ABSTRACT

The head-twitch response (HTR) is widely used as a preclinical assay for the hallucinogenic potential of compounds, but its fidelity has not been thoroughly tested. Here, we examine how lisuride and lysergic acid diethylamide (LSD) influence behavioral and physiological outcomes in mice to test whether the HTR reliably reflects psychoactivity. Lisuride (0.5 mg/kg) elicited no HTR yet impaired locomotion and coordination, evoked a pronounced stress response, disrupted cognitive function, and markedly reduced prefrontal cortex (PFC) electroencephalogram (EEG) amplitude across several frequency bands. In contrast, LSD (0.1 mg/kg) produced a robust HTR but had minimal impact on locomotion, coordination, stress responsivity, cognitive function, or PFC EEG power. None of these behavioral or physiological effects of lisuride or LSD were mediated by 5-HT_2A receptors, as pretreatment with the selective antagonist MDL 100907 did not alter outcomes. These results reveal a striking dissociation: the compound that evoked no HTR produced broad behavioral, physiological, and cortical disruptions, while the compound that elicited robust HTRs had little effect. Our findings demonstrate that HTR is not a sufficient index of psychoactivity and should not be relied upon to predict hallucinogenic potential or guide dose selection.