Sirolimus

- Pharmacokinetics and tissue distribution of intranasal administration of rapamycin in rats
- Defective PINK1-dependent mitophagy is involved in high glucose-induced neurotoxicity
- Gorham-Stout disease of the craniovertebral junction causing basilar impression and Chiari malformation type I: illustrative case
- Combination treatment with rapamycin and glucocorticoid protects the death of mesostriatal dopaminergic neurons in animal model of Parkinson's disease
- Chronic Rapamycin Prevents Electrophysiological and Morphological Alterations Produced by Conditional Pten Deletion in Mouse Cortex
- Modulating mTOR-dependent astrocyte substate transitions to alleviate neurodegeneration
- Biomimetic astrocyte cell membrane-fused nanovesicles for protecting neurovascular units in hypoxic ischemic encephalopathy
- Effects of Catheter-Based Renal Denervation in Hypertension: A Systematic Review and Meta-Analysis

Sirolimus (INN/USAN), also known as rapamycin, is a macrolide (one of a group of drugs containing a macrolide ring) produced by the bacterium Streptomyces hygroscopic.

Indications

Sirolimus for cerebral cavernous malformation treatment.

Sirolimus for chronic subdural hematoma treatment.

Sirolimus, also known by its brand name Rapamune, is an immunosuppressive medication that is typically used to prevent organ transplant rejection and to treat certain autoimmune diseases.

It has immunosuppressant functions in humans and is used to prevent rejection in organ transplantation; it is especially useful in kidney transplants. It prevents activation of T cells and B cells by inhibiting the production of interleukin-2 (IL-2). Sirolimus is also used as a coronary stent coating.

Sirolimus was isolated for the first time in 1972 by Suren Sehgal and colleagues from samples of Streptomyces hygroscopicus found on Easter Island.

The compound was originally named rapamycin after the native name of the island, Rapa Nui.

Sirolimus was initially developed as an antifungal agent. However, this use was abandoned when it was discovered to have potent immunosuppressive and antiproliferative properties due to its ability to inhibit mTOR. It has since been shown to prolong the life of mice and might also be useful in the treatment of certain cancers. It was approved by the US Food and Drug Administration in September 1999 and is marketed under the trade name Rapamune by Pfizer (formerly by Wyeth).

Results identify systemic rapamycin as a treatment that protects the entorhinal cortex and perforant pathway projection from tau -mediated neurodegeneration, axonal and synapse loss, and neuroinflammatory reactive gliosis. The findings support the potential for slowing the progression of Alzheimer Disease (AD) by abrogating tau-mediated neurotoxicity at its earliest neuropathological stages [1].

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Rapamycin inhibits the mTOR (target of rapamycin) pathway and extends lifespan in multiple species. The tuberous sclerosis complex (TSC) protein is a negative regulator of mTOR. In humans, loss of the TSC protein results in a disorder characterized clinically by the growth of benign tumors in multiple organs, due to overactivation of mTOR inhibition.

Identifying mTOR phosphorylation/activation may represent a difference in biology and a new marker to guide chemotherapy with recently approved mTOR inhibitors [2].

In a phase 1–2, open-label study in 28 patients with evidence of serial Subependymal giant cell astrocytoma growth, the mTOR inhibitor everolimus (Afinitor, Novartis, East Hanover, NJ) was associated with a reduction in SEGA volume and improved quality of life [3].

A study investigated the neuroprotective effects of rapamycin on intracerebral hemorrhage (ICH)-induced brain damage and the possible involvement of activated microglia. ICH was induced in rats by injection of type IV collagenase into striatum. Different dose of rapamycin was systemically administrated by intraperitoneal injection beginning at 1 h after ICH induction. Western blot analysis showed that ICH led to a long-lasting increase of phosphorylated mTOR and this hyperactivation of mTOR was reduced by systemic administration of rapamycin. Rapamycin treatment significantly improved the sensorimotor deficits induced by ICH, and attenuated ICH-induced brain edema formation as well as lesion volume. Nissl and Fluoro-Jade C staining demonstrated that administration with rapamycin remarkably decreased neuronal death surrounding the hematoma at 7 d after ICH insult. ELISA and real-time quantitative PCR demonstrated that rapamycin inhibited ICH-induced excessive expression of TNF-α and IL-1β in ipsilateral hemisphere. Furthermore, activation of microglia induced by ICH was significantly suppressed by rapamycin administration. These data indicated that treatment of rapamycin following ICH decreased the brain injuries and neuronal death at the peri-hematoma striatum, and increased neurological function, which associated with reduced the levels of proinflammatory cytokines and activated microglia. The results provide novel insight into the neuroprotective therapeutic strategy of rapamycin for ICH insult, which possibly involving the regulation of microglial activation [4].

1)

Siman R, Cocca R, Dong Y. The mTOR Inhibitor Rapamycin Mitigates Perforant Pathway Neurodegeneration and Synapse Loss in a Mouse Model of Early-Stage Alzheimer-Type Tauopathy.

PLoS One. 2015 Nov 5;10(11):e0142340. doi: 10.1371/journal.pone.0142340. eCollection 2015. PubMed PMID: 26540269.

2)

Johnson MD, O'Connell M, Walter K, Silberstein H. mTOR activation is increased in pilocytic astrocytomas from older adults compared with children. Surg Neurol Int. 2017 May 26;8:85. doi: 10.4103/sni.sni_367_16. eCollection 2017. PubMed PMID: 28607819; PubMed Central PMCID: PMC5461564.

3)

Krueger DA, Care MM, Holland K, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 2010;363:1801–1811

4)

Li D, Liu F, Yang T, Jin T, Zhang H, Luo X, Wang M. Rapamycin protects against neuronal death and improves neurological function with modulation of microglia after experimental intracerebral hemorrhage in rats. Cell Mol Biol (Noisy-le-grand). 2016 Sep 30;62(11):67-75. PubMed PMID: 27755955.