Diabetic Complications Consortium

Application Title: Targeting PKM2 in chronic hypoperfusion for the treatment of cognitive impairment in type 2 diabetes.

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1. Project Accomplishments:

We propose to study the role of PKM2 in a mouse model of vascular cognitive impairment and dementia (VCID) with Type 2 diabetes (T2D). Our hypothesis was that T2D exacerbate brain damage and cognitive decline in VCID mice, leading to dysregulation of PKM2 in astrocyte. We fed conditional PKM2 knockout in astrocyte (PKM2 KO) and PKM2 flox mice with 60% of HFD or regular diet (RD) for 16 weeks. We found that T2D exacerbate the white matter damage and cognitive decline in VCID PKM2 flox mice fed with HFD when compared to VCID or sham PKM2 flox mice fed with RD. We observed that genetic lack of PKM2 in astrocyte protects mice from cognitive dysfunction in VCID mice with T2D compared with VCID PKM2 flox mice with T2D. We did not observe changes in the hippocampus between PKM2 KO and PKM2 flox VCID mice with T2D. However, we found that VCID PKM2 KO mice with T2D has less white matter damage compared to VCID PKM2 flox mice with T2D.

2. Specific Aims:

Aim 1: Determine the role of PKM2 on astrocyte in VCID mice with T2D. To evaluate the effects of conditional PKM2 knockout in astrocyte on cognitive decline, BBB leakage and hippocampus damage in VCID mice with T2D.

Results: We did not see changes on glucose levels and body weight between PKM2 KO and PKM2 flox mice during 16 weeks of HFD. We found that T2D exacerbate cognitive decline and cerebral hypoperfusion in VCID PKM2 flox mice compared to VCID PKM2 flox mice fed with RD. We observed that VCID PKM2 KO mice with T2D improve cognitive decline measured by novel object recognition compared with VCID PKM2 flox mice with T2D. Cerebral hypoperfusion measured by laser doppler flowmetry was not changed between VCID PKM2 KO or PKM2 flox mice with T2D. We performed immunofluorescence for MAP-2 (neurons), SMI312 (axons) and MBP (myelin) in mice with or without VCID and fed with HFD or RD. We did not observe changes in the hippocampus between VCID PKM2 KO and PKM2 flox mice with T2D on MAP-2, SMI312 and MBP. However, we found that VCID PKM2 flox mice with T2D have less luxol fast blue staining compared to VCID PKM2 KO mice with T2D. Our data indicate that PKM2 knockout in astrocyte protects against myelin degeneration in VCID mice with T2D. We have had decreased fertility of mouse breeding during the project. Therefore, the experiments are still on-going for blood brain barrier leakage and immunofluorescence.

Aim2 : Test the effectiveness of PKM2 activator in VCID mice with T2D. We proposed to test the hypothesis that increasing PKM2 activity with TEPP-46 would reverse cognitive decline and regulate the glucose metabolism in astrocytes of VCID mice with T2D.

Results: We evaluated the effects of PKM2 activation in VCID mice with T2D on cognitive decline using intervention studies with TEPP-46 administered for 15 days, starting 2 weeks after VCID surgery. We did not observe an improvement on cognitive decline in VCID mice with T2D treated with TEPP-46 for 15 days on novel object recognition when compared to VCID mice with T2D treated with vehicle. In addition, the treatment protocol with TEPP-46 did not protect against myelin degeneration in VCID mice with T2D compared to animals treated with vehicle. Then, we decided to start the intervention with TEPP-46 right after VCID surgery for 30 days. We found that VCID mice with T2D treated with TEPP-46 for 30 days showed improvement on cognitive decline compared to VCID mice with T2D treated with vehicle. We are currently working to (a) measure BBB leakage and inflammatory markers (b) evaluate metabolomics differences.

We anticipate completion of all the measurement in a couple of months. We will submit an abstract to a diabetes or dementia society meeting to allow dissemination of results. Subsequently, data generated through this project will support a R01 grant application and a manuscript for submission to a journal.

3. Publications:

None.