

Preview

PFC mTOR signaling as a biological signature for cognitive deficits in bipolar disorder without psychosis

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Vanderplow et al.¹ report decreased PFC Akt-mTOR signaling in males with bipolar disorder (BD) without psychosis compared with those with psychosis, possibly related to cognitive deficits. Understanding how cognition differs between these BD subtypes clinically and biologically remains a challenge.

The role of the Akt-mTOR pathway with both of its isoforms (mTORC1 and mTORC2) has been hypothesized to play a key role in the pathogenesis in many psychiatric conditions including autism, substance use, bipolar disorder, schizophrenia, and depression.² Consistent with this evidence, it is believed that some of the therapeutic effects of psychotropic drugs, such as lithium and ketamine, are mediated by their stimulating effects on mTOR activity.^{3–7}

In the study by Vanderplow et al.,¹ the authors expand on this work to delineate alterations along the Akt-mTOR pathway in individuals with history of bipolar disorder (BD), schizophrenia, and healthy controls in male and female cohorts.¹ The BD group was further stratified for the presence or absence of psychosis. The work focused on the dorso- and ventro-lateral prefrontal cortices (DLPFC and VLPFC, respectively)—two brain regions involved in cognition, working memory, and language processes. Intriguingly, the authors revealed decreased activity of the Akt-mTOR pathway across both regions in males with BP but without psychosis compared with males with BP and psychosis, and/or to healthy controls. No alterations were documented in the female cohort. The most profound alterations involved the mammalian target of rapamycin (mTOR) branch of the Akt signaling pathway (Figure 1A), rather than the GSK3 branch. This is important for the design of adequate treatment strategies because some psychotropic drugs (e.g.,

lithium) differentially target these components of Akt signaling.^{5,8}

To determine the functional significance of reduced PFC Akt signaling, the authors applied a backward translation strategy involving a PFC-targeted injection of dominant negative Akt. Interestingly, from a large battery of mouse behaviors indicative of socio-affective and memory processes, deficits were only found in models of short-term episodic-like memory (Figure 1B). Moreover, reduced Akt signaling also resulted in impaired excitatory transmission and reduced density of basal dendritic spines. Lastly, unlike the male-specific association of impaired Akt signaling with no psychosis BP, reduced Akt signaling similarly affected male and female mice.

To fully understand the implications of these findings for humans, one would need to considerably expand this line of research in several directions. First, deep behavioral phenotyping in humans is needed to link PFC Akt signaling cognitive deficits driving BD. Given that indices of working memory (Y maze) were not affected by PFC Akt signaling, and that long-term episodic memory was not investigated, emphasis on short-term episodic memory is especially important for validation of the rodent data.⁹ Second, it is not clear whether the Akt signaling deficits is PFC specific or extends to neuronal circuits more generally. Third, the sex-specific differences in humans but not rodents are puzzling, especially with respect to lack of Akt signaling changes in female BD patients. Whether

these patients' symptoms are driven by different signaling cascades or involve different neuronal circuits, or other factors, needs to be established. Lastly, the proposed specific association of Akt signaling deficits with BD cognitive symptoms needs further confirmatory work, particularly in view of ample evidence for cognitive deficits in BD patients with psychosis. The possibility that such deficits might differ between these two patient populations needs further investigation.

Clinically, this study addresses an important concern of cognitive impairment for individuals who suffer from psychiatric conditions including for those with BD, psychotic conditions, and unipolar depression. Cognitive alterations can remain even when the mood symptoms or psychosis resolve leading to ongoing disability.¹⁰ As such, findings raise an important question as whether cognitive deficits among those with somewhat overlapping conditions, namely BD with and without psychosis, entail distinct neural alterations and etiology. As discussed by the authors, converging evidence suggest that BD with and without psychosis may have different genetic underpinnings. The next important question to address is whether alterations in the Akt-mTOR pathway documented in BD-no psychosis will be present in those with unipolar depression. Similarly, as the field has incorporated the research domain criteria approach (RDoC) focusing on behavioral constructs across disorders, this study highlights the concern that similar behavioral constructs may entail distinct



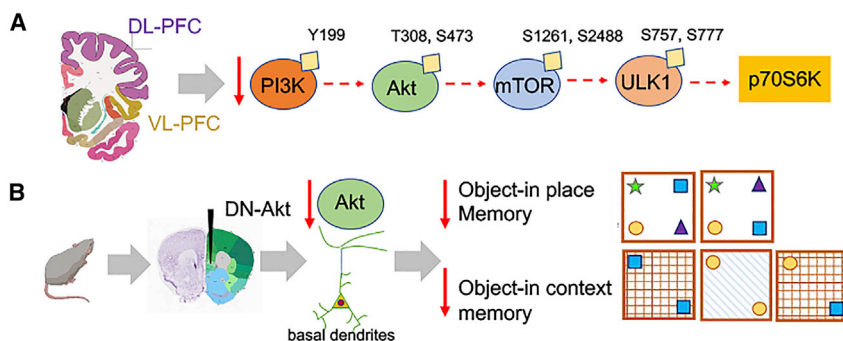


Figure 1. Implication of Akt family of protein kinases in BD without psychosis

(A) Decreased levels of phosphorylated (active) forms of multiple components of Akt signaling in human DL and VL PFC. (B) Deficits of short-term episodic-like memory in mice injected with dominant negative Akt in the prelimbic and infralimbic PFC areas. DN-Akt, dominant negative Akt; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; mTOR, p70S6K, p70 S6 kinase. Human and mouse PFC image credit: Allen Institute.

etiology among different psychiatric syndromes and that mechanisms underlying cognitive deficits may even differ within one clinical group (e.g., BD). Alternatively, as new findings emerge such as those reported by the Cahill lab, our diagnostic criteria will evolve to represent the distinct pathogenetic mechanisms underlying these clinical phenomena while taking sex as a factor as well. This study provides an important knowledge that can lead to new therapeutic targets for cognitive alterations in individuals suffering from psychiatric conditions.

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