Liver X receptor

The liver X receptor (LXR) is a member of the nuclear receptor family of transcription factors and is closely related to nuclear receptors such as the PPARs, FXR and RXR. Liver X receptors (LXRs) are important regulators of cholesterol, fatty acid, and glucose homeostasis. LXRs were earlier classified as orphan nuclear receptors, however, upon discovery of endogenous oxysterols as ligands, they were subsequently deorphanized.

Liver X receptors (LXRs), including LXRα and LXRβ isoforms, have been implicated in multiple physiological functions including promoting neurogenesis, improving synaptic plasticity, preventing neurodegeneration, inhibiting inflammation as well as regulating cholesterol metabolism. However, a potential role of LXRs in the treatment of major depressive disorder (MDD) has never been investigated previously. Our present results demonstrated that levels of hippocampal LXRβ but not LXRα were down-regulated in rats exposed to chronic unpredictable stress (CUS) and were negatively correlated with the severity of CUS-induced depressive-like behaviors. Furthermore, rats with LXRβ knockdown by short hairpin RNA (shRNA) in hippocampus displayed depressive-like behaviors and impaired hippocampal neurogenesis similar to those observed after CUS exposure. Conversely, LXRs activation by GW3965 (GW), a synthetic dual agonist for both LXRα and LXRβ isoforms, could improve depression-like behaviors and reverse the impaired hippocampal neurogenesis in rats exposed to CUS. LXRβ knockdown by shRNA completely abrogated the antidepressant and hippocampal neurogenesis-promoting effects of GW, suggesting that LXRβ isoform mediated the antidepressant and hippocampal neurogenesis-promoting effects of the LXRα/β dual agonist. However, ablation of hippocampal neurogenesis with x-irradiation only partly but not completely abolished the antidepressant effects of GW in the behavioral tests, implying that the antidepressant effects mediated by LXRβ isoform are likely through both neurogenesis-dependent and -independent pathways. Thus, our findings suggest that LXRβ activation may represent a potential novel target for the treatment of MDD and also provide a novel insight into the underlying mechanisms of MDD [1)].

1)
Peng Z, Deng B, Jia J, Hou W, Hu S, Deng J, Lin W, Hou L, Sang H. Liver X receptor β in the hippocampus: A potential novel target for the treatment of major depressive disorder? Neuropharmacology. 2018 Apr 11. pii: S0028-3908(18)30169-2. doi: 10.1016/j.neuropharm.2018.04.014. [Epub ahead of print] PubMed PMID: 29654801.