

EVALUATING MK-801 INDUCED NEUROTOXICITY IN ZEBRAFISH USING SPATIAL BEHAVIOR AND MEMORY TASKS

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INTRODUCTION: The N-methyl-D-aspartate receptor (NMDAR) antagonist dizocilpine (MK-801) is known to disrupt locomotor, cognitive, and spatial functions, serving as a chemical model for schizophrenia-like behaviors. Due to its neurotoxicity at high doses, MK-801 is used in low, acute concentrations to ensure safety in animal models. Zebrafish (*Danio rerio*) have emerged as valuable organisms in neurobehavioral research given their rich behavioral repertoire, sensitivity to psychoactive drugs, and conserved neurochemical pathways. Although MK-801's effects on learning and memory are well documented, its impact on homebase behavior in the open field test (OFT) remains less explored.

OBJECTIVE: This study aimed to evaluate the effects of MK-801 on spatio-temporal exploration dynamics in zebrafish, with emphasis on homebase behavior using the OFT.

MATERIALS AND METHODS: In Experiment 1, adult zebrafish received intraperitoneal injections of saline (0.9%) or MK-801 (2.0 mg/kg), followed by 15 minutes of absorption and a 30-minute OFT. Experiment 2 involved an initial OFT, immediate post-test treatment, and re-evaluation 24 hours later. Experiment 3 applied an inhibitory avoidance task to assess aversive memory.

RESULTS AND CONCLUSION: Acute MK-801 administration significantly increased locomotor activity and induced stereotyped movements, including repetitive circling and erratic swimming. Spatial exploration was altered, with reduced time in the homebase area and decreased stability in location preference. Despite these changes, zebrafish maintained spatial reference across sessions and showed reduced thigmotaxis upon re-exposure, suggesting preservation of some exploratory strategies. Furthermore, MK-801-treated animals exhibited impaired aversive memory consolidation, as shown by

performance deficits in the inhibitory avoidance task. These findings indicate that acute MK-801 exposure induces hyperlocomotion, stereotypy, and spatial disorganization, while core spatial strategies remain partially intact. The results reinforce the utility of zebrafish as a translational model for studying glutamatergic dysfunction and behavioral alterations relevant to neuropsychiatric disorders such as schizophrenia.

Keywords: MK-801; Zebrafish; Open Field Test;