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## A novel role of minocycline: attenuating morphine antinocceptive tolerance by inhibition of p38 MAPK in the activated spinal microglia.

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### Abstract

We have previously demonstrated that activation of p38 mitogen-activated protein kinase (p38 MAPK) in the spinal microglia mediates morphine antinocceptive tolerance. Minocycline, a selective inhibitor of microglia activation, has been reported to attenuate peripheral inflammation-induced hyperalgesia by depressing p38 MAPK in the spinal microglia. The aim of the present study is to explore the effect of intrathecal minocycline on the development of morphine antinocceptive tolerance and p38 activation in the spinal microglia induced by chronic morphine treatment. Minocycline (20, 50 and 100 microg) was given intrathecally 30 min before each morphine (15 microg) administration for consecutive 7 days. It was shown that minocycline attenuated tolerance to morphine analgesia in a dose-dependent manner. Minocycline administration (50 microg) which was initiated on day 4 followed by another 4 days administration partially reversed the established morphine antinocceptive tolerance. However, minocycline treatment which was started on day 8 followed by its administration for 4 more days failed to reverse the established morphine tolerance. Immunohistochemical analysis showed that chronic intrathecal morphine-induced activation of p38 MAPK in the spinal microglia. Minocycline at a dose that was shown to antagonize tolerance to morphine analgesia significantly inhibited the increase in p38 MAPK activation in the spinal microglia. To our knowledge, this is the first study to demonstrate that minocycline antagonizes morphine antinocceptive tolerance, possibly due to the inhibition of p38 activation in the spinal microglia.

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