Guanylate cyclase stimulation is a trigger of migraine pain.

DISEASE/KEY WORDS: headache, pain, nitric oxide, nitroglycerin, hypersensitivity

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BACKGROUND: Migraine is a complex brain disorder that affects hundreds of millions of individuals worldwide. Although there have been great advances in migraine medication, the available treatments are only effective in a limited number of patients, therefore it is necessary to identify novel therapeutic targets. Nitroglycerin (NTG) is a known migraine trigger, and produces migraine-related hyperalgesia in mice. How NTG induces migraine is unclear, as it activates the nitric oxide-guanylate cyclase pathway but also produces radical oxygen species which lead to oxidative stress. The aim of this study was to determine the specific contribution of the guanylate cyclase pathway to migraine-associated pain.

METHODS: C57Bl6/J mice were treated acutely and chronically with either vehicle or the guanylate cyclase stimulator VL-102. Basal and post-treatment mechanical responses were determined using von Frey hair stimulation.

RESULTS: VL-102 produced acute hyperalgesia in a dose-dependent manner. Chronic administration of VL-102 produces both acute and basal hypersensitivity. VL-102-induced hyperalgesia was blocked by the anti-migraine medications sumatriptan and topiramate. These results are similar to the migraine-related pain induced by NTG.

CONCLUSIONS: Stimulation of guanylate cyclase mimics the effects of NTG-induced pain, and appears to be migraine-associated. These results suggest that the effects of NTG on migraine are due to direct activation of the nitric oxide pathway and not to other non-specific effects. Furthermore, this work indicates that guanylate cyclase may be a novel therapeutic target for the treatment of migraine.