Dopamine 2016
Vienna, 5–8 September 2016

MEETING ABSTRACT

A18.16

Loss of PICK1 in mice causes hyperdopaminergia associated with enhanced dopamine release and attenuated behavioral response to cocaine

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Tuning dopaminergic signaling is critical for several physiological functions of the brain including motor behavior, reward and cognitive function. The presynaptic plasma membrane dopamine transporter (DAT) sequesters dopamine from the extracellular space, and thereby sustains physiological dopamine levels. DAT contains at its C-terminus a PSD-95/Discs-large/ZO-1 (PDZ)-domain binding sequence, shown to interact with the scaffolding protein, protein interacting with C-kinase 1 (PICK1). PICK1 regulates subcellular trafficking of its binding partners but the explicit role of PICK1 for DAT function and dopamine homeostasis has remained elusive. Here, we present a detailed investigation of the dopaminergic system in mice lacking PICK1. Compared to wild-type (WT) mice, we found that DAT surface expression was unaltered in striatal terminals from PICK1 knock-out (KO) mice together with DAT localization to membrane microdomains. However, PICK1 KO mice were characterized by hyperlocomotion and attenuated locomotor response to cocaine although unaltered postsynaptic dopamine receptor activation. Intriguingly, PICK1 KO mice showed increased levels of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis in striatum and elevated striatal dopamine content. Chronoamperometric recordings in striatum revealed elevated dopamine release in PICK1 KO mice supporting a hyperdopaminergic phenotype. PICK1 KO mice showed impaired behavioral sensitization to a cocaine-challenge and reduced chronic self-administration of cocaine suggesting long-term maladaptive plasticity changes. Lentiviral knock-down of PICK1 in midbrain dopaminergic cultures resulted in elevated TH expression and thus imply that PICK1 acts as negative regulator of dopamine synthesis. We infer that loss of PICK1 alters subcellular distribution of TH in striatum leading to elevated striatal dopamine content and development of a hyperdopaminergic phenotype.

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