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## The effects of crocin on allodynia and anxiety-induced by nerve injury and its interaction with $\alpha_1$ and ,-adrenoceptors in the anterior cingulate cortex

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**Background:** Anterior cingulate cortex (ACC) is a well-known brain region that is part of the neuromatrix involved in pain processing. Neuropathic pain is a chronic pain state that arises from peripheral or central nerve damage. Despite recent rapid development of neuroscience and drug discovery, effective drugs based on clear basic mechanisms are far from clear. Therefore, the purpose of the current study is to evaluate therapeutic potential of intra-ACC microinjection of crocin, a saffron bioactive ingredient, on cold allodynia in chronic constriction injury (CCI)-induced neuropathic pain in rats. Additionally, clinical studies show that anxiety and neuropathic pain are concomitant. Then, we also evaluate the anti-anxiety effects of crocin in CCI model rats. We also assess the interaction of crocin with ACC α1 and 2-adrenoceptors following nerve injury.

**Methods:** CCI model was induced by applying 4 loose ligatures around the left sciatic nerve on day 5 after cannulation surgery. Intra-ACC microinjections (right side of ACC) of saline, crocin (40  $\mu$ g/5  $\mu$ l), crocin+prazosin ( $\alpha$ 1-adrenoceptors antagonist, 30  $\mu$ g/5  $\mu$ l) or crocin+yohimbine ( $\alpha$ 2-adrenoceptors antagonist, 30  $\mu$ g/5  $\mu$ l) were started 1 day after induction of neuropathic pain and continued until 6 days' post-surgery. Thermal allodynia (using acetone drop) and anxiety (using elevated plus maze, EPM) evaluates on 2, 4 and 6 days' after CCI.

**Results:** The CCI rats showed apparent cold allodynia and anxiety-like behaviors on 2, 4 and 6 days after neuropathy. Intra-ACC injection of crocin could suppress cold allodynia and anxiety behaviors on 4 and 6 days after neuropathy. Co-administration of both  $\alpha$ 1 and 2-adrenoceptors antagonists (prazosin or yohimbine) with crocin markedly attenuate the anti-allodynia and anti-anxiety effects of crocin.

**Conclusion:** Our findings indicate that intra-ACC injection of crocin after induction of CCI model has a therapeutic effect against neuropathic pain. Moreover, it is likely that anti-allodynia and anti-anxiety effects of crocin is related to its interaction with  $\alpha$ 1, 2-adrenoceptors in the ACC.

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