Rapamycin reduces orofacial neuropathic pain and TNC glia activation in trigeminal nerve-injured mice

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Neuropathic pain caused by trigeminal nerve injury is a typical refractory orofacial chronic pain accompanied by the formation of hyperalgesia and allodynia. This pain is also associated with glia activation in trigeminal nucleus caudalis (TNC). However, it is unclear whether glia activation is related to the activation of mTOR signaling. Infraorbital nerve was exposed and partial nerve ligation (ION-PL) was performed using silk suture (8-0). At 14 days after surgery, neuropathic pain behaviors were examined on the left lips, and rapamycin (0.1, 0.3, 1 mg/kg) was intraperitoneally treated. The mechanical and cold sensitivity in left orofacial region was quantified using von-Frey filaments and acetone solution, respectively. The western blot for mTOR and related protein expression was performed in trigeminal ganglia (TG) and TNC, and the immunohistochemistry for p-S6, p-p38, GFAP and Iba-1 was also examined in TNC. ION-PL mice showed significant mechanical and cold allodynia at 2 weeks after injury. The injection of rapamycin (1mg/kg) potently reduced both mechanical and cold allodynia. In addition, S6 and p-S6 expression, but not 4E-BP1 increased in TG in ION-PL group, and this increase decreased in mice treated with rapamycin. In TNC region, rapamycin treatment also significantly reduced the increased GFAP, Iba-1 and p-p38 MAPK expression in ION-PL mice. The p-p38 MAPK positive cells were also co-localized with the microglial marker Iba-1. These findings demonstrated that mTOR signaling related changes (the increase of S6 and p-S6) were observed after trigeminal nerve injury, and that the inhibition of mTOR signaling with rapamycin could reduce both mechanical and cold allodynia. Moreover, this anti-allodynic effect of rapamycin might be associated with the modulation of microglial activation in TNC.