Autonomic Neuroscience: Basic and Clinical 198 (2016) 28–32

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Intrapericardial capsaicin and bradykinin induce different cardiac-somatic and cardiovascular reflexes in rats

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ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 10 June 2016
Accepted 12 June 2016

Keywords:
Capsaicin
Bradykinin
Cardiac-somatic reflex
Cardiovascular reflex

ABSTRACT

Patients with myocardial infarction experience various types of chest pain and autonomic disturbance symptoms. Studies in rats have shown that pericardial infusions of certain chemicals induce cardiac-related muscle pain and cardiovascular reflexes. In the present study, bradykinin or capsaicin was injected into the pericardial sac and the resulting cardiac-somatic reflexes and blood pressure (BP) alterations were record. We found that the cardiac-somatic reflex induced by bradykinin had a longer latency, shorter duration, and lower firing rate than that induced by capsaicin ($p < 0.05$). We also found that bradykinin induced a hypertensive response ($p < 0.05$), while capsaicin induced a hypotensive response ($p < 0.05$). Bilateral vagotomy had no effect on the cardiac-somatic reflex induced by bradykinin ($p > 0.05$) but reduced the reflex induced by capsaicin ($p < 0.05$). However, vagotomy had no effect on the BP alterations induced by both bradykinin and capsaicin ($p > 0.05$). These results suggest that bradykinin and capsaicin activate different pathways to induce cardiac-somatic and cardiovascular reflexes and that the vagus nerve is involved in TRPV1-related muscle pain modulation.

1. Introduction

During myocardial ischemia, the locally affected myocardium releases a variety of compounds, including potassium, lactate, adenosine, bradykinin and prostaglandins (Fu et al., 2005; Fu and Longhurst, 2002; Gaspardone et al., 1999; Huang et al., 1995), which are capable of activating afferent sensory nociceptors located on sensory nerve endings in the heart. Once this nociceptive signal propagated by cardiac sympathetic and vagal afferents is received by the brain (Cervero and Laird, 2004; Foreman, 2004; Schwartz and Gebhart, 2014), patients experience chest pain, generally referred to as angina pectoris, as well as symptoms of blood pressure (BP) changes (Baker et al., 1980; Cervero, 1995; Perez-Gomez et al., 1979).

Bradykinin is one compound that is released during myocardial ischemia (Kimura et al., 1973), and it activates kinin B2 receptors on cardiac sensory afferents to evoke a sympathoexcitatory reflex (Khan et al., 2002; Tjen-A-Looi et al., 1998). Capsaicin is a ligand for transient receptor potential vanilloid receptor 1 (TRPV1), which is involved in cardiac nociception (Zahner et al., 2003). Both capsaicin and bradykinin are the most commonly used chemicals in the study of cardiac nociception and cardiovascular reflexes (Liu et al., 2011; Liu et al., 2012a,b; Qin et al., 2007). Functional evidence has shown that capsaicin-sensitive afferents are important for the cardiac sympathetic reflex response, but the bradykinin-elicited reflex response is not dependent upon the TRPV1 receptors located at the endings of cardiac sympathetic afferents (Zahner et al., 2003). However, the results of studies examining the effects of capsaicin and bradykinin in cardiac nociception and cardiovascular reflexes are inconsistent (Liu et al., 2012b; Wang et al., 2006; Zahner et al., 2003). Previous and our recent studies have shown that intrapericardial injection of chemicals could induce a stable and dose-dependent somatic nociceptive reflex as well as dynamic cardiovascular reflexes (Jou et al., 2001; Liu et al., 2012a,b). The purpose of the present study was to discriminate the differences in capsaicin- and bradykinin-induced cardiac-somatic and cardiovascular reflexes.

2. Materials and methods

2.1. Animals

Experiments were performed in adult male Sprague–Dawley rats (weighing 280–310 g). All animals were housed singly with free access to food and water and maintained on a 12-h light/dark cycle. The experimental protocol was in accordance with the guidelines of the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, Eighth Edition, revised 2011). All efforts were made to minimize the number of animals used and any distress to the animals.

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http://dx.doi.org/10.1016/j.autneu.2016.06.001
1566-0702/

2.2. Surgery

Animals were initially anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal). The right carotid artery was catheterized to monitor BP, and the left jugular vein was catheterized to permit continuous infusion of sodium pentobarbital (10–15 mg/kg/h) delivered using a syringe pump (KD100; KD Scientific Inc., USA). A tracheal cannula was inserted for artificial ventilation (55–60 breaths/min, 5.0–6.0 mL tidal volume). Bilateral cervical vagus nerves were exposed below the level of the recurrent laryngeal nerve and isolated from the other tissue. A silk suture was passed through the nerve and remained in place for the ensuing experiment. A midsternal incision from the first to the third rib was made to expose the thymus. A silicone catheter (0.020 ID, 0.037 OD, 14–16 cm long) with four small holes in the distal 2 cm was inserted into the pericardial sac between the lobes of the thymus. The tissues were sutured layer by layer, and the animals maintained in a prone position. A concentric electrode was inserted in the left spinotrapezius muscle to record electromyography (EMG) signals. The EMG signals were amplified and bandpass-filtered (1.0 kHz) with a Dual-Trace Amplifier (AVM-11; Nihon Kohden, Japan) and were monitored with an oscilloscope (VC-10; Nihon Kohden, Japan) and an audio monitor. Traces of EMG signals were collected and analyzed using a Biological Experimental System (BL-420; TaiMeng, China).

2.3. General protocol

The nociceptive cardiac-somatic reflex was evoked by pericardial administration of chemicals as described previously (Jou et al., 2001). Briefly, 2 h after surgery, EMG activity and BP were record during pericardial sac infusion of 0.2 mL of saline (control), capsaicin (0.2 mL), or bradykinin (0.2 mL). After the chemical infusion, warm saline was infused and then withdrawn to remove any remaining chemicals. There was a minimum 40-min interval between each injection. The anesthesia was maintained at the same level during the experiment based on the animal's BP and pupil diameter which kept the same from the beginning of the recording to the end of the recording.

In the vagotomy group, EMG activity was record at the time of administration of capsaicin or bradykinin before bilateral cervical vagotomy and was again administered into the pericardial sac 40–60 min after vagotomy.

2.4. Drugs

The capsaicin stock solution was dissolved to a concentration of 1 mg/mL in saline containing 10% ethanol and 10% Tween-80, and was diluted to a final concentration of 10 μg/mL. Bradykinin was mixed with normal saline to create a stock solution of 0.2 mg/mL. On the day of an experiment, the stock was diluted with saline to 10 μg/mL for intrapericardial injection. All drugs were obtained from Sigma (St. Louis, MO).

2.5. Data analysis

The EMG signals were measured as the total number of motor unit potentials occurring during the intrapericardial injections. The latency of the EMG or BP was measured as the time from the start of the infusion of the chemical to the start of the reflex. The duration defined as the time of the reflex from the start to the end. All data are expressed as the mean 7 ± SEM. Data were analyzed using one-way analysis of variance with repeated measures. Values of $p < 0.05$ are considered statistically significant.

3. Results

3.1. Characteristics of the cardiac-somatic reflex after intrapericardial injection of capsaicin or bradykinin

Both bradykinin and capsaicin induce a stable cardiac-somatic reflex (Jerry Jou et al., 2002; Liu et al., 2011). To determine whether the compounds induced different cardiac-somatic reflexes, we separately injected the two compounds into the same animal ($n = 10$) with a 40–60 min interval between the injections. The latency of the EMG signal responses induced by bradykinin (3.6 ± 0.6 s) was much longer than that induced by capsaicin (0.2 ± 0.1 s; $p < 0.0001$; Fig. 1A). The duration of the EMG signal responses after administration of bradykinin (26.7 ± 11.8 s) was shorter than that after capsaicin (36.4 ± 11.1 s; $p < 0.05$; Fig. 1B). The EMG firing rate was lower following

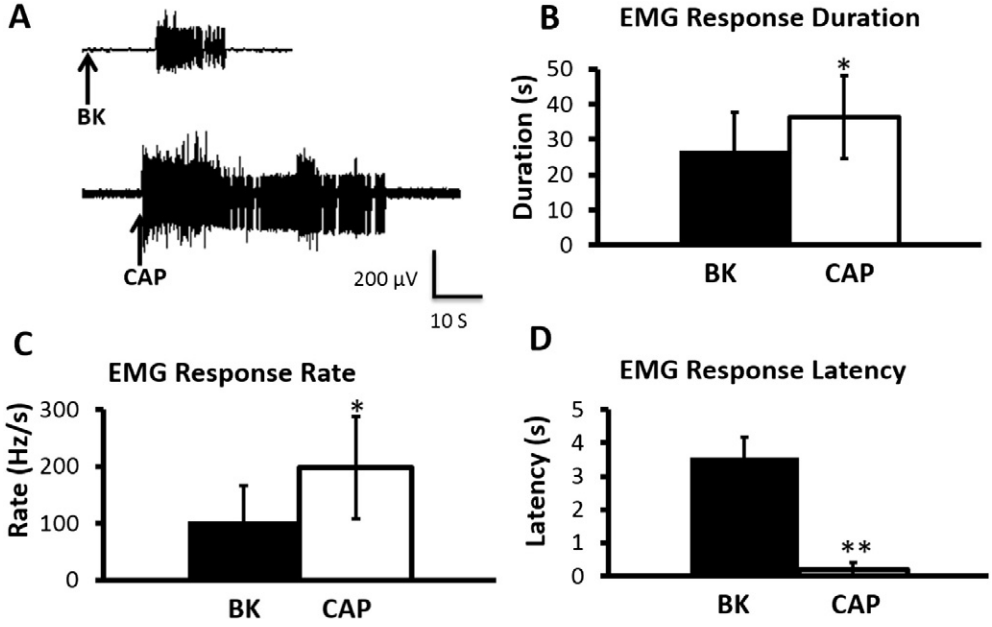

Fig. 1. Cardiac-somatic reflex evoked by intrapericardial injection of capsaicin or bradykinin. The electromyography (EMG) signal response evoked by intrapericardial capsaicin (CAP) administration has a shorter latency (A), longer duration (B) and higher firing rate (C) than that evoked by bradykinin (BK). (D) EMG activity traces after bradykinin or capsaicin. *$p < 0.05$; **$p < 0.001$.