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Large-scale survey of metabolite concentrations in human, chimpanzee, macaque and Mouse tissues

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The metabolic processes that maintain our tissues' functionality and structure generate a large variety of metabolites. While differences in metabolite concentrations reflect differences in organization and functionality of tissues, nothing is presently known about metabolic changes specific to humans, as well as about overall extent of metabolic divergence among the mammalian species. Here, we conducted large-scale analysis of metabolite concentrations in the three brain regions (prefrontal cortex [PFC], primary visual cortex [V1] and cerebellar cortex [CBC]) and two non-neural tissues (skeletal muscle and kidney) of humans, chimpanzees, macaques and mice using a total of six mass spectrometry-based metabolomics approaches. In total we assayed 17,087 metabolite peaks, including 2,469 annotated ones in 365 tissue samples. In addition, transcript concentrations were measured in a subset of 120 tissue samples using RNA-sequencing (RNA-seq). We show that concentrations of 94% metabolites differed among tissues and 44% among species. Among tissues, 78% of hydrophobic metabolites showed brain-specific concentration profiles, while this proportion equaled 42% for hydrophilic metabolites. On the chimpanzee, macaque and mouse evolutionary lineages the extent of metabolic divergence scaled with the genetic distances in all five tissues. By contrast, on the human lineage metabolic divergence scaled with genetic divergence only in V1 cortex area and, to an extent, in kidney. PFC and muscle tissues showed 4-and 7-fold excess of metabolic changes one the human evolutionary linage compared to the chimpanzee one. These results were validated across multiple metabolic datasets and confirmed by expression of corresponding metabolic enzymes. Using macaques as a model system to test environmental effects of stress, diet and exercise on metabolite concentrations, we detected less than 1.2% of observed species-specific changes that could be attributed to these environmental factors. Human brain was previously shown to be a metabolically expensive organ compared to brains of other primates, which presumably reflects energetic cost of human cognitive capacities.

The large metabolic change we observe in the human muscle might represent the metabolic counter-balance of the expensive brain organ. Among the metabolites showing elevated concentrations in the human PFC we find overrepresentation of those involved in neural functioning and glutamate metabolism pathways. Among the metabolites showing decreased concentrations in human muscle we find overrepresentation of those involved in several energy pathways. We demonstrate the difference of the human and primate muscle strength in simple tests of pulling weights in which chimpanzee and macaque muscle corrected for the body mass shows a markedly higher performance compared to the human muscle.

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