Phenotypic Profiling of Psychedelics in Mice Using SmartCube to Find the Next Generation of Psychedelic Drug Candidates

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Background: SmartCube® is a phenotypic screening platform designed for rapid behavioral evaluation in mice. In partnership with Sunovion, this platform has resulted in the discovery of the novel antipsychotic candidate, SEP-363856 (Ulotaront), which is now in Phase III clinical studies.
Aims and Objectives: Here we have profiled selected reference psychedelic compounds in mice using SmartCube and compared the behavioral signatures to those from our screening library of >7,000 behaviorally active compounds using various analytical tools. Compounds with high similarity scores to psilocin, ketamine, or MDMA were evaluated as starting points for a drug discovery program aimed at identifying molecules with behavioral similarity to psychedelics, but without producing side effects typical of dissociative or hallucinogenic molecules.
Methods: Mice were treated with test or reference compounds, administered intraperitoneal 15 min prior to the study, and were then placed in the SmartCube system, which runs through an automated configuration for 45min involving several behavioral challenges. Behavior was monitored by high-resolution cameras in each plane and mechanical actuators. Behavioral features were identified using deep learning, and behavioral similarity was analyzed using machine learning. Subsequently, psilocin-similar compounds were evaluated for agonist activity at 5-HT2A receptors, followed by behavioral testing in the mouse tail suspension test, which was used as an early screen for antidepressant potential. MDMA-similar compounds were evaluated in the mouse extinction of conditioned fear test. Compounds with activity in early efficacy screens were tested for effects on prepulse inhibition in rats, which is disrupted by serotonergic hallucinogens, noncompetitive NMDA receptor antagonists, and by psychostimulants like MDMA.
Results: Here we demonstrate how the SmartCube signatures of reference compounds (in this case, known psychedelics) can be used to identify molecules that produce similar behavioral responses, often through different mechanisms. PGI-33 was identified as a compound with similarity to psilocin and MDMA, while PGI-81 was similar to psilocin, although neither of these molecules have agonist activity at 5-HT2A receptors. Both PGI-33 and PGI-81 significantly reduced immobility in the mouse tail suspension test at 10 mg/kg, and PGI-33 also reduced freezing during extinction of conditioned fear at this dose. Neither molecule disrupted rat PPI at 30 mg/kg.
Discussion and Conclusion: The SmartCube platform is uniquely positioned for target-agnostic polypharmacology drug discovery programs. The platform has also demonstrated unique sensitivity to differential pharmacologic profiles due to minor changes to drug candidate structure, allowing it to support rapid structure-activity relationship studies and prediction of therapeutic utility.