Low-dose dextromethorphan reverses hyperalgesia in men

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Video Abstract

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Abstract

New research shows that hyperalgesia, a neuropathic condition causing heightened sensitivity to pain, can be effectively reversed in a human experimental model. For the hundreds of thousands who suffer from this hard-to-treat condition, the study's findings could offer much-needed pain relief. Treating neuropathic pain is notoriously difficult. Clinicians must wade through numerous patient-reported symptoms just to source the pain. And even when the presence of neuropathy is established, finding a treatment that works can be painstaking. In recent years, researchers have focused on neural receptors of N-methyl-D-aspartate, or NMDA; these receptors are linked to the central sensitization that gives rise to hyperalgesia. Specifically, they've explored the effects of NMDA receptor antagonists, such as ketamine, memantine, and dextromethorphan. Dextromethorphan has proven especially effective in combating hyperalgesia. But only in animals or at high doses in humans—which poses some risk, as dextromethorphan can alter cognition. In the recently published study, however, researchers demonstrated that low-dose dextromethorphan could reverse induced hyperalgesia in a group of 20 healthy volunteers. The researchers placed a copper rod stored at -28°C on the forearm to create a freeze-burn injury and two hyperalgesia zones: a primary one corresponding to the area contacted by the rod, and a secondary one radiating a few centimeters beyond. Unlike other injury models, which maintain hyperalgesia for a few hours at most, this freeze-burn model is reported to remain stable for up to 3 days, allowing enough time to assess the effects of medication. Volunteers received either 30 mg oral dextromethorphan or placebo. Over the next three hours, the research team used a light poke from a calibrated plastic "hair" to provoke pain and monitor the volunteers' pain threshold. On average, the dextromethorphan group's threshold for pain significantly exceeded that of the placebo group. Interestingly, dextromethorphan didn't affect pain responses in healthy skin. That suggests that NMDA receptors must be "primed for pain" for dextromethorphan to exert an antihyperalgesic effect. Despite their encouraging results, the researchers offer a few caveats. Because the study didn't examine females, non-Caucasians, or volunteers outside the ages of 18 to 45, the findings can't be generalized to the general population. Additionally, only half of participants experienced hyperalgesia stable enough to last more than 1 day. It's also unknown whether this freeze-burn model is generalizable to other types of pain, or to pain in patients as well as healthy volunteers. The team is currently exploring more extensive trials to confirm their initial results and provide a viable therapeutic option for the many vulnerable patients who suffer from hyperalgesia.