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Topic: C.16.b Mental disorders: Affective disorders

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Abstract title: Stress coping behaviour, brain connectivity and LPA1 receptor: Similarities and differences between the genetic and the pharmacological approach

LPA_1_ receptor is one of the six characterized G protein-coupled receptors (LPA_1-6) through which lysophosphatidic acid acts as an intercellular signalling molecule. It has been recently proposed that this receptor has a key role in controlling depression-like behaviours and in the detrimental consequences of stress. Here, we sought to establish the involvement of the LPA_1 receptor in brain activity after an acute stressor. To this end, we examined behavioural despair in mice with a constitutive depletion of the LPA_1 receptor (maLPA_1-null mice), wild-type mice and mice receiving one single icv dose of the LPA_1 receptor antagonist Ki16425 or vehicle. Furthermore, the expression of c-Fos protein in stress-related brain areas and the corticosterone response following acute stress were examined. Our data indicated that, contrary to the knockout model, the antagonism of the LPA_1 receptor significantly increased immobility in the Forced Swim Test. However, latency to first immobility was reduced in both experimental conditions. Immunohistochemistry studies revealed an increased in activity in key limbic structures such as medial prefrontal cortex in both the LPA_1 antagonist-treated mice and maLPA_1-null mice, with an interesting opposed effect on hippocampal activity. Following acute stress, the sole infusion of Ki16425 in the cerebral ventricle increased corticosterone levels. In conclusion, the alteration of LPA_1 receptor function, through both genetic deletion or pharmacological antagonism, is involved in behavioural despair and hyperactivity of brain stress systems, thus contributing to explore specific susceptibility mechanisms of stress as targets for therapeutic recovery.