$LPA_{1/3}$ RECEPTOR ANTAGONIST KI16425 AS A NOVEL TREATMENT FOR THE NEUROBEHAVIORAL EFFECTS OF ETHANOL

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Aims. The lysophosphatidic acid (LPA) is an ubiquitous lysophospholipid that acts through G-protein coupled receptors (LPA_{1-6}), and it is involved in the modulation of emotional and motivational behaviors. Recent literature suggests a relevant role of the LPA signaling system in alcoholism, specially through the LPA_1 receptor. This work aims to elucidate whether systemic $LPA_{1/3}$ receptor blockade with ki16425 would modulate ethanol effects on the brain and behavior.

Methods. This study consisted of four experiments assessing the effect of intraperitoneal ki16425 administration (20 mg/kg) on ethanol-related behaviors. Male Wistar rats or mice (Swiss, C57BL/6J or hybrid C57BL/6J×129X1/SvJ background) were employed in various procedures: I) oral ethanol self-administration; II) loss of righting reflex; III) ethanol-induced conditioned place preference (CPP) and IV) ethanol-withdrawal behavioral symptoms (by assessing nest building, physical signs and spatial working memory). Immunohistochemistry was carried out in order to evaluate basal neuronal activity (c-Fos) in the medial prefrontal cortex (mPFC) and in the hippocampus, as well as adult hippocampal neurogenesis (AHN) using proliferating cell nuclear antigen (PCNA) and doublecortin (DCX) markers.

Results. Systemic Ki16425 administration reduced oral self-administration of ethanol in previously trained rats. Likewise, ki16425 pretreatment in mice attenuated the sedation induced by ethanol, blocked ethanol rewarding effect in a CPP paradigm and reduced behavioral symptoms induced by ethanol withdrawal. Immunohistochemistry revealed a protective effect of ki16425 against ethanol actions on basal neuronal activity in the mPFC and on AHN.

Conclusions. Our results suggest a potential usefulness of systemic $LPA_{1/3}$ receptors antagonists as a novel treatment for alcohol-related disorders.

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