AMPK activation is sufficient to inhibit incision induced chronic pain

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Abstract

Surgery is a major cause of persistent pain suggesting that treatments that directly target the molecular pathology 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-relatedly 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 injection dose-dependently and efficaciously attenuates incision-induced mechanical hypersensitivity as well as the development of hyperalgesic priming precipitated by hindpaw injection of PGE2 following resolution of incision-induced mechanical hypersensitivity. Interestingly, systemic A-769662 was not effective in blocking incision-induced acute mechanical hypersensitivity; however it significantly blocked hyperalgesic priming. This effect was paralleled by lower doses of metformin, which had no acute effect yet blocked hyperalgesic priming. Finally, co-treatment with systemic metformin and local resveratrol at individually sub-efficacious doses at the time of incision blocked acute hypersensitivity and hyperalgesic priming suggesting potential super-additive effects of combined AMPK activator use. 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.

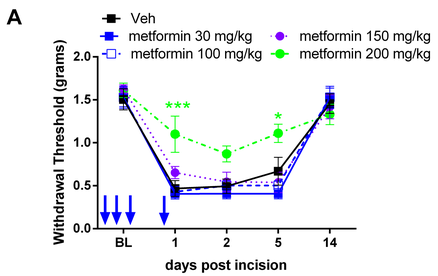
Incision associated with surgery causes acute pain and surgery has been identified as a potential major cause of chronic pain conditions. Between 10 and 50% of patients develop chronic pain following surgical procedures and despite improvements in post-surgical pain treatment strategies, the incidence of moderate to severe pain after surgery is still high in several patient populations suggesting that treatments that directly target the molecular pathology of post-surgical pain, particularly those that prevent the transition to chronic post-surgical pain, are needed. Interleukin 6 (IL-6) and nerve growth factor (NGF), endogenous mediators released as a result of incision, have been shown to be significant mediators of nociceptive plasticity in pre-clinical pain models and is implicated in several human pain conditions. In animal models of post-surgical pain, there is an increase in IL-6 and NGF levels in the serum and skin around the incision. NGF and IL6 can lead to engagement of the mTORC1 and ERK pathways, respectively, in nociceptors and their axons. Engagement of these pathways can lead to the development of acute mechanical allodynia following NGF or IL-6 injection and hyperalgesic priming to subsequent noxious stimuli following recovery from the initial NGF and/or IL-6 injection.

We have recently demonstrated that both these pathways can be negatively regulated by an endogenous signaling factor, adenosine monophosphate protein kinase (AMPK). AMPK is a ubiquitous energy-sensing kinase which can be activated physiologically by increase in intracellular AMP/ATP ratio which occurs during energy deprivation or cell starvation. AMPK can be activated pharmacologically as well by a number of clinically available drugs e.g. metformin or natural products such as resveratrol. AMPK can also be activated by a number of investigational compounds e.g. AICAR or A769662. We demonstrated that the AMP activated protein kinase (AMPK) activators, metformin and A769662, inhibited translation regulation signaling pathways and nascent protein synthesis in injured nerves neurons resulting in a resolution of neuropathic allodynia induced by peripheral nerve injury. In addition, we also demonstrated that resveratrol, a potent and efficacious activator of AMPK, profoundly inhibits ERK and mTOR signaling in sensory neurons in a time- and concentration-dependent fashion and local injection of resveratrol around the surgery site attenuates the surgery induced acute mechanical hypersensitivity and hyperalgesic priming in a model of post-surgical pain.

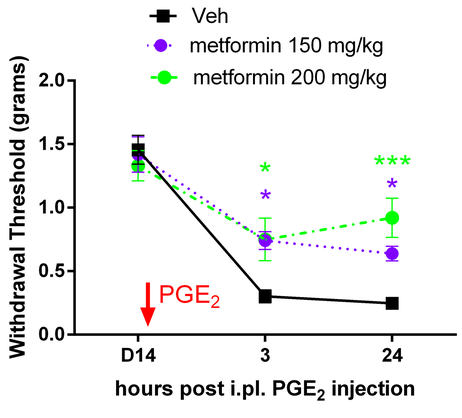
The aim of the present study is to establish AMPK activation as a bona-fide mechanism for the alleviation of post-surgical, and possibly other persistent pain states and to invent novel therapeutics and therapeutic strategies that employ this mechanism of action for use in humans. To do this, we utilized multiple AMPK activators, including resveratrol, metformin, and A-769662, which possess different mechanisms of AMPK activation to demonstrate a shared endpoint – inhibition of incision-induced mechanical hypersensitivity and hyperalgesic priming.

Results

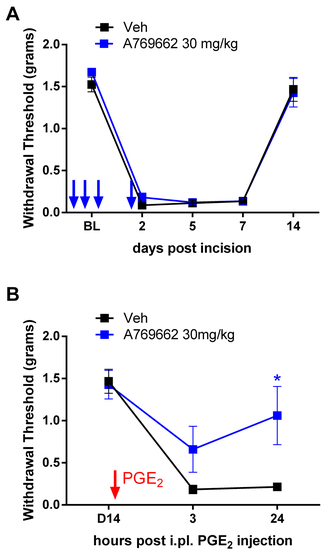
Metformin inhibits acute mechanical hypersensitivity induced by plantar incision



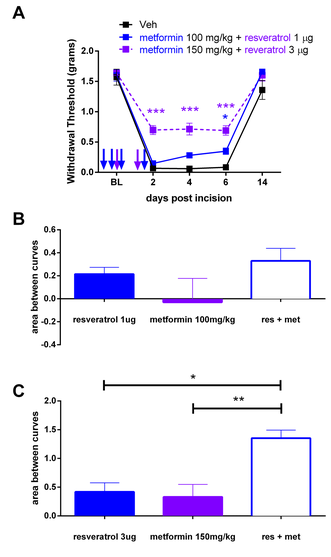
Metformin inhibits plantar incision induced hyperalgesic priming precipitated by PGE_2 injection



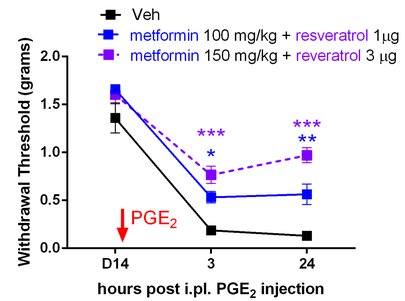
A-769662 blocks hyperalgesic priming precipitated by PGE_2 injection



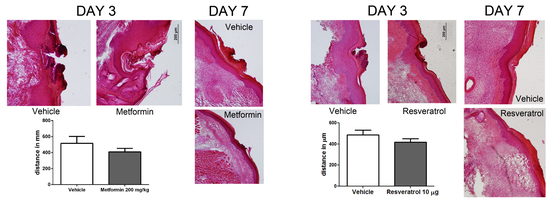
Co-treatment with systemic metformin and local resveratrol inhibits acute mechanical hypersensitivity induced by plantar incision



Co-treatment with systemic metformin and local resveratrol inhibits plantar incision-induced hyperalgesic precipitated by PGE_2 injection



AMPK activators do not adversely affect wound healing in a model of post-surgical pain



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.

Acknowledgements

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