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Effects of Intraperitoneal Psilocybin on DNA Methylation and Electrophysiological Markers of Plasticity

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Increasingly, psychedelic compounds are being investigated for the treatment of various neuropsychiatric disorders, including major depressive disorder (MDD). Unlike classic antidepressants, psychedelic compounds are characterized by the rapid onset and lasting duration of their effects after only one or a few doses. For example, the classical serotonergic psychedelic psilocybin has been shown to produce significant reductions in depressive symptoms and functional disability up to 6 months after a single dose. Despite the growing public interest in psychedelic treatment, the mechanisms of action underlying psychedelic therapeutic effects are not entirely clear. While psychedelic-induced increases in synaptic plasticity are often posited as a driving force behind the antidepressant effects of these drugs, the mechanisms leading to increased plasticity are unknown. Furthermore, how psychedelic compounds induce persistent effects, which long outlast drug clearance, is unknown. It has been posited by our group and others that psychedelic compounds achieve lasting therapeutic benefit via epigenetic mechanisms, such as DNA methylation. However, the epigenetic effects of psychedelics are understudied. Here, we examine the effects of a single intraperitoneal injection of psilocybin (1.0 mg/kg) on DNA methylation in the prefrontal cortex (PFC) of adult C57BL/6J mice. Additionally, we utilize ex vivo whole-cell patch clamp electrophysiology to examine changes in neuronal properties and synaptic function in layer 5 pyramidal cells of the PFC. Together, these data provide valuable insight into the potential mechanisms underlying psychedelic therapeutic action and lay the groundwork for more detailed studies investigating psychedelics as potential treatment options for MDD and other neuropsychiatric disease.