Arc, GAD67, and the Orbitofrontal Cortex: Reconsidering the Molecular and Systemic Basis of Major Depressive Disorder

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Major depressive disorder (MDD) is a psychiatric condition affecting 6.7% of the U.S. population and costing over $210B domestically each year. For decades, research of MDD has majorly concerned monoamine neurotransmitters, but medications still function with limited efficacy and late onset. However, pharmaceutical research for MDD has been reinvigorated following recent investigations of ketamine and other rapid-acting glutamatergic drugs for their comparatively fast and universal therapeutic effects. The administration of ketamine yields several molecular effects, but it is unknown which events in particular alleviate the symptoms of MDD, making the development of safer and less invasive treatments difficult. Here, a molecular effect of ketamine is isolated in order to assess the relevance of said effect; specifically, a knock-in mouse line (ArcKR) is thought to exhibit increased expression of the Arc protein in the orbitofrontal cortex (OFC) similar to an effect of ketamine. This postulation is verified through immunohistochemistry ($p<.05$), finding that this effect may explain decreased depressive-like behavior in ArcKR. The OFC is also investigated through Western blot to find that expression of the GAD67 protein expresses a trend toward significant increase in ArcKR mice when compared to wild-type counterparts ($p<.10$). Collectively, this suggests that ketamine accomplishes its therapeutic effects through increased excitation of the medial OFC (mOFC) and increased inhibition of the lateral OFC (lOFC) as accomplished through the modulation of Arc and GAD67, respectively; this allows for increased positive-valence and decreased negative-valence encoding in the hippocampus and effectively conveys the relevance of Arc, GAD67, and the OFC in the morphology of MDD.

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