Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst135P.pdf

Anti-diabetic drug metformin attenuates morphine tolerance and potentiates morphine effects in a mouse model of neuropathic pain

A. Alsubayiel, E. R. Middleton, E. Battell, I. Obara. School of Medicine, Pharmacy and Health, Durham University, Stockton on Tees, UNITED KINGDOM.

Introduction: Recently, the mammalian target of rapamycin complex 1 (mTORC1), a kinase which controls protein synthesis, was shown to regulate nociceptor sensitivity[1,2] and modulate opioid efficacy. However, direct mTORC1 inhibitors are only used in limited clinical indications due to adverse effects. Thus, this study explored the effect of the widely used anti-diabetic drug metformin that inhibits mTORC1 through activation of the adenosine monophosphate-activated protein kinase (AMPK)[2], on the modulation of morphine efficacy in neuropathic mice.

Methods: Adult male C57BL/6J mice (n=5-6/group) were subjected to peripheral neuropathy induced by spared nerve injury (SNI)[1]. Opioid tolerance was induced by morphine (40 mg/kg, i.p.) given twice daily at 12 h intervals for 10 consecutive days. The influence of metformin on opioid tolerance was assessed by repeated injections of metformin (200 mg/kg, i.p.)[2] once daily, 24 h before morning morphine injection on each testing day. Also, a separate group of morphine tolerant SNI mice received a single injection of metformin (200 mg/kg, i.p.) to determine the effect of mTORC1 inhibition on restoring morphine analgesia. In an additional separate experiment, morphine analgesic effect was assessed in SNI mice treated with morphine alone (3, 10, 20 mg/kg, i.p.) or in combination with metformin (200 mg/kg, i.p.). Pain threshold was assessed by tail-flick test while mechanical and cold hypersensitivity was determined by von Frey and acetone tests. Statistical analysis was performed using two-way ANOVA with Bonferroni's test.

Results: Administration of morphine to SNI mice resulted in tolerance to its analgesic effect after 8 days (day 1: 8.8±0.1s vs. day 8: 4.2±0.4s, $P<0.0001$). However, chronic metformin co-administration blocked the development and maintenance of morphine tolerance observed as an elevated withdrawal threshold to all test stimuli (e.g. tail-flick after chronic morphine on day 10: 5.8±0.6s vs. tail-flick after chronic morphine and metformin on day 10: 8.8±0.2s, $P<0.05$). In addition, a single metformin injection in SNI mice restored and potentiated dose-dependently the analgesic effect of morphine tested in mechanical and cold hypersensitivity tests (e.g. von Frey after morphine 20 mg/kg: 0.4±0.1g vs. von Frey after morphine 20 mg/kg and metformin: 1.3±0.2g, $P<0.0001$).

Conclusions: Our results support the idea that metformin, a widely available anti-diabetic drug, may offer a novel and clinically promising strategy for enhancing morphine analgesic efficacy, especially in neuropathic pain that was shown to be resistant to opioids.

References: 1. Obara *et al.* (2011). *Pain* **152:** 2582-2595 2. Obara *et al.* (2015). *Pain* **156:** 1519-1529.