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AKTing/acting up in the dopamine hypothesis of psychosis and probability-based decision-making: new insights and links from Akt1 mutant mice and schizophrenic patients

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Abnormalities in the dopamine (DA) system have long been implicated in the explanation of schizophrenia/psychosis, and the DA D₂ receptor continues to be the key target for many antipsychotics. AKT (protein kinase B) is a key signaling intermediate downstream of DA D₂ receptors, and its signaling cascade is important for the expression of DA-associated behaviors. Accumulating evidence from human genetic studies suggests AKT1 is one of susceptibility genes for schizophrenia and stimulation of PI3-kinase/AKT signaling pathway might be related to delusional ideation. “How does genetic deficit lead to DA dysfunction and psychotic phenomena?” is a million-dollar question. It was proposed that dysregulation of DA systems could alter the appraisal of stimuli through a process of aberrant salience and eventually lead to psychosis. Accordingly, the assessment of reward prediction error in decision-making could provide a potential behavioral index for dopaminergic activity in the brain that allows for the evaluation of psychosis. Taking advantage of probability-based decision-making and model-fitting, we tackled this issue in Akt1 mutant mice and schizophrenic patients. In the mouse studies, we examined the role of Akt1 in the regulation of DA sensitivity, motivational salience, and decision-making. We found that (1) Akt1 mutant mice revealed a sex- and region-specific effect in the regulation of DA-dependent behaviors and methamphetamine sensitivity; (2) mutant mice normally attributed their motivational salience to the stimulus but they updated their reward values more rapidly and have more exploratory decisions than controls in the probabilistic rewarding task; (3) age-specific effects of Akt1 on the regulation of striatal DA D₂ receptor activity using micro-PET scan; and (4) alterations of neural oscillations activity and event-related potentials in the striatum of Akt1 mutant mice during decision-making. In a similar vein, we developed a probabilistic rewarding task for schizophrenic patients and found that patients with low and high psychosis show higher learning rates and more exploratory decisions as we reported in Akt1 mutant mice. We also found that the degree of exploration increases with the severity of the psychotic symptoms. Together, our studies revealed epistatic effects of Akt1 variations on the regulation of DA-associated functions and provided a potential link from a genetic deficiency, to neurobiological abnormalities, to higher cognitive functions.

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