Investigating brain regional variation under adult onset hypothyroidism in a mouse model using GC-MS metabolomics

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ABSTRACT

The mammalian brain is a highly complex organ that integrates multiple regions with diverse functional roles, biochemical characteristics and physiological dynamics. To-date, the study of brain biochemistry is mainly studied with respect to few selected "biomarker" molecules in specific brain region(s) considered to be correlated with the investigated physiological conditions. However, there is the need to study brain physiology under deficiency in a systemic and systematic way in the context of brain regional variation. In this project, we investigate the effect of adult onset hypothyroidism (AOH) on brain metabolic physiology. The brain had for long been considered as metabolically nonresponsive to perturbations in the thyroid hormone (TH) levels and thus was not among the main tissues studied in the context of hypothyroidism. However, a large number of studies have provided evidence that the mammalian brain is a TH target tissue. Still, the current knowledge about the effect of AOH on brain metabolism remains fragmented with respect to the brain regions that have been studied and the involved experimental setups. It is expected that a holistic view of the AOH effect on brain metabolic physiology using omic analysis will enhance our knowledge about the disease.

The aim of the presented work is to study the metabolic physiology of the brain under AOH based on the integrated analysis of the metabolic profile of five brain regions, i.e. cerebral cortex, cerebellum, midbrain, striatum and hippocampus in both sexes of an AOH Balb-c/J mouse model. To enable our multi-organ analysis of AOH in these animals, heart and liver tissues were also collected. In this mouse model, AOH is induced chemically by administration of 1% w/v $KClO_4$ in the drinking water of 2 month old mice for 60 days. The metabolic profiles were measured using Gas Chromatography-Mass Spectrometry (GC-MS) metabolomics. Our results validated the significant variation in the metabolic profiles between the various brain regions, confirming the need for this variation to be considered in the interpretation of the metabolomic data in the context of AOH; the same holds true for sex differentiation. We are currently analyzing the effect of perfusion on the brain metabolic profile of AOH in the same mouse model and we intend to combine the observations in the brain with information from the metabolomic analysis of the peripheral tissues to obtain a more elaborate characterization of the brain metabolic physiology.

REFERENCES

[1] Constantinou C, Chrysanthopoulos PK, Margarity M, Klapa MI. 2011. GC-MS metabolomic analysis reveals significant alterations in cerebellar metabolic physiology in a mouse model of adult onset hypothyroidism. *J. Proteome Res*. 10:869-79.