

# Metabolomic Analysis of Adult Hypothyroidism Effects on Different Brain Regions

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Although hypothyroidism, as any other major metabolic disease to-date, is mainly considered with reference to its hallmark metabolites (thyroid hormones: T<sub>3</sub> and T<sub>4</sub>) biochemical pathways are not isolated systems. Rather, they are part of the integrated whole that constitutes human metabolism; the enzymes, cofactors, substrates, intermediate and final products as well as specific enzyme kinetics and many other factors influencing metabolic pathways' fluxes have been studied during the last century [2]. However, this knowledge is fragmented, as was the research on which it is based; the latter was mainly focused on specific aspects of enzyme activities or pathways, independent of metabolism as a whole.

High-throughput ('omics') techniques have revolutionized the way in which problems in life sciences, and especially metabolic disorders such as hypothyroidism, are now investigated. The rapidly emerging field of *metabolomics* can provide biological and medical sciences an integrated look at metabolism and how its defects could affect human health. Indeed, our previous studies have shown that hypothyroidism does affect major aspects of the cellular metabolic network activity of adult mouse cerebellum [3]. In addition, significant qualitative and quantitative differences in the metabolic profiles between adult mouse brain regions, which have also been observed in our group [4] imply differential response of these brain regions to deranged metabolism.

In this context, metabolomic profiling analysis using Gas Chromatography-Mass Spectrometry (GC-MS) was performed on cerebral cortex and cerebellum of adult hypothyroid mouse brain. The brains were isolated from 120-days old Balb-c mice, in which hypothyroidism had been induced by 60 days of treatment with 1% KClO<sub>4</sub> in their drinking water. The free polar metabolite content of the brain tissues was obtained by methanol/water extraction [5] and

subsequently derivatized to be run in the GC-MS [6]. The acquired datasets were appropriately normalized according to Kanani and Klapa [6] and analyzed using multivariate statistical analysis techniques. The derived results provide strong evidence of differential effects of hypothyroidism between adult mouse cerebral cortex and cerebellum metabolic network activities. These differences will be discussed in the context of the current knowledge regarding the cellular and molecular mechanisms of thyroid hormone depletion effect on brain function.

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