Neuroscience 132 (2005) 49–56

ANTINOCICEPTIVE EFFECTS OF CHOLINE AGAINST ACUTE AND INFLAMMATORY PAIN

Y. WANG,[a,b1] D.-M. SU,[a,b1] R.-H. WANG,[a1] Y. LIU[b] AND H. WANG[b]*

[a]*Thadweik Academy of Medicine, Beijing 100850, PR China*

[b]*Beijing Institute of Pharmacology and Toxicology, 27 Taiping Road, Beijing 100850, PR China*

Abstract —We used the hot plate test and the formalin test to evaluate the antinociception of choline after i.c.v. or i.v. administration. The analgesic mechanism of choline was also studied. The response latency of mice was significantly prolonged in the hot plate test after choline (90–120 μg/animals) i.c.v. administration in a dose-dependent manner. Pretreatment with methyllycaconitine citrate (MLA), α-bungarotoxin, or atropine blocked the antinociception of choline in the hot plate test. In contrast, mecamylamine and naloxone had no effect. No antinociceptive action of choline was found in the hot plate test, but it did have an effect in the late phase of the formalin test after i.v. administration. The effect of choline on anti-inflammatory pain was blocked by MLA, but not by mecamylamine, naloxone and atropine, which is indicative of the involvement of α7 receptors in peripheral sites. When choline (2 mg/kg) was coadministered with aspirin (9.4 mg/kg), the licking/biting times in the late phase significantly decreased, although no effects were shown when these doses of drugs were used alone. Similarly, coadministration of choline (2 mg/kg) with morphine (0.165 mg/kg) significantly increased the antinociception of morphine in the late phase, but had no effect in the early phase. These results demonstrate that activation of α7 nicotinic receptors by choline elicits antinociceptive effects both in an acute thermal pain model and in an inflammatory pain model. Choline holds promise for development as a non-addictive analgesic drug and in reducing the regular dose of aspirin or morphine in inflammatory pain. **© 2005 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: antinociception, choline, hot plate test, formalin test, nicotinic receptors.

Pain is one of the most common reasons for patients to seek medical care, yet modern pharmacological treatments are limited. Current analgesics fall into two major classes: nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, both of which have critical liabilities and limitations. Gastrointestinal side effects and effectiveness only in mild to moderate levels of pain limit NSAIDs use (Frolich, 1997; Kingery, 1997). Although effective in severe and neuropathic pain (McQuay, 1999; Przewlocki and Przewlocka, 2001), opioids are severely controlled because of their addictive effects and other serious side effects (McQuay, 1999). Given the clear need for new analgesic agents, novel molecular targets are being identified (Williams et al., 1999). Among these are nicotinic acetylcholine receptors (nAChRs; Decker et al., 2004).

Activation of neuronal nAChRs produces antinociception in a variety of preclinical pain models (Decker and Meyer, 1999; Decker et al., 2001; Flores, 2000); antinociception is also found in human use of nicotine (Pomerleau, 1986; Jamner et al., 1998). Various subtypes of nAChRs are involved in different functions, depending on their location in tissues (Picciotto et al., 2000; Marubio and Changeux, 2000). Therefore, up to now, definition of the nAChRs with antinociception is difficult, although some evidences have shown the α4β2 nAChRs in central nervous system were key receptors (Kesingland et al., 2000; Boyce et al., 2000; Meyer et al., 2000; Bitner et al., 2000; Marubio et al., 1999). Whether another subtypes of nAChRs, α7 receptors, which are distributed extensively in CNS and peripheral sites and are involved in many important functions (Broide and Leslie, 1999; Levin et al., 1999; Genzen et al., 2001; Wang et al., 2001; Skok 2002), are related with antinociception is largely unknown. Choline, the precursor of acetylcholine (ACh), is a selective endogenous agonist for α7 receptors (Alkondon et al., 1997). In this study, we used choline to observe the antinociceptive action of α7 receptors. Choline is a charged cation and cannot easily pass through the blood–brain barrier (BBB) (Allen and Lockman, 2003), so the antinociceptive effect of α7 receptors in CNS or peripheral was evaluated by i.c.v. and i.v. administered choline respectively. The hot plate test, an acute thermal pain model that depends mainly upon supra-spinal mechanisms (Dennis et al., 1980) and the formalin test, an inflammatory pain model (Murray et al., 1988; Tjolsen et al., 1992) were used here. Previous studies have demonstrated the interaction of NSAIDs and cholinergic agonists in antinociception (Miranda et al., 2002). Additionally, cholinergic agonists exert a positive modulatory action on opioid antinociception (Eisenach and Gebhart, 1995; Hood et al., 1997). Until now, the characteristics of the possible interactions between choline with aspirin or morphine, two representative drugs of NSAIDs and opioids, have not been evaluated. For this purpose, coadministration of choline with aspirin or morphine was measured.

[1] These authors equally contributed to this paper.

*Corresponding author. Tel: +86-10-6693-2651; fax: +86-10-6818-8180.
E-mail address: wh9588@yahoo.com.cn (H. Wang).

Abbreviations: ACh, acetylcholine; AMMS, Academy of Military Medical Sciences; BBB, blood–brain barrier; α-Bgt, α-bungarotoxin; COX, cyclooxygenase; DRG, dorsal root ganglion; MLA, methyllycaconitine citrate; nAChR, nicotinic acetylcholine receptor; NSAID, nonsteroidal anti-inflammatory drug.

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doi:10.1016/j.neuroscience.2004.12.026

EXPERIMENTAL PROCEDURES

Animals

Experiments were performed on Kun Ming female mice, weighing 18–22 g, obtained from the Experimental Animal Center of the Academy of Military Medical Sciences (AMMS, Beijing, China). All animal experiments were performed in accordance with the animal care and use guidelines set by AMMS Animal Care and Use Committee. The Helsinki Declaration and IASP's guidelines for pain research in animals were followed (Zimmermann, 1983). Animals were housed in groups of six and had free access to food and water. We attest that all efforts were made to minimize the number of animals used and their suffering.

Drugs

Morphine sulfate salt and naloxone hydrochloride dihydrate were synthesized by Beijing Institute of Pharmacology and Toxicology, (−) nicotine bitartrate, methyllycaconitine citrate (MLA), α-bungarotoxin (α-Bgt), choline dihydrogen citrate salt, mecamylamine hydrochloride, oxotremorine and atropine were purchased from Sigma, St. Louis, MO, USA. Aspirin was obtained from Shandong Xinhua Pharmaceutical Corporation (Jinan, China). All drugs were dissolved in physiological saline (0.9% sodium chloride).

Intraventricular injections

Intraventricular injections were performed according to the method of Pedigo et al. (1975). After being lightly anesthetized with ether, mice were positioned on a stereotaxic apparatus with ear-bars plugged and jaws fixed to a biting plate. A small incision was made in the skin above the skull along the midline. The bregma point was identified under the surgical scope and a burr hole was drilled at the site 2 mm rostral and 2 mm lateral to the bregma. Then 5 μl of drugs were injected using a microsyringe whose needle tip was at the depth of 2 mm. A small amount of solder was placed 2 mm proximal to the needle tip to ensure reproducibility and the accuracy of the depth of the injections.

Systemic injections

All drugs were administered through veins in the tails of mice in a total volume of 1 ml/100 g body weight. In the formalin test, mecamylamine, MLA, atropine and naloxone were i.p. administered.

Antinociceptive test

Hot plate test. The hot plate test is a preclinical model used to understand the mechanisms through which acute pain is endogenously controlled and exogenously altered by analgesics. The model represents the supraspinal antinociceptive effect (Dennis et al., 1980).

Mice were placed on the hot plate (Shandong, China) maintained at 52.5±0.5 °C. The time between placement of mice on the hot plate and the occurrence of the licking of the hind paws, shaking or jumping off the surface was recorded as response latency. Mice with baseline latencies of less than 12 s or more than 18 s were excluded from the study. A cutoff of 60 s was established in order to prevent tissue damage.

Response latency was recorded before and 15 min after choline (30–120 μg/animals, i.c.v., 4–64 mg/kg, i.v.), nicotine (10 μg/animals, i.c.v.), oxotremorine (0.5 μg/animals, i.c.v.) and morphine (0.2 μg/animals, i.c.v.). Separate groups of mice were pre-treated with atropine (0.1 μg/animals, i.c.v), naloxone (2 μg/animals, i.c.v), mecamylamine (5 μg/animals, i.c.v), MLA (50 μg/animals, i.c.v.) and α-Bgt (2 μg/animals, i.c.v.) 5 min before choline, nicotine, morphine and oxotremorine administration respectively.

Formalin test. Mice were injected s.c. with 10 μl of 5% formalin into the plantar surface of the left hind paw. Mice were immediately returned to a glass chamber (r=10 cm, 25 cm high), and the total time spent by the animal licking or biting the injected paw, an index of nociception, was recorded for the following 30 min. Formalin-induced pain behavior is biphasic. The initial acute phase (0–5 min) is followed by a relatively short quiescent period, which is then followed by a prolonged tonic response (15–30 min). The animals were treated with vehicle, choline, aspirin and morphine 15 min before formalin administration.

Data analysis

All data were expressed as the mean±S.E.M. for each group. Data were analyzed using one-way analysis of variance followed by the Student-Newman-Keuls test. A probability of 0.05 or 0.01 was accepted as significant.

RESULTS

Antinociceptive effect of choline in the hot plate test after i.c.v administration in mice

Choline was first evaluated in the hot plate test after i.c.v administration. To determine the duration of the test after choline treatment, we used choline at a dose of 90 μg/animal and observed the change of response latency over time. As seen in Fig. 1A, the maximal antinociceptive effect of choline appeared 15 min after injection. This time point was therefore used as the test time in subsequent tests.

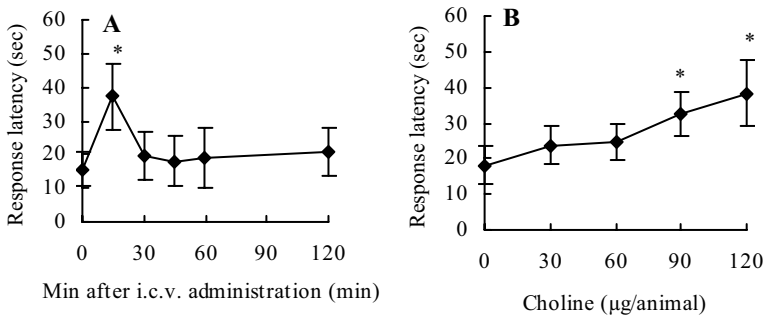

Fig. 1. Antinociceptive effects of choline on the hot plate test after i.c.v. administration in mice. Time course of the antinociceptive effect of choline (90 μg/animal, i.c.v., A), * P<0.05. Effect of increasing concentrations of choline on the hot plate test 15 min after i.c.v. administration (B). Each point represents the mean±S.E.M. for eight to 10 mice. * P<0.05, compared with saline-treated mice.

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