Involvement of endogenous nitric oxide in the mechanism of bradykinin–induced peripheral hyperalgesia

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ABSTRACT When NO synthase (NOS) inhibitor was intradermally administered with bradykinin (BK) into the instep of rodent hind–paws, a dose–related suppression of BK–induced hyperalgesia in the rat assessed by the paw–pressure test was produced. The BK–induced hyperalgesia was abolished by both a guanylate cyclase inhibitor and a PKG inhibitor. The carrageenin–induced hyperalgesia was significantly attenuated by a NOS inhibitor in a dose–dependent manner. Activators of NO–cGMP pathway failed to produce any significant relieving effect on the nociceptive threshold. Concomitant administration of forskolin with 8–Br–cGMP induced significant hyperalgesia. In the superfusion experiment of a blister base on the instep of rodent hind–paws, intradermally administered BK significantly increased the outflow of both cGMP and cAMP. Concomitant administrations of a NOS inhibitor with BK significantly reduced the BK–induced outflow of cGMP without affecting the cAMP content. These results suggest that the NO–cGMP pathway is involved in the mechanism of BK–induced hyperalgesia, and an activation of both cGMP– and cAMP–second messenger system plays an important role in the production of peripherally induced mechanical hyperalgesia.
有意に抑制された。カラゲニン誘発痛覚過敏もNO合成酵素阻害剤の投与により用量依存的に抑制された。NO-cGMP系だけを活性化しても痛覚過敏は発現しなかったが、cAMP系とcGMP系を共に活性化すると痛覚過敏が発現した。ラット後肢足甲部に水疱を作成し、その水疱底を灌流したところ、灌流液中に放出されるcAMPとcGMPはブラジキニンの皮内投与によって有意に増加した。またNO合成酵素阻害剤はブラジキニンによるcGMPの増加のみを抑制し、cAMPの増加には影響を及ぼさなかった。これらの結果より、ブラジキニン誘発痛覚過敏の発現にはNO-cGMP系の活性化が関与しており、さらに末梢性痛覚過敏の発現にはcGMP系とcAMP系の両セカンドメッセンジャー系の活性化が重要な役割を果たしていることが示唆された。