1-LBS-05 Late-Breaking Session

QPRT Deficit Leads Motor and Cognitive Dysfunction through Increase of Oxidative Stress in the Dopaminergic Neuronal System by Quinolinic Acid

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Quinolinic acid phosphoribosyltransferase (QPRT) metabolizes quinolinic acid (QA) to nicotinamide adenine nucleotide (NAD^+) via kynurenine pathway. QA is a excitotoxic substance that activate N-methyl-D-aspertate (NMDA) receptors and NAD^+ is essential for cell survival. In this study, we evaluated QPRT knock out (KO) mice to explore the physiological role of QPRT in central nervous system. QPRT KO mice demonstrated motor deficits (decrease of locomotor activity, decrease of duration time to maintain balance on the rotarod, wide stance in footprint pattern test) and cognitive deficits (decrease of spontaneous alternation behavior in Y-maze test, and prolongation of latency to enter the target hole in the Barnes-maze test). But emotional change was not observed except for decrease in number of buried marbles in marble burying test. Dopaminergic dysfunction was observed in prefrontal cortex, nucleus accumbens and striatum of QPRT KO mice. Dopamine D_1 receptor agonist (SKF81297)-induced hyperactivity is not observed in QPRT KO mice. Dopamine D_2 receptor antagonist (raclopride)-induced catalepsy is more sensitive in QPRT KO mice. The activation of dopaminergic function by methylphenidate attenuated the impairment of short-term memory and hypoactivity of QPRT KO mice. QPRT KO mice showed increased level of QA in serum but normal level of NAD+ in brain. QA-mediated NMDA receptor signaling (phosphorylation of CaMK2 and activation of calpain) and oxidative stress were enhanced in prefrontal cortex, nucleus accumbens and striatum of QPRT KO mice. These results suggested that deficiency of QPRT lead motor and cognitive deficits associated with dopaminergic dysfunction via QA-induced calpain activation and oxidative stress.