Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 3, pp. 641–644, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00106-9

BRIEF COMMUNICATION

An Attempt to Attenuate Experimental Pain in Humans by Dextromethorphan, an NMDA Receptor Antagonist

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Received 6 May 1994

KAUPPILA, T., M. GÖNROOS AND A. PERTOVAARA. *An attempt to attenuate experimental pain in humans by dextromethorphan, an NMDA receptor antagonist.* PHARMACOL BIOCHEM BEHAV **52**(3) 641–644, 1995.—Dextromethorphan (100 mg, orally), an NMDA receptor antagonist, did not significantly attenuate pain intensity or unpleasantness induced by experimental ischemia or by topical capsaicin in healthy human subjects, nor did it increase the threshold for heat pain or mechanical pain. A dose of 200 mg produced marked side effects. Thus, systemically administered dextromethorphan does not attenuate pain at clinically applicable doses in humans.

Analgesia Capsaicin Dextromethorphan *N*-methyl-D-aspartate receptor antagonist Pain modulation

THERE is abundant evidence indicating that NMDA receptors have a role in the pain signalling system (28,32). According to animal studies in particular, responses based on temporal summation of the signals from the primary afferent C-nociceptors are sensitive to the attenuating effect of NMDA receptor antagonists (3,4,7,8). In animal studies, NMDA receptor antagonists have proved effective in attenuating sensory and neuronal responses, especially to tonic pain stimuli, as well as in suppressing pain induced by experimental neuropathy or inflammation (5,6,11,17,20,23–27,33), although attenuation of phasic pain has also been described (15). In human studies ketamine, an NMDA receptor antagonist, has proved effective in alleviating experimental ischemic pain (13,18,21) and chronic neuropathic pain (1). However, the clinical use of ketamine is hampered by the considerable psychological side effects at analgesic doses and by need to administer ketamine parenterally. Furthermore, intrathecal administration of CPP, also an NMDA receptor antaganonist, attenuated neurogenic pain in a human patient (16).

Dextromethorphan is a commonly used antitussive (2) that has properties of an NMDA receptor antagonist (31). Unlike ketamine, it is readily available for oral clinical use. In animal studies, dextromethorphan, or its metabolite dextrorphan, have proved effective in attenuating temporal summation of nociceptive signals in the spinal dorsal horn neurons (9) and in alleviating hyperalgesia induced by experimental mononeuropathy (17,26). These previous studies raised the question of whether dextromethorphan was effective in alleviating pain in humans at doses that do not produce marked side effects. In the present study we evaluated the pain-modulating effect of dextromethorphan in four experimental pain tests in healthy humans. Two of the pain tests represented phasic pain (mechanical and thermal pain threshold), which, according to animal studies, should not be sensitive to attenuation by NMDA receptor antagonists [however, see (15)]. Two of the pain tests represented tonic pain (ischemia and capsaicin-induced chemical pain). An NMDA receptor antagonist-reversible temporal summation of pain signals in the spinal dorsal horn presumably contributes to the pain sensation with these tonic pain stimuli (11,24).

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METHODS

Eight healthy human volunteers (three women and five men, age 22–54 years) participated in this experiment. Informed consent was obtained from the subjects before the experiments.

Heat pain thresholds were determined using a feedback-controlled contact thermostimulator (LTS3-Thermostimulator; Thermal Devices, Minneapolis, MN) (29). Thermal stimuli of 5 s duration was delivered at four temperatures in random order (stimulus interval of 20 s) to three consecutive locations in the forearm. The four stimulus temperatures used in the actual experiments were chosen individually for each subject in a preliminary experiment so that at least one of the stimulus temperatures was below the pain threshold and at least two were at or above the threshold in control conditions. The stimulating surface of the thermostimulator was 11.8 cm^2, the rate of temperature change was 6.0°C/s, and the adaptation temperature was thermoneutral 35°C. A psychometric function curve describing the relative frequency of pain responses at various stimulus temperatures was plotted. The temperature at which the subject reported pain to 50% of the stimuli was defined as the heat pain threshold.

The threshold for mechanical pain was quantified with a Basile Analgesymeter (Ugo Basile, Varese, Italy), which applied a linearly increasing force to the palmar skin of the fingertip. Three fingers were consecutively tested and their mean result was the mechanical pain threshold for the condition.

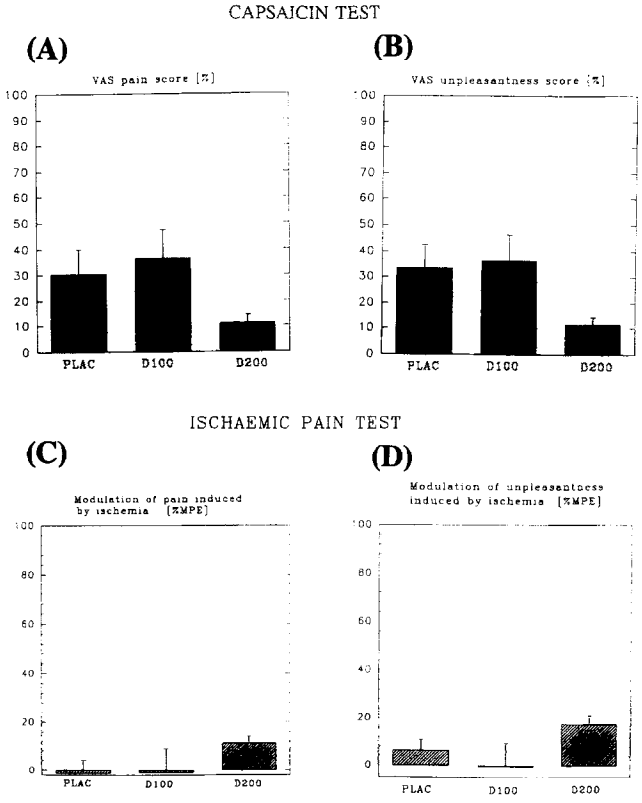

FIG. 1. Upper panels: Capsaicin-induced pain intensity (A) and unpleasantness (B) over all subjects. 100% = the worst imaginable pain or unpleasantness, 0% = no pain or unpleasantness. Lower panels: Effect of drug treatment on pain intensity (C) and unpleasantness (D) induced by experimental ischemia. In the lower panels, 0% = control score before drug treatment, >0 = analgesic effect, and <0 = hyperalgesic effect. PLAC, placebo; D100 and D200 = 100 and 200 mg of dextromethorphan, respectively. The error bars represent SEM (with PLAC and D100, n = 8; with D200, n = 4).

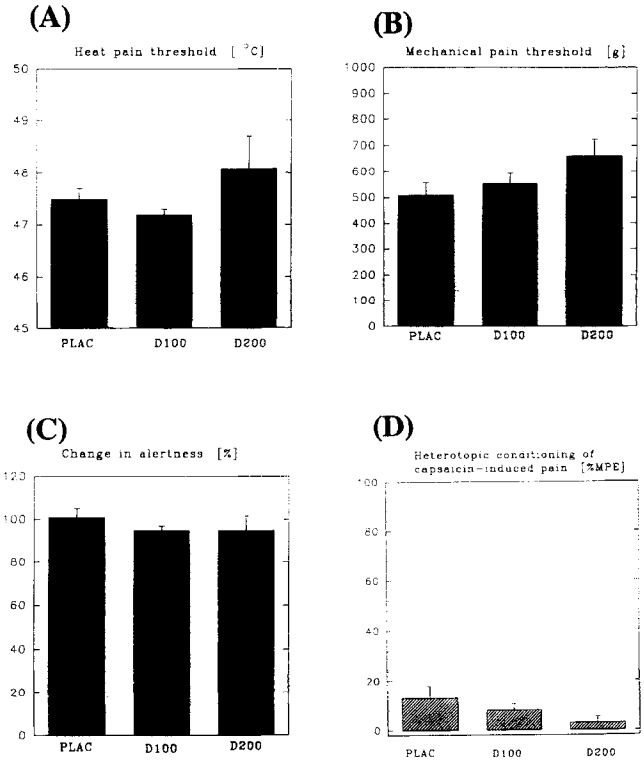

FIG. 2. (A) The mean heat pain threshold and (B) mechanical pain threshold over all subjects. (C) Drug-induced effect on alertness. 100% = alertness in the corresponding predrug condition; >100% = increased alertness; <100% = decreased alertness. (D) Change in the effect of the heterotopic noxious conditioning (concurrent ischemic pain) on the intensity of pain induced by capsaicin. 100% = maximum analgesic effect; 0% = no effect; <0% = hyperalgesic effect. For further explanations, see Fig. 1.

The ischemic pain test was performed using a tourniquet placed proximal to the cubital fossa and inflated to 200 mm Hg (26.7 kPa (12). After cuff inflation, the subjects performed a controlled submaximal exercise with the ischemic hand. Following the exercise, the subjects evaluated the intensity and unpleasantness induced by ischemia every 2 min for 6 min with separate visual analogue scales. The total sum of these scores in each session was calculated and used in further analysis. The ischemic test was performed before and after each drug administration.

Tonic activation of cutaneous C-nociceptors was produced by topical application of capsaicin (1% in 70% ethanol; Fluka, Buchs, Switzerland) to a 4-cm^2 area in the skin of the forearm (14). Pain intensity and unpleasantness produced by capsaicin were evaluated using a visual analogue scale.

Dextromethorphan (Pharmacal, Helsinki, Finland) or placebo (lactose) was dissolved in a mixture of bitter lemon and sugar to camouflage the bitter taste of dextromethorphan. The effect of dextromethorphan at a dose of 100 mg was tested in a double-blind, placebo-controlled, crossover design with eight subjects. Dextromethorphan at the dose of 200 mg

produced strong side effects (dizziness, clumsiness, severe diarrhea in one subject, etc.), which made a true double-blind design impossible. Because of the strong side effects, the testing of the higher dextromethorphan dose was limited only to four of the subjects.

Each drug (placebo or dextromethorphan at one of the doses) was tested on a separate day with at least a 1-week interval. On each day, predrug alertness and predrug ischemic pain were evaluated with visual analogue scales first, followed by drug administration. Capsaicin was applied 15 min after the drug, and the postdrug alertness and the capsaicin-induced sensations were evaluated 45 min after drug administration. This was immediately followed by postdrug ischemic tests and the measurement of the thermal and mechanical pain thresholds. The drug-induced effects on ischemic pain and unpleasantness were calculated by the formula: percent maximum possible effect (%MPE) = [(predrug score − drug score)/(maximum possible score − mimimum possible score)] × 100. The attenuating effect of concurrent ischemic pain on the capsaicin-induced pain in the contralateral limb (heterotopic noxious conditioning) (22,30) was also evaluated with a visual analogue scale at 5 min of ischemia in the postdrug condition. The effect of heterotopic noxious conditioning on capsaicin-induced pain was calculated by the formula: %MPE = [(preischemia pain score − pain score during ischemia)/(maximum possible pain score − minimum possible pain score)] × 100. In the statistical evaluation of the data, paired *t*-test (two-tailed) was used. $p < 0.05$ was considered to represent a significant difference.

RESULTS

Placebo and dextromethorphan at a dose of 100 mg caused no side effects. Two of the eight subjects correctly identified the drug and placebo conditions when the dextromethorphan dose was 100 mg. However, the higher dextromethorphan dose (200 mg) produced strong side effects in all subjects tested, as described earlier, which limited its use to only four subjects.

In general, dextromethorphan at a dose of 100 mg produced results in all tests identical to those obtained with placebo. The order of testing placebo and the dose of 100 mg of dextromethorphan in eight subjects was not significant. Although the pain intensity and unpleasantness induced by ischemia or capsaicin were lower with the higher dextromethorphan dose (200 mg; $n = 4$), these effects were not significant (paired *t*-test) (Fig. 1). Similarly, the effect of drug treatment on heat and mechanical pain thresholds was not significant (Fig. 2). The drug-induced changes in alertness and the attenuation of the capsaicin-induced pain by concurrent ischemic pain (heterotopic noxious conditioning) were also not statistically significant (Fig. 2).

DISCUSSION

Our results indicate that systemically administered dextromethorphan does not attenuate pain at doses that are clinically applicable. It is likely that at higher doses or with more subjects tested at a dose of 200 mg, significant pain-attenuating effects by dextromethorphan would be obtained, but with unbearable side effects. According to animal studies, NMDA antagonists applied intrathecally or systemically provide an excellent means to alleviate hyperalgesia and excessive pain caused by the temporal summation of pain signals with little influence on tactile sense or phasic pain (7–9,24). Because the side effects at analgesic doses following systemic administration seem to be a problem with dextromethorphan as well as with ketamine (10,21) and CPP (16), further studies with other compounds with properties of an NMDA receptor antagonist are needed to explore practical possibilities to apply this theoretically highly promising approach to pain therapy. Because the psychotomimetic side effects are due to supraspinal actions, and because there is evidence indicating that NMDA receptor antagonists supraspinally may even oppose the spinal antinociceptive effects (19), intrathecal administration may provide a better way of reaching critical drug concentrations for blocking spinal NMDA receptors.

ACKNOWLEDGEMENTS

This study was supported by the Sigrid Juselius and Paulo Foundations, Helsinki, and the Academy of Finland.

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