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14. ABSTRACT

Blast-related mild traumatic brain injury (mTBI) is widespread amongst service members and veterans who served in Iraq and Afghanistan. TBI has many long term adverse health consequences as summarized in a recent report by the Institute of Medicine[1]. However, it remains unclear if TBI increases the susceptibility to **diabetes** (one of the FY17 PRMRP Topic Areas) and other metabolic diseases. Given the tremendous impact that diabetes and metabolic diseases have on the quality of life and morbidity by fueling cardiovascular disease, cancer, impaired cognition and reducing life expectancy, it is important to establish if mTBI can indeed cause metabolic disease and if so, through which mechanisms.

The biggest impact of these studies to be in the realization that TBI through brain damage impairs metabolic control and increases the risk for type 2 diabetes. Secondly, they give hope to those that may suffer from metabolic disease and have TBI as we have begun to identify drugs that seem to be promising in treating TBI induced metabolic disease.

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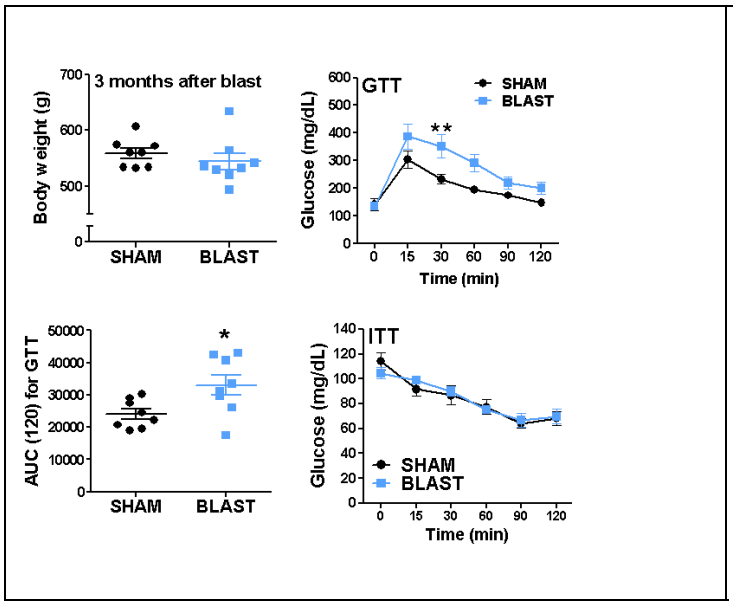
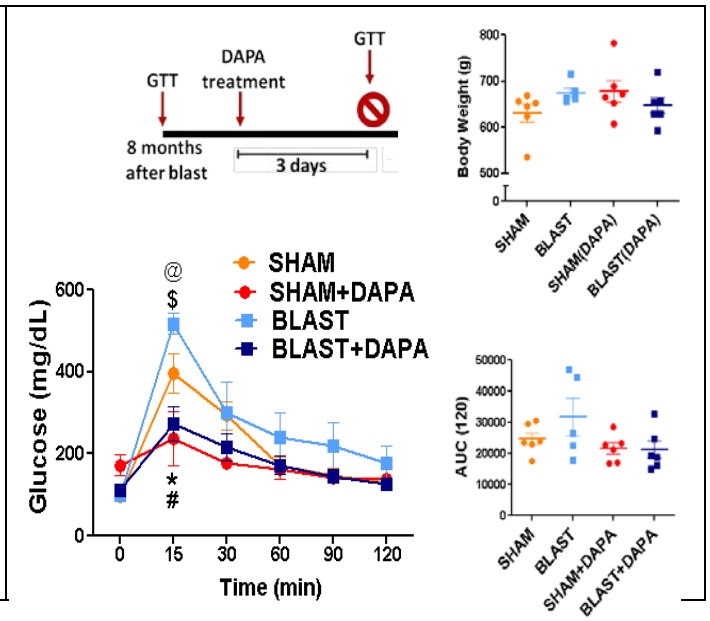
Blast-related mild traumatic brain injury (mTBI) is widespread amongst service members and veterans who served in Iraq and Afghanistan. TBI has many long term adverse health consequences as summarized in a recent report by the Institute of Medicine[1]. However, it remains unclear if TBI increases the susceptibility to diabetes (one of the FY17 PRMRP Topic Areas) and other metabolic diseases. Given the tremendous impact that diabetes and metabolic diseases have on the quality of life and morbidity by fueling cardiovascular disease, cancer, impaired cognition and reducing life expectancy, it is important to establish if mTBI can indeed cause metabolic disease and if so, through which mechanisms.

Here we find that TBI induces long lasting glucose intolerance, which can be completely reversed by an SGLT2 inhibitor.

Diabetes, traumatic brain injury, insulin resistance, metabolic disease, glucocorticoid signaling, stress, metabolic phenotyping

To dissect the mechanisms through which TBI disrupts brain control of metabolism we used a rat model of TBI created by the Naval RC. 8-week old rats were anesthetized and received a 74.5 kPa blast exposure daily for 3 consecutive days; with sham animals not receiving the blast. We followed these rats for a total of 10 months and as shown below did find consistent glucose intolerance (GTT) with significantly increased AUC, even though body weight and insulin tolerance was not altered.





Glucose tolerance at 3 months after the blast injury.	8 Months after the blast injury, the glucose intolerance persists. We decided to treat two subcohorts with an SGLT2 inhibitor and find that this treatment completely reversed the glucose intolerance.Glucose tolerance at 3 months after the blast injury.

When we originally submitted the application we had found that the GR blocker mifepristone ameliorated the TBI induced glucose tolerance and hence we proposed to study this drug as a therapeutic intervention to ameliorate TBI induced glucose intolerance. In independent studies we have found that glucose toxicity (effect of hyperglycemia, which can be caused by glucose intolerance) that worsens metabolic control and causes brain inflammation, can be ameliorated by a drug that allows one to excrete glucose through the urine, an Sglt2 inhibitor, prevented the brain inflammation. Hence we tested if an Sglt2 inhibitors ameliorated TBI induced glucose intolerance. We find that the glucose intolerance and the prediabetes is completely reversed through an SGLT2 inhibitor, and that the effect is much more profound than that of mifepristone. Hence, we would like to replace studies of mifepristone with Sglt2 inhibitors as a therapeutic option for TBI induced prediabetes. Because sglt2 Inhibitors seem to be much more potent for TBI induced prediabetes and are also very safe (more so than mifepristone) and are already commonly used for diabetes therapy, this also makes clinical sense. It also could lead to a translational trial in humans with TBI as we have discussed.
The second change we would like to make is based on our preliminary experience with the quite old rats that we planned to study by clamps to assess insulin action. In preliminary studies we find that the catheter surgery (done in preparation for the euglycemic clamp studies) has a high mortality. This is likely due to the old age of these animals (usually we study 3 month old Sprague-dawley rats) and in these studies we are using Long Evans rats and so either the age or the strain makes these rats very stress susceptible. So the concern is that a. the mortality is high if we do the clamps as proposed and b. because the quality of the data is not as robust as it usually is when we perform clamp studies and hence the scientific value will be low.
Instead we will metabolically characterize these rats with glucose and insulin tolerance tests, and perform insulin signaling studies to define insulin action. In addition we will perform careful molecular analysis of tissues such as adipose and liver, and study brain inflammation through IHC and transcriptional studies and the effects of the Sglt2 inhibition on all of these read outs. The hope is that by reducing brain inflammation with an SGlt2 inhibitor we would also reduce some of the post traumatic stress disorder that these TBI rats suffer. To study the latter we would perform some initial neurocognitive testing such as the splash test.

Opportunities for training and professional development was provided to the fellow supported by this awards Dr. Claudia Liberini as well as a summer student during the summer. This work gave Dr Liberini the opportunity to acquire the skills to perform euglycemic clamp studies in rats as well as perform insulin signaling studies, both methods and procedures that she had not performed before she joined this project.

The results so far have been distributed during talks presented at other institutions such as the Mayo Clinic, the NIH /Niddk intramural program, and Diabetes Grand rounds here at Sinai and at Einstein.

During the year next reporting period, we will finish the project as proposed.

4. Impact

The biggest impact of these studies to be in the realization that TBI through brain damage impairs metabolic control and increases the risk for type 2 diabetes. This is an important Public Health insight that should guide providers of patients that suffered TBI and makes screening for diabetes imperative. This is a completely novel insight that before these Studies, had not been realized.

Secondly, they give hope to those that may suffer from metabolic disease and have TBI as we have begun to identify drugs that seem to be promising in treating TBI induced metabolic disease.

5. Changes/Problems

Studies that have not completed and aim to replace with the below studies are: The euglycemic clamps from subtask 3 of aim 1 and from Subtask 2 from Aim 2. We further have forgone the treatment with mifepristone.

We would like to replace studies of mifepristone with Sglt2 inhibitors as a therapeutic option for TBI induced prediabetes. Because sglt2 Inhibitors seem to be much more potent for TBI induced prediabetes and are also very safe (more so than mifepristone). SGLT2 inhibitors are already commonly used for diabetes therapy, this makes clinical sense. It also could lead to a translational trial in humans with TBI as we have discussed. Preliminary data illustrating the benefit of dapagliflocin is shown above.
The second change we would like to make is based on our preliminary experience with the quite old rats that we planned to study by clamps to assess insulin action. In preliminary studies we find that the catheter surgery (done in preparation for the euglycemic clamp studies) has a high mortality. This is likely due to the old age of these animals (usually we study 3 month old Sprague-dawley rats) and in these studies we are using Long Evans rats and so either the age or the strain makes these rats very stress susceptible. So the concern is that a. the mortality is high if we do the clamps as proposed and b. because the quality of the data is not as robust as it usually is when we perform clamp studies and hence the scientific value will be low.
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6. Products

None as of yet, but a publication of these findings is under preparation.

7. Participants & Other Collaborating Organizations

No change

8. Special Reporting Requirements

none

9. Appendices

none