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Abnormalities in Human Brain Creatine Metabolism in Gulf War Illness Probed with MRS

Principal Investigator: BRIGGS, RICHARD W

Institution Receiving Award: TEXAS, UNIVERSITY OF, SOUTHWESTERN MEDICAL CENTER AT DALLAS

Program: GWIRP

Proposal Number: GW110034

Funding Mechanism: Investigator-Initiated Research Award

Partnering Awards:

Award Amount: \$878,051.00

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PUBLIC ABSTRACT

Scientific Objective and Rationale: The goal of this research is to measure amounts of the molecules phosphocreatine (PCr) and free creatine (Cr) in brains of Gulf War Illness Veterans and to measure an important parameter of these molecules that affects accurate quantification, using phosphorus (^{31}P) and proton (^1H) magnetic resonance spectroscopy (MRS). This will add more detailed and specific information about the previously reported abnormal levels of these metabolites in brains of ill Gulf War Veterans, validating this potential diagnostic marker and providing better understanding of underlying pathophysiology. Size and motion of molecules detected in MRS and interaction with nearby ions and molecules affect parameters called relaxation times, which in turn affect signal intensities. Accurate quantification of amounts of biochemicals in the brain or other body tissue by MRS requires measuring these relaxation times or acquiring MRS data under conditions which makes the dependence of the MRS signals on relaxation times negligible, which is often difficult or impractical.

Because total creatine (tCr) concentration is typically constant even though amounts of PCr and Cr may vary individually, the tCr signal is often used in ^1H MRS as a concentration standard. Total creatine (tCr) is usually determined by ^1H MRS from the superimposed signals of the methyl (CH_3) groups of phosphocreatine (PCr) and free creatine (Cr), without measuring relaxation times. However, it has recently been reported that T2 values for the overlapping PCr and Cr methyl peaks constituting the tCr methyl differ nearly three-fold at 1.5 Tesla (T). This means that subject group differences in relative amounts of PCr and Cr or interconversion of PCr and Cr could lead to differences or changes in the tCr peak intensity and errors in quantification. Group differences or temporal changes in PCr and/or Cr T2 values could further complicate matters, creating inaccuracies and ambiguities when the tCr resonance is used as an internal concentration reference or standard.

Applicability of Research: Types of patients it will help and how: This research will directly benefit ill Veterans of the 1991 Persian Gulf War by better characterizing biochemical abnormalities in their brains.

Potential clinical applications, benefits, risks: Better understanding of how brain metabolism is affected by Gulf War illness will inform treatment strategies. The only potential risk to this study is the need to exclude subjects with metal implants which are contraindications for MR scans.

Projected time to achieve a patient-related outcome: This project will provide useful new knowledge about important brain biochemicals by the end of the two-year study.

Interim outcomes, if too basic for clinical applicability: The new information about compromised brain metabolism in ill Gulf War Veterans

obtained by this study will enable more certain interpretation of the 1H MRS data in Gulf War Illness, increase the usefulness of MRS data as a diagnostic biomarker, and help in data-driven approaches to treatment and therapy.

Likely contributions in advancing GWI research: This project will extend the original 1H MRS studies of brain metabolites in Gulf War Illness, including our recent follow-up studies showing persistent brain abnormalities in ill Gulf War Veteran, and will enable more certain interpretation of and conclusions from 1H MRS data. This additional knowledge about a well-defined, well-characterized previously studied representative Veteran sample will increase the potential of 1H MRS for providing a diagnostic biomarker. This study will also obtain the first 31P MRS data from brains of Gulf War Veterans, which will provide new information about effects of Gulf War Illness on levels of the phosphate-containing biochemicals adenosine triphosphate (ATP) and inorganic phosphate (Pi) and on intracellular pH and magnesium ion (Mg²⁺) concentrations.

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