



頭脳循環を加速する戦略的国際研究ネットワーク推進プログラム・特別講義  
(CBIR・ONSA 共催)

## Understanding the Roles for Serine Racemase and D-Serine in Normal Brain Function and Disease

演者

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日時

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会場

M&D タワー 2階 共用講義室 2

講演要旨

N-methyl-D-aspartate receptors (NMDARs) belong to the class of ionotropic glutamate receptors that are essential mediators of synaptic plasticity. These receptors require the concomitant binding of glutamate and a co-agonist, glycine or D-serine. D-serine is synthesized from L-serine by the enzyme serine racemase (SR). SR and D-serine are enriched in excitatory and inhibitory neurons of cortico-limbic brain regions, although reactive astrocytes express SR and D-serine under certain pathological conditions. There is substantial evidence that NMDAR hypofunction is a core pathophysiological mechanism underlying schizophrenia. Recent findings from genome wide association studies have implicated genes encoding proteins involved in glutamatergic neurotransmission with increased risk for schizophrenia, including SR. Mice lacking SR (SR<sup>-/-</sup>) exhibit NMDAR hypofunction and recapitulate many of the neuropathologies observed in schizophrenia. SR<sup>-/-</sup> mice have morphological brain abnormalities, diminished neurotrophic signaling, and impaired cognition. Treatment with D-serine or positive allosteric modulation of the metabotropic glutamate receptor 5 (mGluR5) in adulthood corrects the electrophysiological, neurochemical, structural, and cognitive deficits in SR<sup>-/-</sup> mice. As NMDARs are important for learning and memory, we have also begun to investigate whether fear conditioning engages the SR/D-serine system. We find that the acquisition and extinction of fear memory up-regulates SR and D-serine in the amygdala and other brain regions that mediate these behaviors. Furthermore, a functional SNP in the SRR gene is associated with post-traumatic stress disorder (PTSD) in humans. These findings have important implications for understanding D-serine mediated NMDAR plasticity in the amygdala and how this system could contribute to disorders with maladaptive fear circuitry.

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連絡先：精神行動医学分野

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