High Throughput Metabolite Profiling Identifies Plasma Anandamide as a Biomarker of Functional Outcome After Aneurysmal Subarachnoid Hemorrhage

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CNS 2017 ANNUAL MEETING
BOSTON, MASSACHUSETTS
OCTOBER 7–11, 2017

Introduction

The quantification of metabolites in plasma samples in patients with aneurysmal subarachnoid hemorrhage (aSAH) can highlight important alterations in critical metabolic pathways. As metabolites reflect changes associated with disease conditions, metabolite profiling (metabolomics) can identify candidate biomarkers for disease and potentially uncover pathways for intervention.

Methods

We performed high throughput metabolite profiling (Figure) across a broad spectrum of chemical classes (173 metabolites) on plasma samples taken from 119 patients with aSAH. Samples were drawn at 3 time points following ictus: 2-4, 7-10, and 12-14 days. Univariate and logistic regression analyses were performed to examine the relation of each metabolite with multiple outcome variables, including short- and long-term functional outcome (modified Rankin Scale, mRS).

Results

A good functional outcome (mRS 0-2) was found in 63.1% and 66.7% of patients at 30 and 90 days, respectively, following aSAH. Plasma concentrations of the endogenous cannabinoid anandamide during days 2-4 after aneurysmal SAH were decreased by 48.1% ($P < 0.0001$) and 57.6% ($P < 0.0001$) in patients with mRS 0-2 at 30 and 90 days, respectively. A similar statistical result was noted with plasma anandamide concentrations averaged across all time periods. Logistic regression further demonstrated that anandamide remained an independent predictor of functional outcome (30 days: $P = 0.04$; 90 days: $P = 0.03$), even after adjusting for other factors that influence outcome, including age, World Federation of Neurological Surgeons grade (WFNS), Fisher grade, and symptomatic vasospasm.

Conclusions

Decreased plasma anandamide following aSAH predicts a good functional outcome at 30 and 90 days. While a role for anandamide in aneurysmal SAH has not been previously reported, elevated anandamide levels have been implicated in neuronal apoptosis and cerebral edema in the acutely injured brain. These data highlight

Learning Objectives

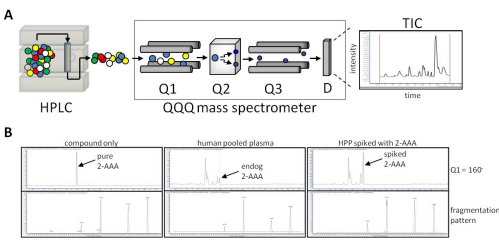
By the conclusion of this session, participants should be able to:

1) Describe the importance of elucidating the molecular and metabolic underpinnings of aneurysmal subarachnoid hemorrhage (aSAH).

2) Postulate a mechanism by which anandamide might influence functional outcome following aSAH.

3) Identify a treatment strategy for improving functional outcomes following aSAH based on the metabolic disturbances uncovered with metabolic profiling.

Figure



Conceptual workflow for metabolite profiling. (A) Following precipitation of protein, the complex matrix is first separated using Amide chromatography followed by tandem mass spectrometry to identify each metabolite. (B) The process for compound identification first involves tuning the instrument to purified compound (left panels). Human pooled plasma is then monitored using the optimized settings (middle panel). Isobaric contaminants demonstrate different retention times and peak identity is further confirmed by comparing fragmentation patterns with the pure compound. Finally, spiked compound is added to the pooled plasma to confirm proper retention time.

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