

A high-salt diet induces synaptic loss and memory impairment via gut microbiota and butyrate in mice

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Introduction

A high-salt diet induces synaptic loss and memory impairment via gut microbiota and butyrate in mice

The decline in cognitive health is rising due to higher and higher life expectancy and unhealthy dietary habits, among which a **high-salt diet(HSD) is associated with cognitive impairment**

Excess salt intake impairs memory function in mice models but its significance on the **gut microbiota** remains **largely unexplored**

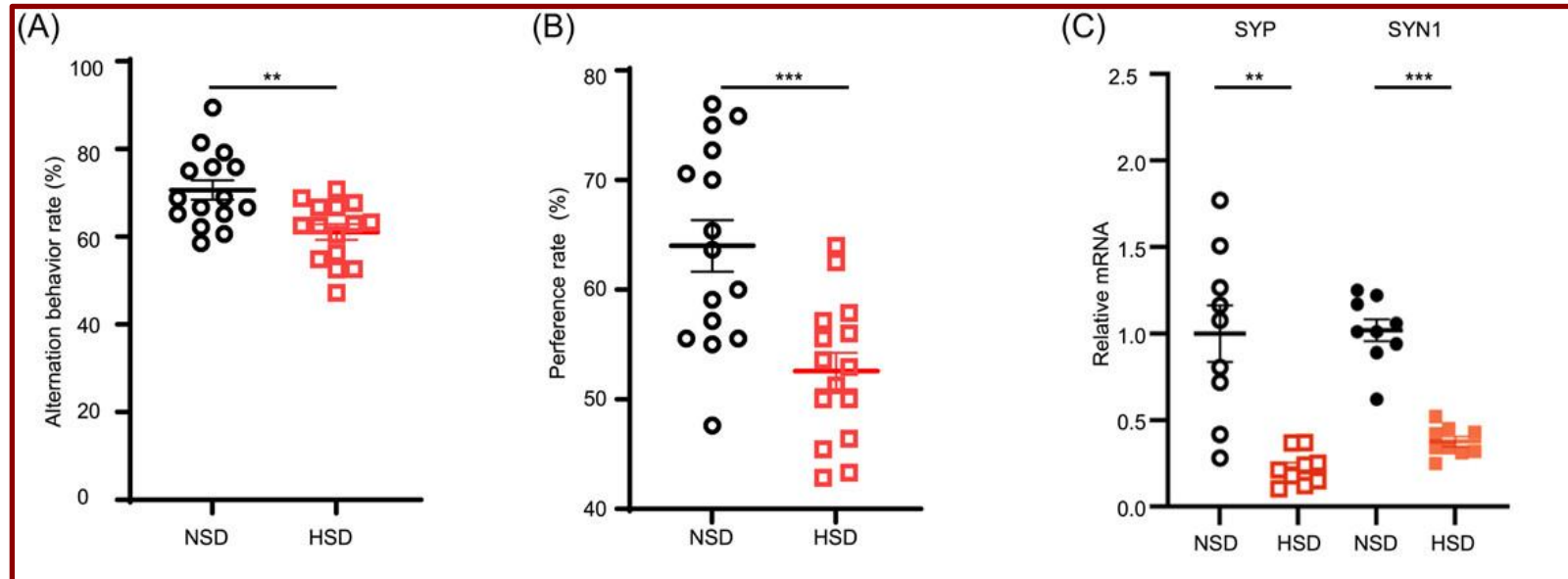
The **microbiota–gut–brain axis** is pivotal in regulating cognitive functions. In addition, there is growing evidence supporting the role of microbiota in cognitive impairment and **specific microbiota** in memory functions

In this study, we explored the **relationship** among the gut microbiota, high-salt diet(HSD), **synapses**, and memory function



Results

Mice fed HSD displays **cognitive impairment** and **lower synaptic protein**



(A) Percentage of spontaneous alternations in performance in the **Y-maze** test

(B) Percentage of exploration time during recognition trail in the **novel object recognition task**

(C) SYP and SYN1 messenger RNA (**mRNA**) levels in the **hippocampus**

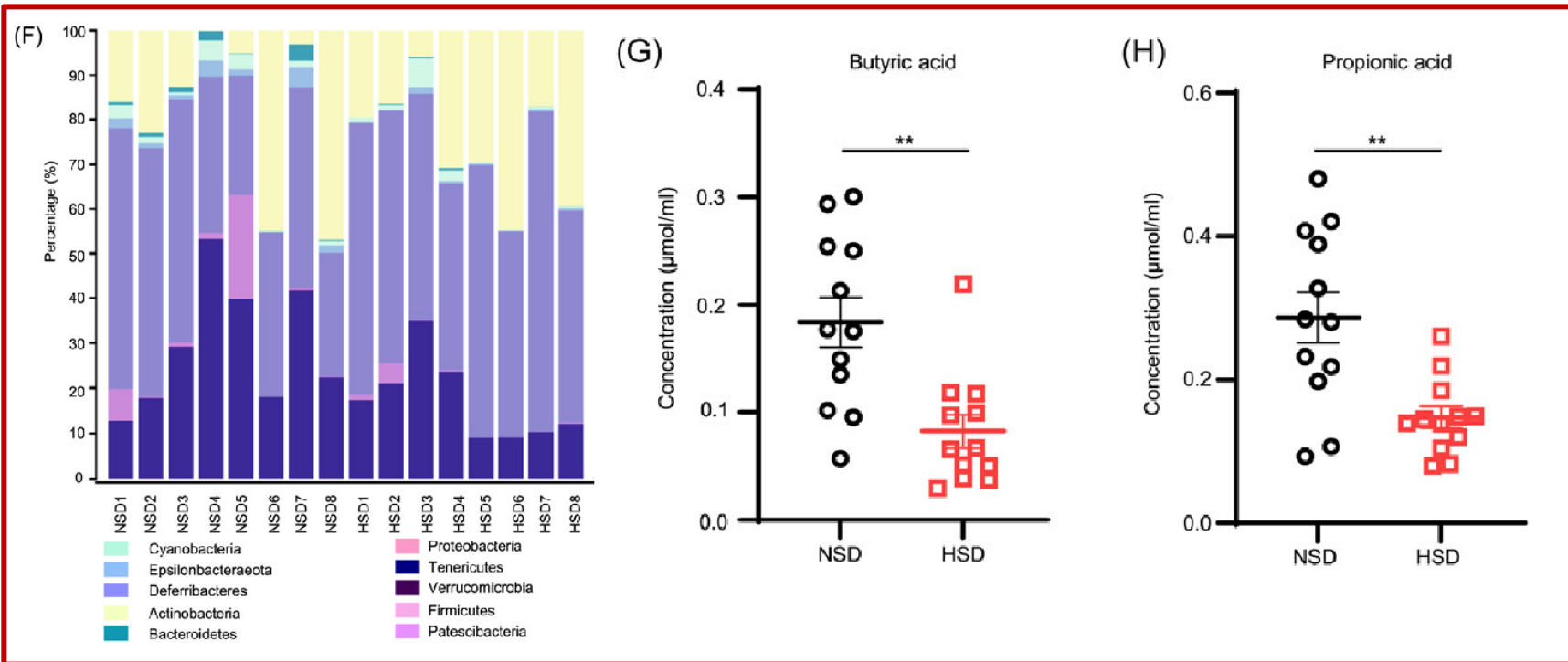
Compared to the NSD group, the **HSD group** displayed:

- ✓ **decreased** continuous spontaneous alternation behavior in Y maze
- ✓ **decreased** ratio of exploration time in the novel object recognition task
- ✓ **decreased** SYP and SYN1 messenger RNA (mRNA) levels



Results

HSD impairs memory and synapse via **gut microbiota composition** and **SCFAs** production



(F) Profiles of the top 10 gut microbiota at the level of phylum

(G,H) The levels of butyric acid and propionic acid measured by gas chromatography–mass spectrometry (GC-MS) from fecal samples

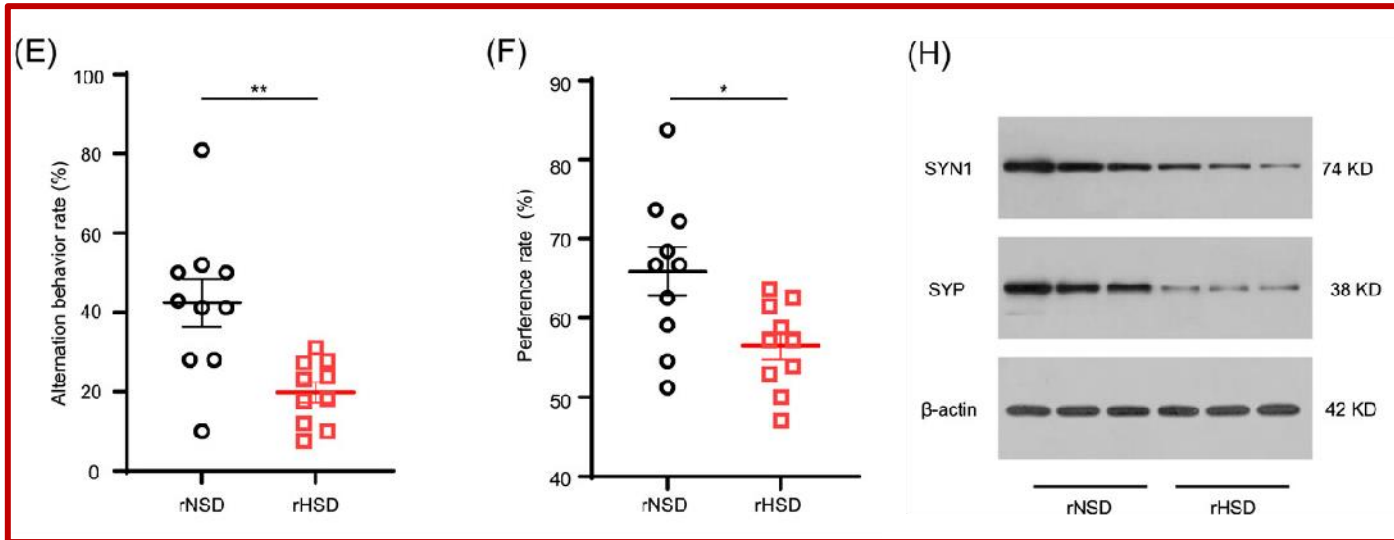
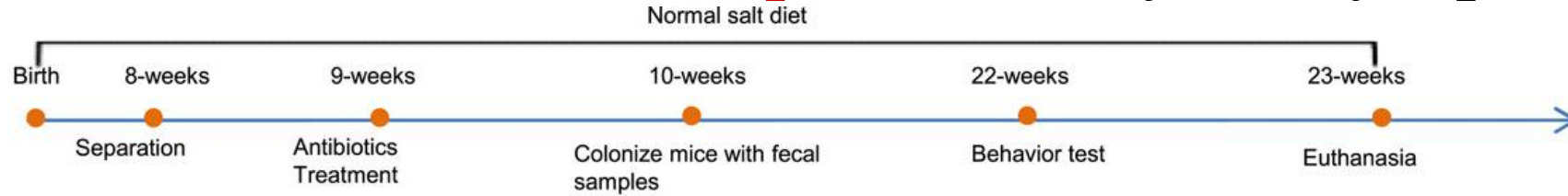
Compared with the NSD group, the **HSD group** displayed:

- ✓ decreased phyla **Bacteroidetes**
- ✓ **different bacterial profiles**, driven by some taxa such as Staphylococcus and Faecalibaculum
- ✓ significantly **decreased abundance** of *B. virosa* and *Lactobacillus johnsonii*, and significantly **increased abundance** of *Faecalibaculum rodentium*, *Staphylococcus xylosus*, and *Parasutterella excrementihominis*
- ✓ decreased levels of **butyric acid** and **propionic acid**



Results

Gut microbiota from HSD impairs memory and synapse



(E) Percentage of spontaneous alternations performance in Y-maze test

(F) Percentage of exploration during recognition trail in the novel object recognition task

(H) Changes of the protein levels of SYP and SYN1 in the hippocampus of mice by western blot analysis

rNSD mice: mice accepted fecal samples from NSD-fed mice

rHSD mice: mice that were transplanted with fecal samples from HSD-fed mice

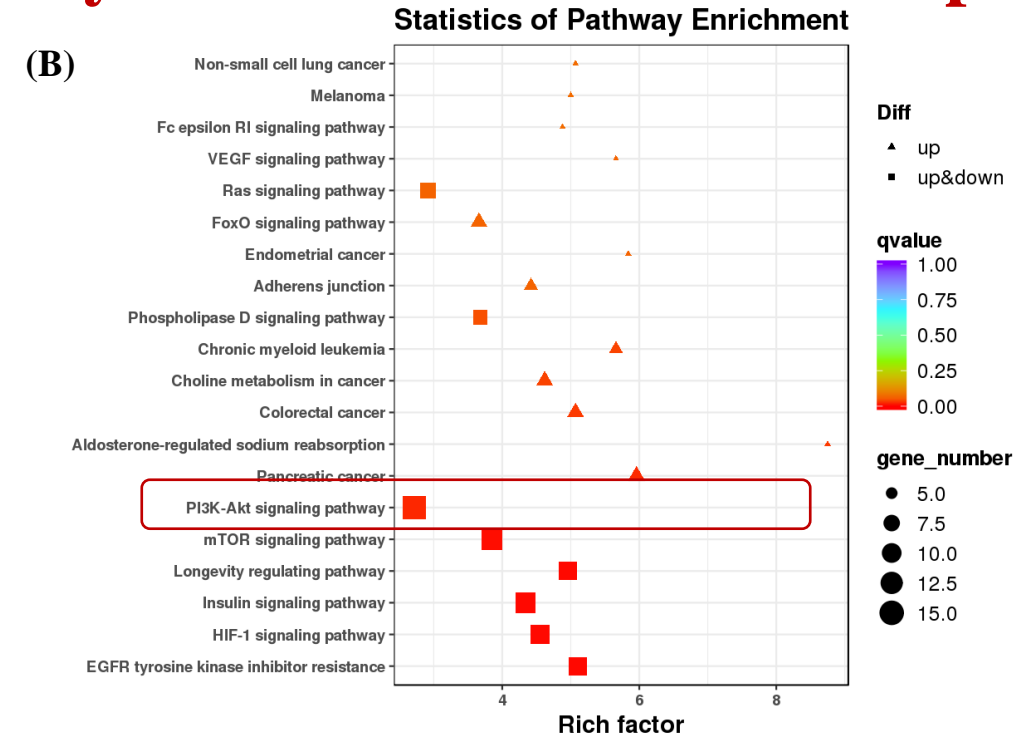
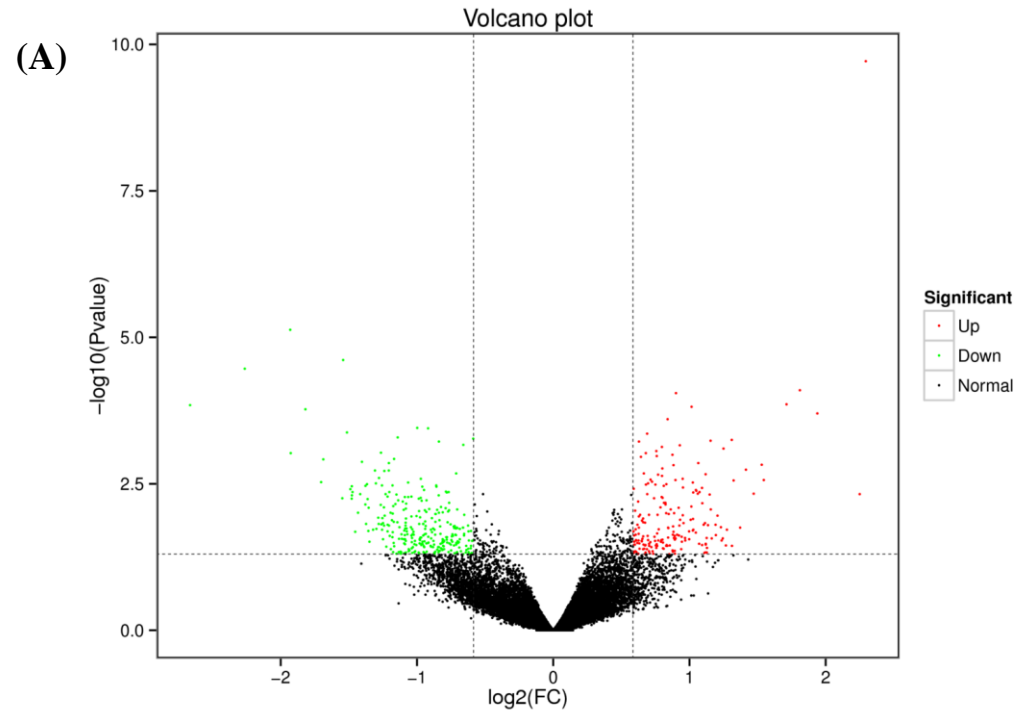
Compared with the rNSD group, the **rHSD group** displayed:

- ✓ **decreased** continuous spontaneous alternation behavior in Y maze
- ✓ **decreased** ratio of exploration time in the novel object recognition task
- ✓ **decreased** SYP and SYN1 protein levels



Results

Microbiota from HSD-fed mice extensively altered the brain transcriptome



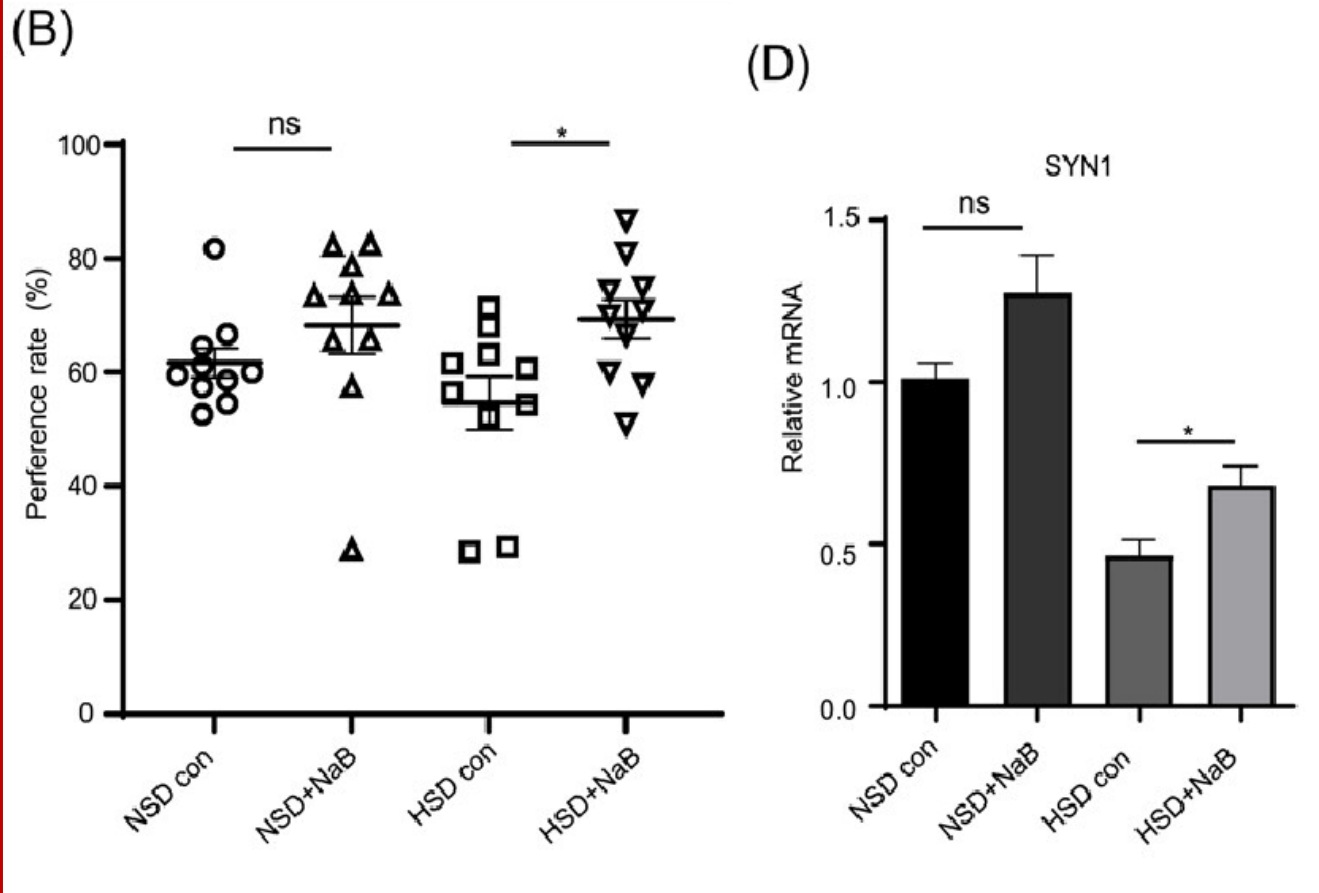
- ✓ a total of **489** genes were significantly and differentially (**DEGs**) expressed between rHSD and rNSD mice, which comprised **197 upregulated** and **292 downregulated** genes
- ✓ The **PI3K/Akt** signaling pathway was significantly dysregulated in rHSD mice brains

(A) Volcano plots of the significantly differentially expressed genes. Fold-change (X-axis) and p-value (Y-axis) of DEGs comparing rHSD group versus rNSD group. green-downregulated, red-upregulated

(B) KEGG pathways-related genes were significantly upregulated and downregulated in the brains of rHSD versus rNSD mice by statistics of pathway enrichment

Results

Butyrate **partially reverses** the memory impairment induced by HSD



(B) Percentage of exploration during recognition trail in the novel object recognition task

(D) Changes in the relative mRNA expression levels of SYP in the hippocampus of mice

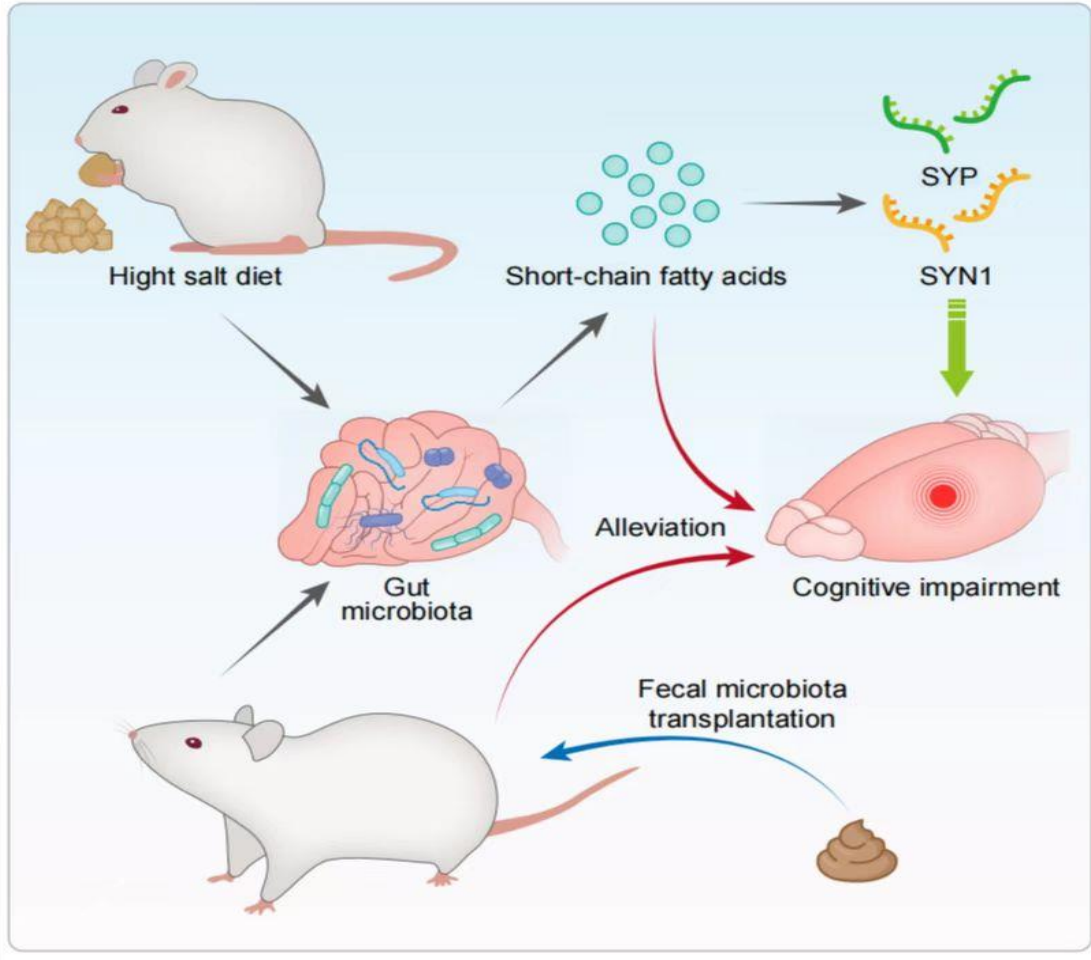
NSD + NaB: NSD with 20 mg/kg Butyrate sodium (S817488, Macklin) in drinking water

HSD + NaB: HSD with 20 mg/kg NaB (S817488, Macklin) in drinking water

- ✓ the addition of butyrate **partially inhibited** the **memory impairment** induced by the HSD diet
- ✓ significant increase in the mRNA expression of SYN1 in HSD-fed mice receiving butyrate compared with simple HSD-fed mice



Summary



This study indicates the important role of the gut microbiota and butyrate production in synaptic loss and memory impairment, and this study mainly on the following parts/demonstration:

- High-salt diet (HSD)-fed mice display cognitive impairment and lower synaptic proteins via changed gut microbiota composition and short-chain fatty acids production
- Gut microbiota from HSD-fed mice impairs memory and synapse in normal salt diet-fed mice
- Butyrate treatment partially reverses memory impairment in HSD-fed mice

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