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Piccolo knockdown in the nucleus accumbens suppressed methamphetamine-induced alterations

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Abuse of psychostimulant is global problems, and methamphetamine (METH) is the most widely used. METH is known to modulate the function of dopamine (DA) neurons in the mesolimbic system, and in particular it projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) which has been implicated in reward. The mechanism of drug dependence is not yet known and there are currently no effective treatments, thus it is important to identify associated molecule. We identified the gene PCLO in NAc of mice which continuously treated with methamphetamine (METH). The protein encoding PCLO, Piccolo, exists in the active zone, and is thought to regulate exocytosis and endocytosis of synaptic vesicles by interacting with other proteins in active zone. Therefore, we injected an adeno-associated virus (AAV) vector into the NAc and generated Piccolo knockdown mice in the NAc (NAc-miPiccolo mice), and evaluated the effects for METH-induced alterations. As a result, significant suppression of METH-induced hyperlocomotion and CPP, and significant decrease in DA release were observed in NAc-miPiccolo mice. Next, noting that 95% of neurons in the NAc are GABAergic medium spiny neurons (MSNs), we measured the amount of GABA in the NAc using *in vivo* microdialysis, and the amount of intracellular GABA was significantly decreased in NAc-miPiccolo mice. Presynaptic protein, Piccolo, has important role for METH-induced behavioral and neurophysiological alterations and is expected to become the therapeutic target.