Role of Metabolomics in Traumatic Brain Injury Research

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KEYWORDS

• Small molecules • Spectroscopy • Metabolism • Principal component analysis • Biomarkers

KEY POINTS

- Metabolomics is the study of the small molecules, which are reactants, intermediaries, and end products of biological processes. Metabolomics can define healthy and disease states. The genome and proteome, along with environmental factors, contribute to the metabolome. Metabolomic studies can be untargeted or targeted.
- Metabolomic analytical techniques include nuclear magnetic resonance spectroscopy and mass spectroscopy, including gas chromatography or liquid chromatography.
- The following 3 major components are required for conducting metabolomics studies: good specimens collected in an accepted manner; a strong analytical facility; and knowledgeable statisticians.
- Common data elements, biobanks, and collaborations/multidisciplinary teams will be necessary to produce meaningful results.
- Heterogeneity of disease and progressive nature mean that applying metabolomics to predicting secondary events and/or long-term risks could be highly impactful.

INTRODUCTION

The explosion of "omics" in various fields of biology has led to new and exciting areas of research. In addition to genomics and proteomics, metabolism, or the biology of small molecules, was an early adapter to the "omics" mania. The overarching aims of "omics" studies are to characterize large collections of molecules and describe their role(s) in biological systems during normal health and disease. The number of molecules quantified in each sample can easily outnumber the subjects, and sophisticated analytical and statistical techniques must be used to exploit the rich information found in the biological specimens. The goal of this article is to briefly describe the current state-of-the-art regarding metabolomics and frame it in the context of traumatic brain injury (TBI).

Metabolomics is concerned with a diverse set of endogenous, low-molecular-weight biochemicals that serve as substrates and intermediates of

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biochemical pathways and/or as signaling molecules. Within the systems biology approach, metabolomics is at the top of the biological continuum and represents a snapshot of the systemic environment created by the genome, transcriptome, and proteome.[1] Following TBI, particularly in the acute setting, biochemical homeostasis is disrupted and reflected in the metabolome.

There are 2 general designs in metabolomics studies[2]:

- Untargeted, or exploratory, metabolomics studies seek to identify a global metabolite fingerprint by quantifying as many metabolites as possible in the same biological sample.
- Targeted metabolomics studies limit the number of metabolites included in analysis to improve data interpretation and answer well-defined clinical questions.

Untargeted studies are used to test whether 2 groups (eg, healthy subject vs TBI patient) can be discriminated from one another on the basis of biofluid metabolites by including as many metabolites as possible no matter the biochemical pathway involved, independent of molecular identity, and assuming bias-free metabolite quantification. Targeted studies will focus on a set of endogenous metabolites and/or may include exogenous isotopically labeled metabolites to track biochemical pathway activity.

Study of the small molecules that enter biochemical pathways has a long history in TBI research, although application of modern metabolomics techniques to these research questions is sparse. For example, glucose and lactate dynamics in the acute period have been studied with respect to outcome, to disease progression, and to mechanisms.

In the first week after injury, hyperglycolysis was reported to occur in 56% of patients.[3] The hyperglycolytic transient response increases cerebral glucose utilization but, despite adequate oxygenation, is not matched by an increase in the metabolic rate of oxygen. The high energy demands are caused by TBI-induced ionic and neurochemical imbalances,[4–6] and increased nonoxidative metabolism of glucose produces excess lactate. High-lactate cerebral spinal fluid (CSF) concentrations have been associated with cerebral lactic acidosis and, when prolonged, with poor outcomes.[7–9]

Global and regional hyperglycolysis are followed by global cerebral metabolic depression, independent of level of consciousness, that can persist for a month following injury.[10–12] Cerebral uptake of both oxygen and glucose is depressed compared with healthy adults, and glucose is relatively more depressed.

Throughout the acute after-injury period, TBI causes metabolic crisis that is long lasting and unresolved by standard clinical resuscitation and control of intracranial pressure (ICP).[13,14] Cerebral metabolic crisis is the coincidence of low cerebral glucose concentration and high lactate:pyruvate ratio (LPR). Nonischemic metabolic crisis results from mitochondrial dysfunction and is exacerbated by and/or increases risk for secondary insults, and prolonged acute metabolic crisis is linked to increased brain atrophy 6 months following injury.[15–18]

In a later publication on blood glucose, lactate, and oxygen, most TBI patients showed cerebral lactate uptake (arteriovenous difference >0) at least once, and the patients with favorable outcome were associated with cerebral lactate uptake at moderately elevated arterial lactate concentrations.[19] The ability of the injured brain to oxidize lactate, and the potential benefits associated with lactate as a cerebral fuel, was recently investigated using the dual isotope tracer technique.[20,21]

Based on the prior interest in small molecules in TBI research, metabolomics is well suited to expand the current understanding of dysfunctional cerebral metabolism.

DISCUSSION

Biospecimen Sources in Traumatic Brain Injury

Table 1 summarizes possible biospecimens for use in metabolomics studies in TBI research. Targeted metabolomics analysis of cerebral tissue has been applied to TBI research on animal models.[22–28]

The range of biofluids typically used for metabolomic analysis includes blood (plasma or serum), urine, saliva, CSF, and microdialysate. Standard operating procedures for collecting and storing biofluids should be followed.[29,30]

Cerebral microdialysate studies based on the hourly metabolite measurements could be considered a type of metabolomics study.[31,32] Metabolic crisis is defined as low microdialysis glucose (less than 0.8 mM considered abnormal) coincident with a high LPR (greater than 40 critical; greater than 25 abnormal) and has been associated with poor recovery.[13–18] Glutamate, glycerol, and urea are also available with the ICSUSflex Microdialysis Analyzer (M Dialysis AB, Stockholm, Sweden), and microdialysis is considered a valuable tool in the neurologic intensive care unit (ICU).[33] The Cambridge group has published research using pooled cerebral microdialysate (generally over a period of 24 hours) and has introduced tracer