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★令和3年度（2021年） 卒業生 「伊藤悠君」の研究成果が、国際的疼痛学専門誌”Molecular Pain”に掲載されました!!!

Research Article

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Phytochemical quercetin alleviates hyperexcitability of trigeminal nociceptive neurons associated with inflammatory hyperalgesia comparable to NSAIDs

Haruka Itou, Ryou Toyota, and Mamoru Takeda

Abstract

Quercetin is a flavonoid that is widely found in fruits and vegetables. Quercetin inhibits cyclooxygenase-2 and modulates voltage-gated ion channels, however, its effect on nociceptive neuron-associated inflammatory hyperalgesia remains unknown. The present study investigated under in vivo conditions whether systemic administration of quercetin attenuates the inflammation-induced hyperexcitability of trigeminal spinal nucleus caudalis (SpVc) neurons associated with mechanical hyperalgesia and compared its effect to the non-steroidal anti-inflammatory drug, diclofenac. Complete Freund's adjuvant was injected into the whisker pads of rats to induce inflammation, and then mechanical stimulation was applied to the orofacial area to assess the threshold of escape. The mechanical threshold was significantly lower in inflamed rats compared to uninjected naïve rats, and this lowered threshold returned to control levels 2 days after administration of quercetin or diclofenac. The mean discharge frequency of SpVc wide-dynamic range (WDR) neurons to both non-noxious and noxious mechanical stimuli in inflamed rats was significantly decreased after quercetin or diclofenac administration under combination of three anesthetic agents (medetomidine, midazolam and butorphanol). In addition, the increased mean spontaneous discharge of SpVc WDR neurons in inflamed rats significantly decreased after quercetin or diclofenac administration. Similarly, quercetin or diclofenac restored the expanded mean receptive field size in inflamed rats to control levels. In this study, the combination of three anesthetic agents did not result in any obvious "noxious pinch-evoked after discharges" in CFA inflamed day 2 rat as described previously in pentobarbital-anesthetized rats. Together, these results suggest that administration of quercetin attenuates inflammatory hyperalgesia associated with hyperexcitability of nociceptive SpVc WDR neurons *via* inhibition of the peripheral cyclooxygenase-2 signaling cascade and voltage-gated ion channels. These findings support the proposed potential of quercetin as a therapeutic agent in complementary alternative medicine strategies for preventing trigeminal inflammatory mechanical hyperalgesia.

ハイライト： これまでに、果物や野菜に含まれるファイトケミカルの一つ「ケルセチン」は非ステロイド性消炎鎮痛薬（NSAIDs）の標的分子であるシクロオキシゲナーゼ2の作用を抑制することは in vitroの実験で示唆されていましたが、in vivo での効果は不明でした。今回、我々は末梢組織の炎症に伴い生じる“痛覚過敏の症状”とこの発症に重要な役割を果たす広作動域ニューロンの興奮性の変化が「ケルセチン」の慢性投与により抑制されることを明らかと致しました。この効果はNSAIDsであるジクロフェナクと同等であることも確認されたので、本研究の成果はケルセチンが臨床の場において非ステロイド性鎮痛薬に変わる新たな副作用のない炎症性疼痛治療薬となる可能性と代替医療に貢献することを示唆しております。