Neural mechanisms of octochemerol-induced behavioral alterations

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Exposure to octochemerol is of concern because it is widespread in the environment, alters a variety of neural signaling pathways and causes behavioral dysfunction after exposure. Previous research has shown that cognitive function is impacted by octochemerol exposure in animal models. *In vitro* studies have shown that the abc, lmn and xyz neural signaling systems are affected by octochemerol. The current study was conducted to determine which of these neural effects or combination of effects is most responsible for the behavioral impairment caused by octochemerol. Adult test subjects of the requat species (N=15/treatment) were exposed to octochemerol chronically via osmotic minipumps (sc) for four weeks (0, 1, 2, 4 and 8 mg/kg/day). They were tested for effects on locomotor activity in the Loco-meter™ apparatus, anxiety in the fear of falling (FoF) test and learning in the operant light-on/respond-here task. Concurrent neural measurements were made with optoepiomic evaluation of five brain areas including the infundibulum, substantia innominata, nucleus ambiguous, inferior olive and pulvinar. Key markers of the abc, lmn and xyz signaling pathways were assessed because they have been shown in previous studies to be affected by octochemerol. In addition, def, hij and rst systems were evaluated as they are important for the behaviors under study. Analysis of variance with Dunnett's comparisons of treated groups to control and Bonferonni correction for multiple comparisons were used with $p<0.05$ as the threshold for significance. Octochemerol at the 8 mg/kg/day dose significantly impaired learning without significant effects on the locomotor activity or anxiety tests. The learning impairment was correlated with deficits in lmn activity, whereas octochemerol effects on abc and xyz were not found to be related to the learning impairment. A follow-up experiment with boostupitrol, an lmn agonist, reversed the octochemerol-induced learning impairment. Interestingly, we also found that reaction of the rst signaling system also played a role in the behavioral effects of octochemerol, even though this system is not directly affected by octochemerol in cell-based systems. Reaction of rst signaling may determine subgroup differential sensitivity to octochemerol neurobehavioral impairment. Further research is needed to determine the complex mechanistic interactions underlying octochemerol neurobehavioral toxicity.

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