Abstract

Surgery is a major cause of persistent pain suggesting that treatments that directly target the molecular pathways promoting post-surgical pain, particularly those that contribute to the progression to chronic pain, are needed. We have previously demonstrated that dysregulated protein translation regulation pathways, in particular ERK/eIF4E and mTOR signaling pathways, underlie persistent pain states and that AMPK activators can profoundly inhibit ERK, and mTOR signaling in sensory neurons. We have also demonstrated that local injection of resveratrol, a potent AMPK activator, into the hindpaw following plantar incision dose-dependently reverses incision-mediated mechanical hypersensitivity as well as hyperalgesic priming induced by incision. The aim of the present study was to pharmacologically establish AMPK activation as a bona-fide mechanism for the alleviation of post-surgical pain. To do this, we utilized multiple AMPK activators, including metformin, and A-769662, that possess different mechanisms of AMPK activation to demonstrate a shared endpoint – inhibition of incision-induced mechanical hypersensitivity and hyperalgesic priming. Metformin, which is clinically available and widely prescribed, stimulates upstream LKB1 activity to activate AMPK whereas A-769662 is a positive allosteric modulator that directly activates AMPK. Using the Brennan incision model in mice, we demonstrate that systemic metformin and local resveratrol at individually sub-eficacious doses at the time of incision blocked acute hypersensitivity and hyperalgesic priming. Finally, co-treatment with systemic metformin and local resveratrol at individually sub-eficacious doses at the time of incision blocked acute hypersensitivity and hyperalgesic priming suggesting potential super-additive effects of combined AMPK activators. None of these treatment approaches adversely affected wound healing. These results provide further evidence for activation of AMPK, as a novel treatment avenue for acute and chronic pain states induced by surgery. These preclinical findings afford the opportunity for immediate clinical testing due to the clinical availability of metformin.

Results

Metformin inhibits acute mechanical hypersensitivity induced by plantar incision

A-769662 blocks hyperalgesic priming precipitated by PGE2 injection

Co-treatment with systemic metformin and local resveratrol inhibits plantar incision-induced hyperalgesic priming precipitated by PGE2 injection

Conclusions

The present findings establish AMPK activation as a bona-fide mechanism for the alleviation of incision-induced mechanical hypersensitivity and for the prevention of hyperalgesic priming.

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