AWARD NUMBER: W81XWH-15-1-0550

TITLE: TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains

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REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2016	Annual	15 Sept 2015 - 14 Sept 2016

4. TITLE AND SUBTITLE
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-1-0550

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Columbia
630 West 168th Street, Box 49
New York, NY, 10032-3702

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of the current study is to demonstrate that blast-induced traumatic brain injury (TBI) and Alzheimer's disease (AD) lead to similar biochemical changes in tau that increase its toxicity and contribute to cognitive and electrophysiological impairments. Specifically we will test the hypothesis that 1) blast-induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments; 2) the formation of soluble tau aggregates contributes to cognitive impairments associated with both blast-exposure and AD; 3) an increase in tau phosphorylation contributes to cognitive impairments associated with both blast-exposure and AD. During the last year we have worked on the first point of the hypothesis. We have found that administration of tau purified from shockwave-exposed mice onto wild-type mice markedly reduces 1) memory including contextual fear memory and spatial memory, and 2) long-term potentiation, a type of synaptic plasticity thought to underlie learning. Additional, planned behavioral and electrophysiological experiments are ongoing that will allow us to complete our test of the hypothesis and provide new insights into the similarities in tau changes between TBI and AD.

15. SUBJECT TERMS Tau, contextual fear memory, spatial memory, synaptic plasticity, traumatic brain injury, Alzheimer's disease					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	13	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1 INTRODUCTION

Although epidemiological studies find a strong link between TBI and an increased risk for dementia (i.e. AD), the molecular mechanisms responsible remain unclear. Evidence continues to accumulate highlighting the similarities between AD and post-TBI pathologies. A similarity between TBI and AD-related neurodegeneration exists at the histological level where both are characterized by the presence of aggregates of hyperphosphorylated forms of the microtubule associated protein, tau [1, 2]. Tau abnormalities and neurofibrillary tangles (NFTs), the classical histopathological hallmark of AD consisting of insoluble aggregated tau, have been reported in multiple animal models of TBI [3-6]. NFTs like those in AD have been reported after a single TBI in humans [7, 8]. Evidence also exists in favor of a link between TBI and amyloid-β (Aβ), the amyloid precursor protein (APP) proteolytic fragment thought to act upstream of tau in AD [9] that deposits in amyloid plaques. After experimental TBI in animal models, Aβ accumulated in injured neurons and axons both acutely [4, 5, 10, 11] and chronically [12]. Similar deposits of Aβ have been observed after a single TBI in humans [7, 8, 13]. The proposed research project seeks to define the toxic molecular mechanism leading to TBI and AD.

2 KEYWORDS

Tau, contextual fear memory, spatial memory, synaptic plasticity, traumatic brain injury, Alzheimer's disease

3 ACCOMPLISHMENTS

a. What were the major goals?

Work performed during this first year of funding aimed to address Aim 1 of the project "Test the hypothesis that blast induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments". Specifically, we had to compare within month 10 toxicity of tau purified from shockwave exposed and sham exposed wild type mice

b. What was accomplished under these goals?

We have found that administration of tau purified from shockwave-exposed mice onto wild-type mice markedly reduces 1) memory including contextual fear memory (Fig. 1) and spatial memory (Fig.2), and 2) long-term potentiation, a type of synaptic plasticity thought to underlie learning and memory (Fig. 3).

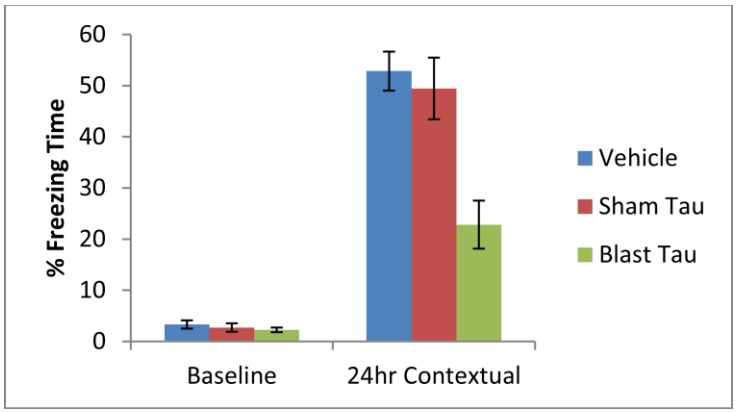

Fig. 1: Contextual fear memory is impaired following injection of tau from shockwave exposed mice onto hippocampus. The percent freezing time in the group injected with tau from shockwave exposed mice was significantly lower than in the vehicle and sham tau groups in the contextual fear conditioning (n=10 for all groups of mice; $p<0.05$, Two way ANOVA, Bonferroni post hoc).

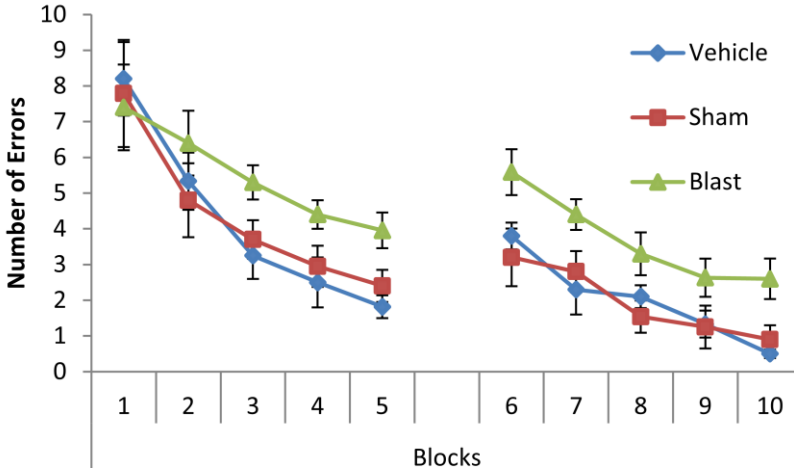

Fig. 2: Spatial memory is impaired following injection of tau from shockwave exposed mice onto hippocampus. Performance in the 2-day radial arm water maze was significantly lowered in the group of mice injected with tau from shockwave exposed mice compared to vehicle and sham tau groups (n=10 for all groups of mice; $p<0.05$, Two way ANOVA, Bonferroni post hoc).

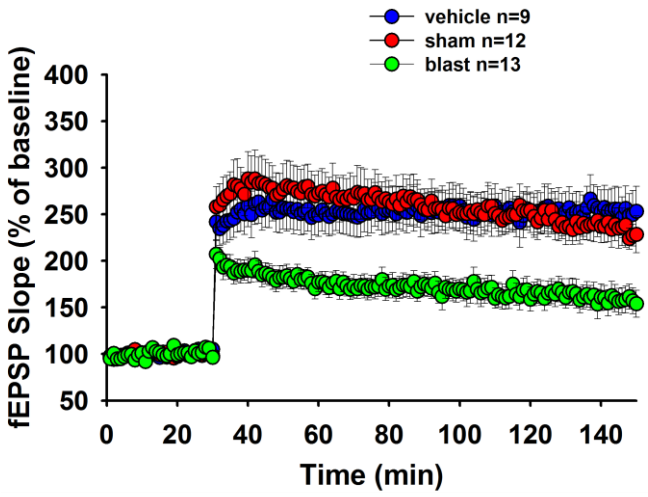

Fig. 3: Long-term potentiation (LTP) is impaired following hippocampal slice perfusion with of tau from shockwave exposed mice. Tetanus induced long-lasting enhancement of synaptic strength was significantly lowered in slices perfused with tau from shockwave exposed mice compared to vehicle and sham tau slices (n corresponds to number of slices per group of mice; $p<0.05$, Two way ANOVA).

c. What opportunities for training and professional development has the project provided

Nothing to Report"

d. How were the results disseminated to communities of interest?

Nothing to Report"

e. What do you plan to do during the next reporting period to accomplish the goals?

We will continue working on the hypothesis that blast induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments". Specifically, we will test 1) the tau-dependency of the behavioral and electrophysiological impairments caused by application of purified tau preparations; and 2) the dose-dependence of tau-induced behavioral and electrophysiological impairments. In addition we will start working on another major goal of the project "Test the hypothesis that the formation of soluble tau aggregates contributes to cognitive impairments associated with both blast-exposure and AD." by testing for a similar increase in tau aggregates in homogenates prepared from shockwave vs. sham-exposed mouse brains and AD vs. healthy control human brains. Finally, we will start working on the last goal of the project "Test the hypothesis that a similar increase in tau phosphorylation contributes to cognitive impairments associated with both blast-exposure and AD." by testing for similar differences in tau phosphorylation in homogenates prepared from shockwave vs. sham-exposed mouse brains and AD vs. healthy control human brains.

4 IMPACT

a. What was the impact on the development of the principal discipline

Our studies have identified tau as a culprit in TBI.

b. What was the impact on other disciplines?

Our studies indicate a very interesting similarity between TBI and Alzheimer's disease with tau being similarly affected in the two conditions and being held responsible for the cognitive problems linked with them.

c. What was the impact on technology transfer?

Nothing to Report"

d. What was the impact on society beyond science and technology?

Our studies are important as they are likely to impact the development of therapies against TBI and Alzheimer's disease.

5 CHANGES/PROBLEMS

No changes, nor problems

6 PRODUCTS

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project

b. Name:	Ottavio Arancio
Project Role:	Principle Investigator
Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	12
Contribution to Project:	Dr. Arancio has supervised the whole project, insuring that the project is conducted in an efficient manner and with the highest scientific standards.
Funding Support:	National Institute of Health, Alzheimer's Drug Discovery Foundation

Name:	Russell Nicholls
Project Role:	Co-PI
Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	12
Contribution to Project:	Dr. Nicholls has provided his expertise on tau biochemistry and behavioral assessment. He has purified tau from sham and blasted mice.
Funding Support:	National Institute of Health

Name:	Barclay Morrison
Project Role:	Co-PI

Researcher Identifier (e.g. ORCID ID):	1234567
Nearest person month worked:	12
Contribution to Project:	Dr. Morrison has provided his expertise on traumatic brain injury and usage of blast tube.
Funding Support:	NIH

Name:	Sowmya Sundaresh
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Sowmya has performed the behavioral experiments
Funding Support:	

Name:	Edward Vogel
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Dr. Vogel has contributed to blasting animals.
Funding Support:	

Name:	Omar Yassin
Project Role:	Technician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Mr. Yassin has contributed to the electrophysiological experiments.
Funding Support:	

c. Has there been a change in the active or other support of the PD or key personnel during the last reporting period?

ARANCIO, OTTAVIO

ACTIVE

W81XWH-15-1-0550 (Arancio, PI) 09/15/2015 - 09/14/2018 1.20 cal mo
DoD
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
This project seeks to determine changes in tau status that are evoked by traumatic brain injury.

R01NS049442 (Arancio, PI) 07/01/11 - 04/30/17 3.00 cal mo
NIH
SUMOylation and Amyloid-beta elevation
This project will determine whether and how amyloid-beta alters SUMOylation, a recently discovered post-translational modification that has been shown to regulate many cellular processes, in amyloid-beta induced synaptic and memory dysfunction. If this project will be successful, SUMOylation will become a possible target for developing therapies against Alzheimer's disease.

U01AG043415 (Watterson, co-PI) 09/30/12 - 05/31/17 0.60 cal mo
NIH
Preclinical Alzheimer's disease drug development of novel MAPK inhibitor
The goal of this project is to perform preclinical development studies necessary for obtaining an Investigational New Drug (IND) approval for a New Molecular Entity (NME) as defined by FDA.

R01NS092045 (Arancio, PI) 02/15/15-12/31/19 1.20 cal mo
NIH/NIND
The regulation of beta-amyloid sensitivity and Alzheimer's related impairments by PP2A

This project seeks to examine the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer's disease patients.

R01AG049402 (Arancio, PI) 09/01/2015 - 03/31/2020 1.20 cal mo
NIH/NINDS
Extracellular tau oligomers and Alzheimer disease
This project seeks to establish extracellular soluble species of tau as major toxic species responsible for reduction of synaptic plasticity and memory in Alzheimer's disease.

20160904 (Arancio, PI) 10/15/2016 – 10/15/2017 0.12 cal mo
Alzheimer's Drug Discovery Foundation
A Novel Isoform Selective Kinase Inhibitor Candidate with In Vivo Efficacy in Two AD Models: Proposal for GLP Tox Package for Phase 1 IND
The goal of this project is to perform a toxicological study on compound MW150 in view of filing an IND with FDA

PENDING

R01000000 (PI: Wai Haung Yu) 07/01/2017-06/30/2022 0.51 cal mo
NIH
GBA-based lysosomal dysfunction and transmission of proteinopathy, and cognitive loss
Examine why a gene called GBA can increase the risk of cognitive decline and another gene and protein called tau is involved in this process leading to a disease spectrum with association with other cognitive-based neurodegenerative diseases like Alzheimer's disease or fronto-temporal lobar degeneration.

DOH01-STEM5-2016-00108 (Arancio, PI) 07/01/2017 – 06/30/2019 0.96 cal mo
DOH

The overall scope of this project is to develop a method for reproducible production of mature human neurons in a more physiological system that have the capability of undergoing synaptic plasticity.

NICHOLLS, RUSSELL

ACTIVE

W81XWH-15-1-0404 (Nicholls, PI) 09/01/2015 – 02/28/2017 3.0 cal mo
DoD
Retinoid X receptor gamma s a potential therapeutic target for fragile X syndrome
The proposed research project addresses the “fragile X syndrome” topic area by seeking to understand the molecular mechanisms that underlie the disease and test a new therapeutic approach for its treatment.

W81XWH-15-1-0550 (Arancio, PI) 09/15/2015 - 09/14/2018 1.20 cal mo
DoD
TBI-Induced Formation of Toxic Tau and Its Biochemical Similarities to Tau in AD Brains
This project seeks to determine changes in tau status that are evoked by traumatic brain injury.

R01NS092045 (Arancio, PI) 02/15/15-12/31/19 3.96 cal mo
NIH/NINDS
The regulation of beta-amyloid sensitivity and Alzheimer's related impairments by PP2A
This project seeks to examine the ability of the serine/threonine protein phosphatase, PP2A, to control sensitivity to the pathological actions of beta-amyloid, a protein that accumulates in the brain of Alzheimer’s disease patients.

R01AG049402 (Arancio, PI) 09/01/2015 - 03/31/2020 2.44 cal mo
NIH/NINDS
Extracellular tau oligomers and Alzheimer disease
This project seeks to establish extracellular soluble species of tau as major toxic species responsible for reduction of synaptic plasticity and memory in Alzheimer’s disease.

PENDING

R2100000 (Nicholls, PI) 07/01/2017 – 06/30/2019 1.20 cal mo
NIH
A role for viral PP2a inhibition in Alzheimer’s disease.
This proposal seeks to address this gap in our understanding by examining the possible contribution of viral proteins that inhibit the serine/threonine protein phosphatase, PP2A, to Alzheimer’s disease.

R0100000 (Mouradian, PI) 04/01/2017 – 03/31/2022 1.20 cal mo
NIH
PP2A Dysregulation in the Pathogenesis of alpha-Synucleinopathies
The principal aim of the proposed research is to investigate the role that protein phosphatase 2A (PP2A) mediated dephosphorylation of □-synuclein plays in the molecular etiology of □-synucleinopathies

OVERLAP
None.

MORRSION, BARCLAY
ACTIVE

AZ140095 PI: Arancio, O. 09/15/2015 09/14/2018 0.96 cal mo
DoD
“TBI-induced formation of toxic tau and its biochemical similarities to tau in AD brains” The purpose of this grant is to explore the molecular mechanisms that underlie the cognitive decline and mental health problems resulting from repetitive traumatic brain injuries.
Aim 1: Test that blast-induced TBI leads to the production of a toxic form of tau that contributes to cognitive and electrophysiological impairments
Aim 2: Test that blast-induced TBI leads to the production of a toxic form of tau, similar to that found in AD brains
Aim 3: Test that the physiological response to and the production of toxic tau is regulated by tau dephosphorylation
This is the current proposal in question. Grant officer:
Elvera M. Messina
US Army Medical Research Acquisition Activity 820 Chandler Street
Fort Detrick MD 21702-5014

58155-LS-MUR PI: Meaney, D.F. 09/01/2010 – 08/31/2016 2.4 cal mo
DoD: Multi University Research Initiative (MURI)
"Blast Induced Threshold for Neural Networks (BITNeT)"

The purpose of this grant is to determine thresholds for brain tissue to blast- induced injury and neuronal dysfunction.
Aim 1: Examine the multiscale physics of blast wave transmission to the brain
Aim 2: Define the threshold for alterations in synaptic function, neural connectivity, and neuronal loss after scaled blast loading
Aim 3: Identify the transition point between synaptic/cellular changes and larger scale, circuit dysfunction, leading to blast thresholds for altering circuit function
Aim 4: Correlate changes at the synapse and circuit level to corresponding neurobehavior deficits in animals

No overlap as the current proposal seeks to understand a link between blast TBI and Alzheimer's disease.

R43 NS086118 PI: Graudejus, O. 7/01/14 – 12/31/2016 1.20 cal mo
NIH: NINDS
Lab-To-Marketplace: Commercialization of a stretchable microelectrode array"
The purpose of this grant is to develop a commercially viable process for producing stretchable microelectrode arrays so that they may be sold for research purposes.
Aim 1: Fabrication of a high resolution sMEA with a high yield, low cost process Aim 2: Evaluation of the sMEAs for TBI applications

PENDING

PI: Morrison III, B. 4% 11/01/2016-10/31/2018 0.48 cal mo
Army Research Laboratory
"Long term potentiation deficits after repetitive primary blast"
The purpose of this grant is to determine thresholds for brain tissue to blast- induced injury and neuronal dysfunction after repetitive blasts.
Aim 1: To better identify the time line of vulnerability and spontaneous recovery between two mild blasts
Aim 2: To develop tolerance criteria for LTP impairment based on blast severity and the interval between those blasts
Aim 3: To explore the effect of three or more mild blasts on outcome

OVERLAP

None.

d. What other organizations were involved as partners?

No other organizations were involved as partners in this funding period

8. SPECIAL REPORTING REQUIREMENTS

Not applicable

9. APPENDICES

List of references

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