INHIBITION OF MAMMALIAN TARGET OF RAPAMYCIN (MTOR) IMPROVES NEUROBEHAVIORAL DEFICIT AND MODULATES INFLAMMATORY RESPONSE AFTER TRAUMATIC BRAIN INJURY

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Traumatic brain injury (TBI) induce primary and secondary damage on endothelium and brain parenchyma, leading neurons die rapidly by necrosis. The mammalian target of rapamycin signalling pathway (mTOR) mediates many aspects of cell growth and regeneration and is up-regulated after moderate to severe traumatic brain injury (TBI). The significance of this increased signalling event for recovery of brain function is presently unclear, here we used two different selective inhibitors of mTOR activity to explore the functional role of autophagy in an validated model of TBI, the controlled cortical impact injury (CCI).

We treated animals with KU0063794, a dual mTORC1 and mTORC2 inhibitor, and with Rapamycin a well-known inhibitor of mTOR, 1 and 4 hours after TBI.

Our results demonstrated that mTOR inhibitors, especially KU0063794, significantly improve motor and cognitive recovery after controlled cortical impact, as well as reduce lesion volumes. Moreover we observed that mTOR inhibitors treatment ameliorate the neuroinflammation associated to TBI and showed that this acute treatment significantly diminished the extent of neuronal death, astrogliosis and apoptotic process after trauma.

Our findings suggest that the neuronal mTORC1/2 activity after TBI is deleterious to brain function, and that acute intervention with mTORC1/2 inhibitor after trauma may represent an effective therapeutic strategy to improve recovery after brain trauma.