Computational prediction of changes in brain metabolic fluxes during Parkinson’s disease from mRNA expression

Farahaniza Supandi¹,²*, Johannes H. G. M. van Beek¹,³

¹ Department of Clinical Genetics, VU University Medical Centre, Amsterdam, the Netherlands, ² Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia, ³ Department of Experimental Vascular Medicine, Academic Medical Center, AZ Amsterdam, the Netherlands

* farahaniza@um.edu.my

Abstract

Background

Parkinson’s disease is a widespread neurodegenerative disorder which affects brain metabolism. Although changes in gene expression during disease are often measured, it is difficult to predict metabolic fluxes from gene expression data. Here we explore the hypothesis that changes in gene expression for enzymes tend to parallel flux changes in biochemical reaction pathways in the brain metabolic network. This hypothesis is the basis of a computational method to predict metabolic flux changes from post-mortem gene expression measurements in Parkinson’s disease (PD) brain.

Results

We use a network model of central metabolism and optimize the correspondence between relative changes in fluxes and in gene expression. To this end we apply the Least-squares with Equalities and Inequalities algorithm integrated with Flux Balance Analysis (Lsei-FBA). We predict for PD (1) decreases in glycolytic rate and oxygen consumption and an increase in lactate production in brain cortex that correspond with measurements (2) relative flux decreases in ATP synthesis, in the malate-aspartate shuttle and midway in the TCA cycle that are substantially larger than relative changes in glucose uptake in the substantia nigra, dopaminergic neurons and most other brain regions (3) shifts in redox shuttles between cytosol and mitochondria (4) in contrast to Alzheimer’s disease: little activation of the gamma-aminobutyric acid shunt pathway in compensation for decreased alpha-ketoglutarate dehydrogenase activity (5) in the globus pallidus internus, metabolic fluxes are increased, reflecting increased functional activity.

Conclusion

Our method predicts metabolic changes from gene expression data that correspond in direction and order of magnitude with presently available experimental observations during Parkinson’s disease, indicating that the hypothesis may be useful for some biochemical