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Identification of substrates in the brain of OCTN1/SLC22A4 based on untargeted metabolomics

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SLC22A4, also known as carnitine/organic cation transporter OCTN1 is ubiquitously expressed in the body. OCTN1 is functionally expressed in neurons, microglia, and neural stem cells in the brain, and may play a protective role in pathophysiological conditions via its *in vivo* substrate ergothioneine, a food-derived antioxidant. On the other hand, we have recently noticed that pentylenetetrazole-induced seizure was limitedly observed in *octn1* gene knockout (*octn1*$^{-/-}$) mice, and this may not be explained by the absence of this antioxidant. To find new OCTN1 substrates in the brain, we here conducted untargeted metabolome analysis using LC-TOF-MS. Hippocampus, cerebral cortex, and plasma of wild-type and *octn1*$^{-/-}$ mice were subjected to metabolomics, and 2,599, 2,676, and 1,697 ion peaks, respectively, were observed. Among them, five ion peaks with m/z 455, 426, 158, 154, and 144 exhibited at least two times difference between the two strains, only m/z 158 being found to be commonly lower in *octn1*$^{-/-}$ in all the samples. Time-dependent and saturable transport of chemically synthesized compound corresponding to this peak was observed in HEK293/OCTN1 cells. In addition, systemic elimination of this compound in *octn1*$^{-/-}$ mice was more rapid compared with wild-type. Thus, we have newly identified OCTN1 substrate in the brain.