## LPA<sub>1/3</sub> 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<sub>1-6</sub>), 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<sub>1</sub> receptor. This work aims to elucidate whether systemic LPA<sub>1/3</sub> 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<sub>1/3</sub> receptors antagonists as a novel treatment for alcohol-related disorders.

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