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MEETING ABSTRACT

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Regulation of anxiety by the Gsk3–FRX1P pathway: a role for dopamine?
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Background: Neuropsychiatric disorders such as bipolar disorders, depression and schizophrenia represent a major public health problem, and a heavy burden for patients and their relatives. Drugs (such as mood stabilizers) used for management of these diseases may exert part of their therapeutic action by regulating Akt/Gsk3 pathway downstream of dopamine D2 receptors. Moreover, several genetic risk factors for mental illnesses encode proteins which either comprise or converge on this pathway. However, Gsk3 has up to 200 substrates, which makes it a non-specific drug target for management of specific psychiatric symptoms. Moreover, it is not clear which targets of Gsk3 regulate particular behaviors. Thus, identification of specific targets of Gsk3 could greatly advance our understanding of mental disorders and open new avenues for specific drug development.

Aims: Identify and characterize novel Gsk3 targets that regulate specific behaviors.

Results: We identified a new target of Gsk3, fragile X mental retardation syndrome-related protein 1 (FXR1P). By using AAV viral delivery we study regulation of anxiety by FXR1P. Here we also use AAV mediated CRISPR/Cas9 technology to knockout genes (Gsk3, Fxr1) in vivo and investigate regulation of anxiety by the Gsk3–FXR1P pathway. Moreover, by combining CRISPR/Cas9 technology in vivo and in vitro with electrophysiology we study single neuron activity and neuronal network activity regulations by the Gsk3–FXR1P pathway.

Conclusions: FXR1P is regulating anxiety downstream of Gsk3 by regulating activity of neuronal networks implicated in anxiety-related behaviors. Dopamine is implicated in regulation of mood and Gsk3 is a downstream of D2 receptor signaling. Having said this, is regulation of Gsk3–FXR1P pathway a new mechanism of how dopamine may regulate anxiety?

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