Effects of Rapamycin on behaviour, cognitive deficits and neurogenesis in a chronic stress model in mice.

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The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that, in the brain, regulates several important physiological functions such as neuronal development and synaptic plasticity, and also seems to be involved in various neurological diseases including epilepsy and psychiatric disorders[1].
Recent data demonstrated that Rapamycin, an immunosuppressant drug and potent inhibitor of mTOR, might provide a significant improvement in several psychopathological features including memory performance, mood, and global psychiatric symptoms[2].
The aim of this study was to evaluate the effect of Rapamycin treatment in a mouse model of anxiety/depressive-like behaviour, induced by chronic Betamethasone 21-phosphate disodium administration (BTM).
A dysregulated hypothalamic-pituitary-adrenal axis (HPA) has been implicated in major depressive disorder and most commonly used animal models of depression are associated with increased circulating levels of plasma corticosterone[3; 4].
CD1 mice were submitted to 7 weeks of BTM 0,25mg/kg/day oral administration and then, behavioural tests such as Open Field (OF), Novelty-Suppressed Feeding (NSF), Elevated plus maze test (EPMT), Forced Swimming Test (FST), Morris Water Maze (MWM). Rapamycin (1 mg/Kg) has been administered for 3 weeks (starting 4 weeks after BTM) and then behavioural changes have been examined.
To investigate the potential cellular mechanisms underlying the behavioural effects of Rapamycin treatment, we evaluated changes in adult hippocampal neurogenesis and spines density[4]. Proliferation and the number of immature neurons in hippocampal dentate gyrus (DG) were assessed using BrdU (5-bromo-2'-deoxyuridine) and DCX (doublecortin) immunohistochemistry respectively and, a stereological procedure was used to quantify labeled cells. Golgi impregnation method was used to evaluate changes in dendritic spines in DG.
Our results show that, Rapamycin treatment significantly ameliorates cognitive performance while it aggravates the anxiety/depressive state caused by chronic BTM treatment. Furthermore, chronic BTM and Rapamycin exposure significantly increased BrdU-positive cells, DCX-positive cells, and the spine-density number in the dentate gyrus of the adult mouse hippocampus.
In conclusion the data arising from this study support the view that Rapamycin exerts a significant positive cognitive effect, however, it may aggravate other psychiatric symptoms. Finally, our data show some peculiar effects of rapamycin treatment supporting a complex regulation of neurological function which deserves to be further investigated.

References

1. Russo et al., 2012. Mol Neurobiol. 46, 662-81.
2. Lang et al., 2009. Transplant Proc. 41:4285-8.
3. Murray et al., 2008. Eur J Pharmacol.583:115-27.
4. Crupi et al., 2011. BMC Complement Altern Med. 27;11:7.