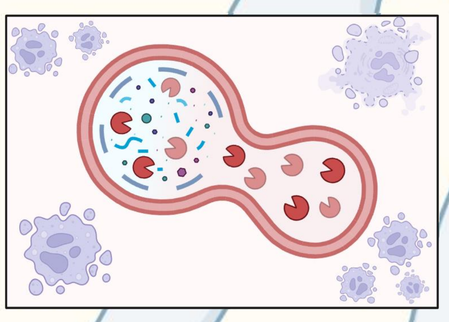
3. ENHANCING CELLULAR STRESS RESPONSE

CR activates the SIRT1 enzyme, which reduces **inflammation** and **maintains barrier function**.
Through bile acid metabolism, SIRT1 can shape the gut microbiome, which in turn modulates bile acid composition.



4. PROMOTION OF AUTOPHAGY

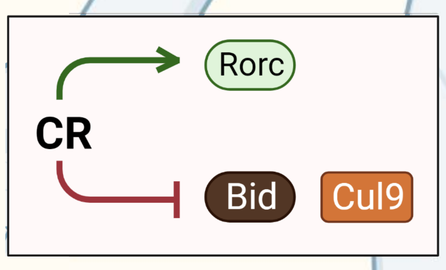
Impaired autophagy is linked to AD pathogenesis. CR stimulates autophagy, **diminishing** the **neurotoxic effects** and decreasing amyloid burden.



5. IMMUNOMODULATION

CR has **anti-inflammatory effects**, reducing the production of pro-inflammatory molecules and **dampening neuroinflammation**, by:

- **Upregulating Rorc**, which counteracts chronic inflammation and microbial translocation.
- **Downregulating** pro-apoptotic genes **Bid** and **Cul9**.



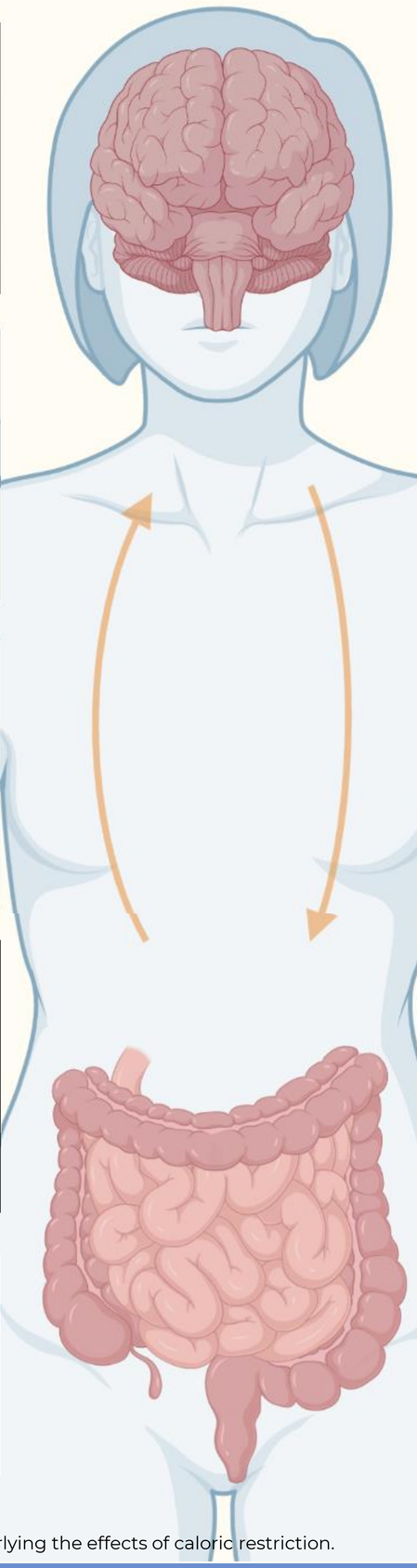


Figure 4: Mechanisms underlying the effects of caloric restriction.

CONCLUSIONS

This review has highlighted the potential of CR as a therapeutic strategy for AD, by:

- Studying **changes caused by CR** in the **gut microbiome**.
- Microbiota changes induced by CR promote a beneficial **anti-inflammatory phenotype**, which has neuroprotective effects.

REFERENCES

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3) Megur, A., Baltriukienė, D., Bukelskienė, V. & Burokas, A**. The Microbiota-Gut-Brain Axis and Alzheimer's Disease: Neuroinflammation Is to Blame?** Nutrients 13, 37 (2020)

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