Navitoclax does not alter genes related to blood-brain barrier proteins, glia, Aβ and tau production in the hippocampus of a porcine model of familial hypercholesterolemia

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Introduction

- High fat diet (HFD) accelerates atherosclerosis.
- Atherosclerosis narrows arterial lumen, reduces blood flow and can cause hypoxia which impairs blood-brain barrier (BBB), contribute to gliosis and neurodegeneration, particularly in the hippocampus.
- Navitoclax (ABT263), an experimental senolytic, was uncovered in preclinical studies to reduce and stabilize atherosclerotic plaques.
- Senolytics specifically remove senescent cells (i.e., aged cells that no longer divide and may play a role in the development of age-related pathology).

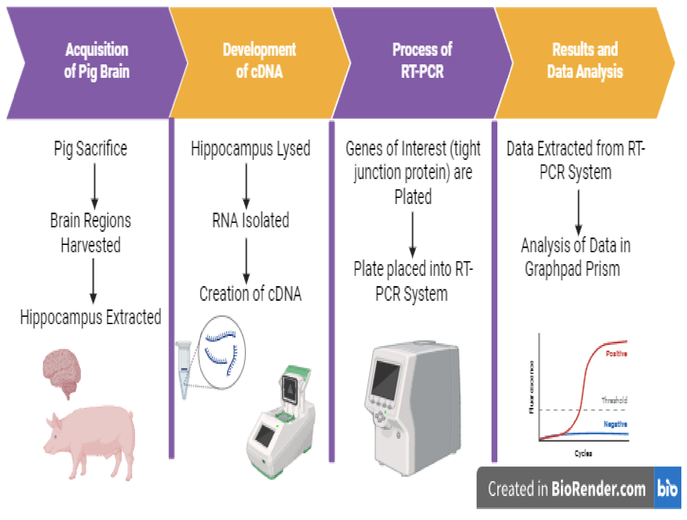
Hypothesis: ***Navitoclax will upregulate genes for BBB tight junction proteins and downregulate genes linked to gliosis, amyloid-beta (Aβ) and tau production in a pig model of familial hypercholesterolemia (FH) and atherosclerosis.***

Materials and Methods

A total of 15 female Rapacz-FH pigs divided into **Groups:**

- 1. Basal (3 months HFD – No treatment)
- 2. Mock (6 months HFD – Vehicle)
- 3. ABT (6 months HFD – Navitoclax)

Experimental protocol:



Results

Genes for BBB Tight Junction proteins

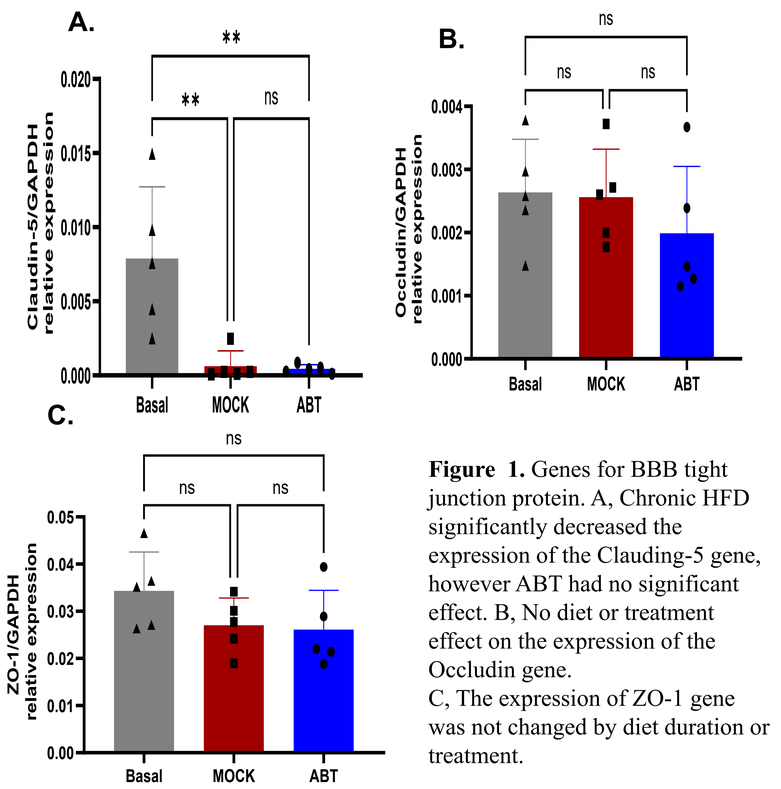


Figure 1. Genes for BBB tight junction protein. A, Chronic HFD significantly decreased the expression of the Clauding-5 gene, however ABT had no significant effect. B, No diet or treatment effect on the expression of the Occludin gene.
C, The expression of ZO-1 gene was not changed by diet duration or treatment.

Gene related to Tau production

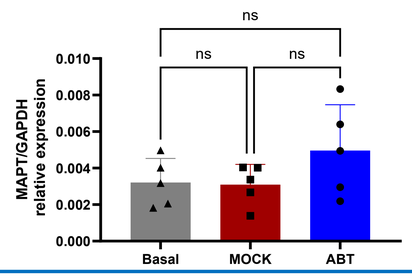


Figure 2. Gene related to tau production. HFD duration and Navitoclax treatment does not alter the expression of MAPT gene.

Glial Genes

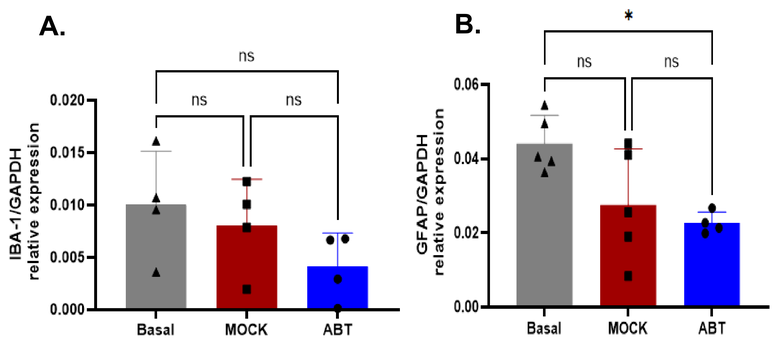


Figure 3. Glial genes. A. HFD nor treatment did not significantly change the expression of the IBA-1 gene. B. HFD duration significantly decreased the expression of GFAP gene ($p < 0.05$), however there is no Navitoclax treatment effect.

Genes related to Aβ production

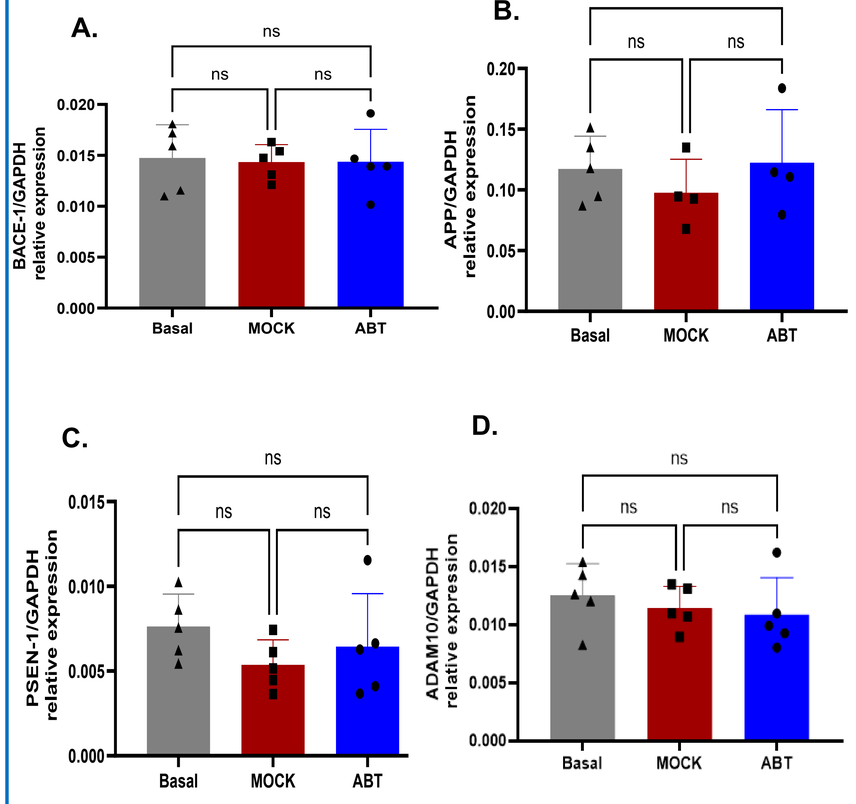


Figure 4. Genes related to Amyloid-beta production. A. HFD duration nor Navitoclax treatment did not significantly change the expression of BACE-1 gene. B. HFD duration nor Navitoclax treatment did not significantly change the expression of APP gene. C. HFD duration nor Navitoclax treatment did not significantly change the expression of the PSEN-1 gene. D. HFD duration nor Navitoclax treatment did not significantly change the expression of ADAM10 gene.

Conclusion and Next Steps

In female Rapacz-FH pigs, Navitoclax does not decrease hippocampal the expression of genes related to BBB tight junction proteins, glia, Aβ and tau production. Additionally, Claudin-5 and GFAP, chronic HFD does not significantly alter genes involved in BBB tight junction proteins, glia, Aβ and tau production.

Next steps: Repeat the RT-PCR experiments for reproducibility. Histologically quantify BBB tight junction proteins, reactive astrocytes and microglia; Aβ and tau.

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