Brains, pains and sugar: an investigational approach of CSF metabolites in pain patients

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Introduction

Although molecular signatures of chronic pain have previously been identified in the CSF looking at small subset of markers (NGF, substance P, 5-HIAA) , examination of the high dimensional metabolome (N=300) in clinical populations has only recently become technically feasible. We report pilot data from a small clinical sample (N=27) of refractory patients.

Exploratory data analysis reviewed the correlation matrix defined by demographic variables (age, gender), structured symptoms checklists (disability, anxiety, depression, autism), concurrent medication use (antidepressants, stimulants, benzodiazepines, lithium, opioids, ketamine), chief complaint (pain, bipolar disorder) and a subset of 18 metabolic variables z-scores. These variables were selected out of the larger metabolome given frequency of appearance greater or lower than 2 z-scores in an individual patient metabolome profile.

Figure 1. The relevance of the biopsy

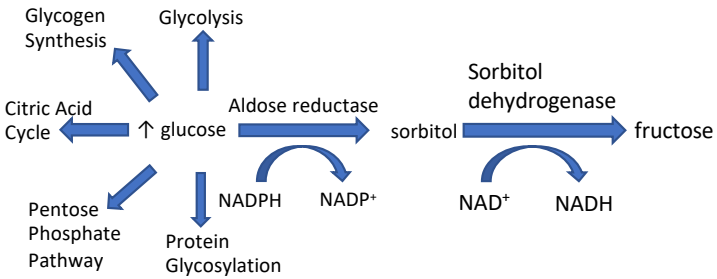

Figure 2. The polyol pathway

	Age	Gender	Pain	Opioid Use	Sorbitol	Fructose	Glucose
Age	--						
Gender	0.26	--					
Pain	0.11	-0.10	--				
Opioid Use	0.32	-0.08	0.47*	--			
Sorbitol	0.43*	0.15	0.45*	0.57**	--		
Fructose	0.12	-0.03	0.11	0.38	0.63**	--	
Glucose	0.31	0.39	0.33	0.36	0.70**	0.53**	--

Figure 3. Selected correlations from a preliminary analysis of thousands of metabolites in the CSF. Fructose is elevated independently of peripheral diabetes traits, age or gender across patient phenotypes.

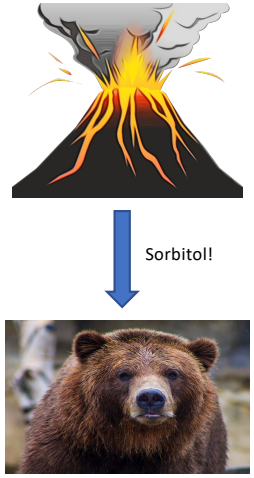

Figure 4. Sorbitol, in the context of starvation and dehydration, defends the osmotic balance in the brain.

Conclusion

Activation of the polyol pathway was uniquely seen in pain patients on opioids. Sorbitol z-scores correlated highly with both pain (r. = 0.451, p.=0. 018) and opioid use (r. =0.573, p. =0.002). Upstream (glucose) and downstream metabolites (fructose) had consistent r. values for both pain (glucose r. = 0.33, fructose r. = 0.11) and opioid use (glucose r.= 0.36, fructose r. = 0.38) although p. values were less compelling (3/4 < p. = 0.1).

Although direction of causation cannot be established with correlational analysis, there is a wealth of evidence implicating polyol pathway activation in painful diabetic neuropathy, subtypes of Charcot-Marie-Tooth Disease, leukoencephalopathy in bipolar disorder, and disability status in multiple sclerosis. Further research is indicated to replicate exploratory univariate analysis, create more sensitive and robust multivariate tools, define possible predictive validity for opioid and/or aldose reductase inhibitor response in drug-naive patients, and potentially link this clinical data with basic science findings on TRP regulation of the sickness behavioral response driven by osmolality changes during hibernation and/or starvation.