

## The Effect of Capsaicin on C-fiber Reflex and Heat Evoked Discharge in the Acute Spinal Cat

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The effects of capsaicin were studied electrophysiologically on C-fiber reflex and heat-evoked discharge in adult spinal cats. The results can be summarized as follows: 1) 125  $\mu\text{g}/\text{Kg}$  of capsaicin, administered intravenously, induced an increase in spontaneous discharge in the  $\text{L}_7$  ventral root; 2) 250  $\mu\text{g}/\text{Kg}$  of capsaicin, administered intravenously, induced an increase in the C-fiber reflex response; 3) 125  $\mu\text{g}/\text{Kg}$  of capsaicin, administered intravenously, induced an increase in the heat-evoked discharge; but 4) 25  $\mu\text{g}/\text{Kg}$  of capsaicin, administered through the femoral artery, did not show significant alteration of the heat-evoked discharge. These findings suggest that capsaicin which produced a release of substance-P from primary afferent nerves may principally act on C-fiber and  $\text{A}\delta$ -fiber. Capsaicin was much more effective on the heat-evoked discharge than on the C-fiber reflex when administered intravenously.

(Key Words: Capsaicin, Substance-P, C-fiber Reflex, Heat-evoked Discharge)

### INTRODUCTION

Capsaicin (8-methyl-N-vanillyl 1-6-nonenamide) is the active ingredient which is largely responsible for the irritating and pungent effects of fruits of the various species of capsacin, including Mexican chile pepper and Hungarian red pepper (paprika). The pharmacological action of capsaicin revealed a wide and interesting profile of biological activity. For example, it is known that capsaicin shows the effects on the cardiovascular, sensory, respiratory, thermoregulatory and gastrointestinal systems from the ultrastructural, neurophysiological and neurochemical aspects. Recently, substance-P and serotonin are reported to be involved in the pharmacological activity of capsaicin. Capsaicin apparently reveals no direct action on the GABA-ergic, enkephalinergic or catecholaminergic systems (10). The effects of acute intravenous administration of capsaicin on anesthetized cats demonstrated the elicitation of the Bezold-Jarisch reflex (hypotension, bradycardia and apnea). The peripheral administration of capsaicin induced hypothermia similar to that brought about by histamine administration. Capsaicin crossed the blood brain barrier and revealed its effect on thermoregulation through the preoptic area of the hypothalamus. Capsaicin has also altered the transmission of impulses in primary sensory nerves. Acute administration of capsaicin has induced an increase of firing rates in peripheral sensory nerves. Capsaicin induced a release of substance P from nerve terminals, and it is well known that the initial liberation of substance P from primary afferent terminals is

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followed by a prolonged depletion of substance P from these neurons. Thus it may play a role in the inflammatory response associated with cutaneous injury and pain (4). In this paper, we examined the C-fiber reflex response and heat-evoked discharge by acute administration of capsaicin. We also compared the discharge of C-fiber with that of A $\delta$  fiber in ventral root when capsaicin was administered systematically.

#### MATERIALS AND METHODS

**C-fiber reflex (modified Bell and Martin's method)** Thirty-five cats of either sex were anesthetized with ether, and then the spinal cord was transected at the C<sub>1</sub>-C<sub>2</sub> level to make an acute spinal cat. The cats were artificially respired by room air. The spinal cord was exposed from the L<sub>6</sub> to the S<sub>2</sub> segment. Skin flaps were elevated, and the spinal cord was covered with warm liquid paraffin oil. The paraffin pool was maintained at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  using a thermister probe, thermoregulator and heat lamp. The L<sub>7</sub> ventral root was sectioned at the point where it exited the dura and placed on a bipolar platinum recording electrode. The superficial peroneal nerve was exposed at the ankle and placed on a bipolar platinum stimulating electrode. Stimulating pulses of 30V, 2 msec-duration, at intervals of 150 msec were applied at 10 sec intervals to evoke the maximal C-fiber reflex. The stimulus applied to the superficial peroneal nerve at intensities of 15 to 30V and 2 msec-duration was sufficient to elicit a reflex response in the L<sub>7</sub> ventral root of a latency of 200 msec. The conduction distance between the site for stimulation and the L<sub>7</sub> ventral root was approximately 200 mm and the conduction velocity of C-fiber was approximately 1 m/sec. Therefore, it was indicated that the long-latency response must be a C-fiber reflex. Koll *et al.* (1961, 1963) found that a characteristic property of the C-fiber reflex was that its discharge was markedly increased by several (3-10) train volleys applied to the afferent nerve. The optimal interval between these volleys was 15 to 300 msec. In our studies, it was found that a train of four pulses (15V-intensity, 2 msec-duration) applied to the superficial peroneal nerve with an interpulse interval of 150 msec was sufficient to elicit a large C-fiber reflex. This pulse-train was applied once every 10 seconds. Carotid blood pressure and electrocardiography were monitored. The drugs were injected into the right cephalic vein. The potentials of the C-fiber reflex were integrated by a gate integrator (Nihon Koden KK) (2, 3, 9). Heat-evoked discharge

Heat-evoked discharge was recorded from the L<sub>7</sub> ventral root while the paw was heated. A stimulating time, of 10-15 seconds a stimulating temperature of 48-50°C, an interval 1,000 msec, and a duration of 150 msec were used. The discharge was integrated by a gate integrator (Nihon Koden KK). The systems for analysis of C-fiber reflex and heat-evoked discharge are shown in Figs. 1 and 2.

Capsaicin from Merck Co. & Ltd. was used. the structure of capsaicin is shown in Fig. 3. Capsaicin was administered in the form of a 0.01%-0.05% solution in physiological saline with one drop of Tween-80 added. The solution was prepared by an ultrasonic shaker. Capsaicin was administered in saline solution slowly at a rate of 5 mininutes per dose. The statistical significance of drug-induced changes in C-fiber reflexes and heat evoked

discharges was determined by Student's *t*-test with consideration given to control values before administration of the drug to 5 cats.

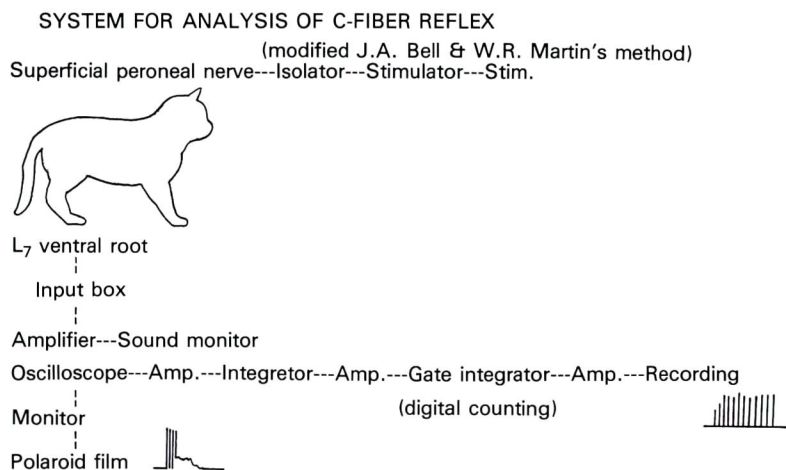


Fig. 1 System for analysis of C-fiber reflex

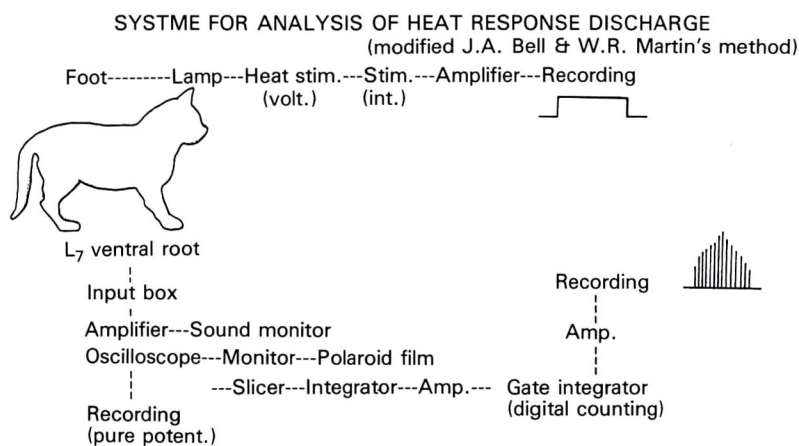


Fig. 2 System for analysis of heat-evoked discharge

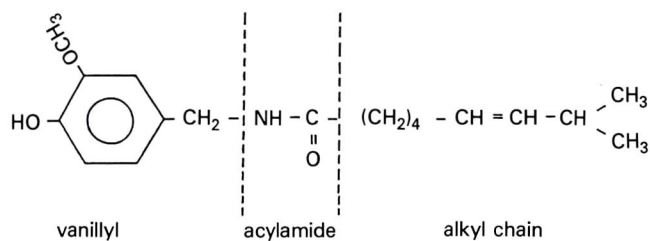
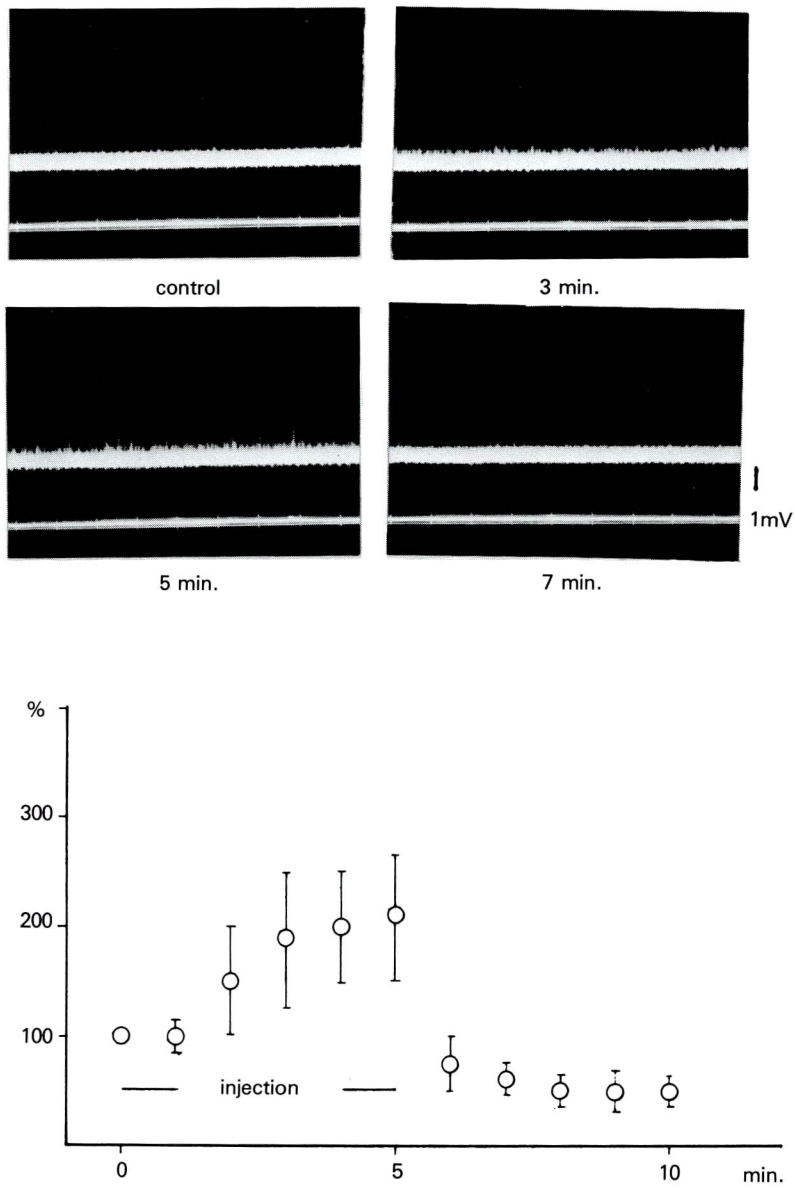


Fig. 3 Structure of capsaicin

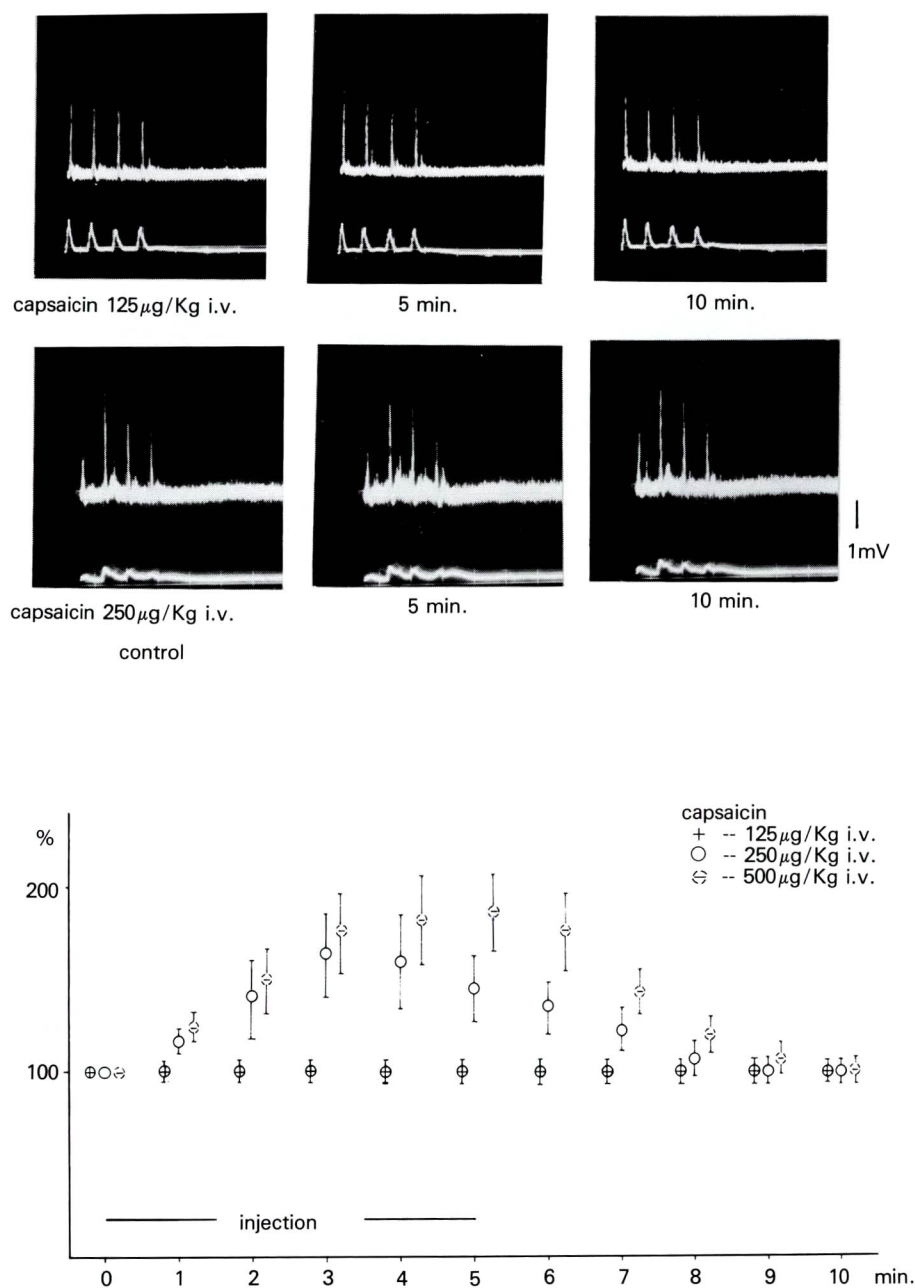


## RESULTS

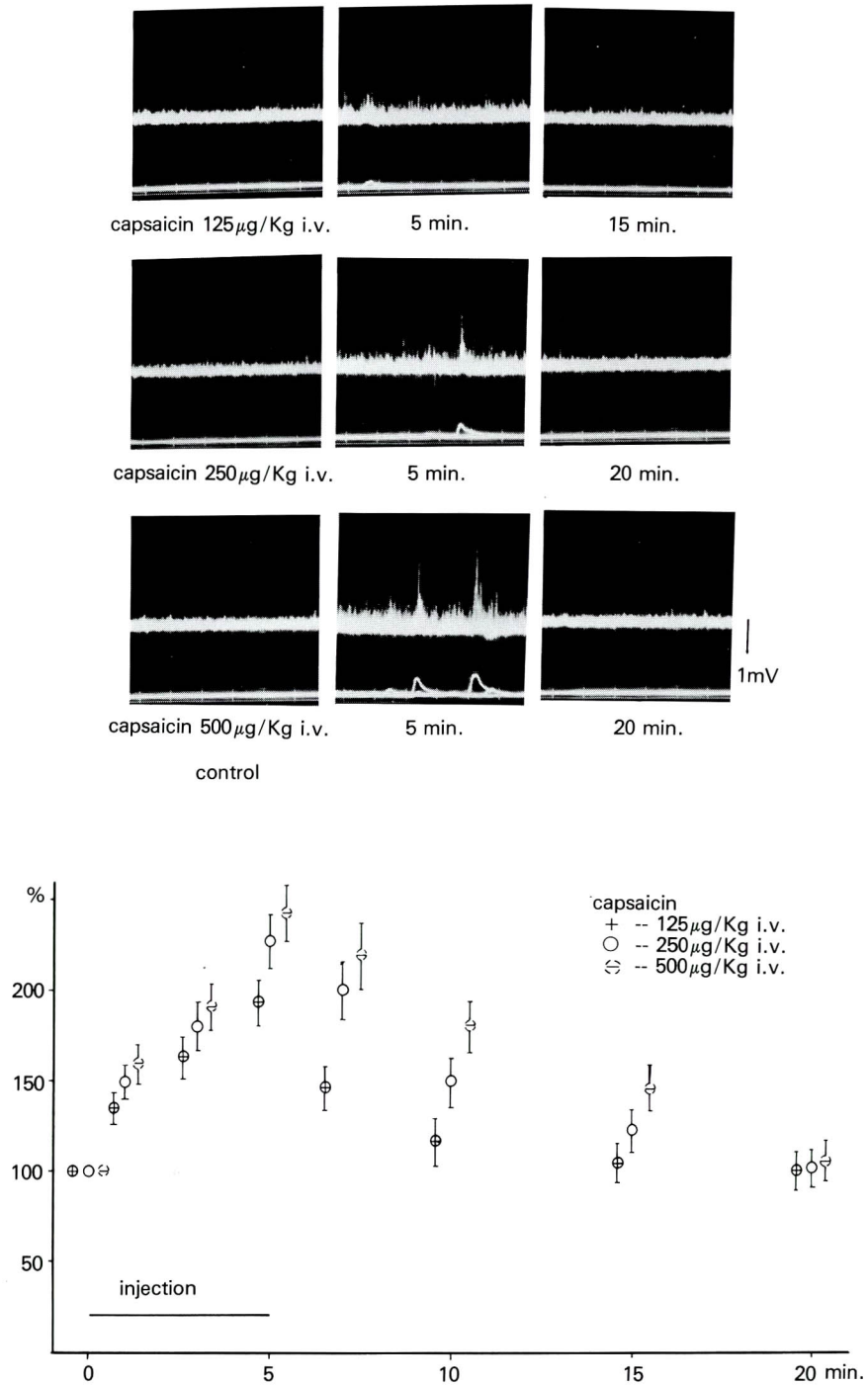
When 125  $\mu\text{g}/\text{Kg}$  of capsaicin was injected into the right cephalic vein in a period of 5 minutes, the spontaneous discharged in the L<sub>7</sub> ventral root increased by 50%  $\pm$  45% (mean  $\pm$  standard error of percentage in comparison with control values before injection,  $n = 5$ ,  $P < 0.005$  (M.S.P.C.)) 2 minutes after start of the injection. At completion of the injection, the discharge increased by 100%  $\pm$  54% (M.S.P.C.), and it decreased soon after the injection. The neural activity decreased by 50%  $\pm$  12% (M.S.P.C.) 3 minutes after completion of the injection. These results are shown in Fig. 4 as the percent changes (mean  $\pm$  standard error) from the control values before administration of the drug. The amplitude of the C-fiber reflex was increased by capsaicin at doses of 250  $\mu\text{g}/\text{Kg}$  or more i.v., i.e. 250  $\mu\text{g}/\text{Kg}$  of capsaicin i.v. facilitated the reflex by 62%  $\pm$  19% (M.S.P.C.) 3 minutes after start of the injection. At completion of the injection capsaicin 250  $\mu\text{g}/\text{Kg}$  of capsaicin i.v. increased the reflex amplitude by 45%  $\pm$  16% (M.S.P.C.). At 4 minutes after completion of the injection, the reflex amplitude returned to the control level. Capsaicin at a dose of 500  $\mu\text{g}/\text{Kg}$  i.v. increased the reflex amplitude by 82%  $\pm$  22% (M.S.P.C.) after completion 4 minutes after start of the injection, and 5 minutes after completion of the injection, the C-fiber reflex returned to the control level. Fig. 5 illustrates these results. The heat-evoked discharge was increased by capsaicin at doses of 125  $\mu\text{g}/\text{Kg}$  or more i.v. Capsaicin at 125  $\mu\text{g}/\text{Kg}$  i.v. facilitated the discharge by 35%  $\pm$  7% (M.S.P.C.) one minute after start of the injection. On completion of the injection. The heat-evoked discharge was increased by capsaicin at doses of 125  $\mu\text{g}/\text{Kg}$  or more i.v. Capsaicin at 125  $\mu\text{g}/\text{Kg}$  i.v. facilitated the discharge by 35%  $\pm$  7% (M.S.P.C.) one minute after start of the injection. On completion of the injection, the heat-evoked discharge increased by 92%  $\pm$  10% (M.S.P.C.), and 15 minutes after completion of the injection, the heat-evoked discharge returned to the control level. Capsaicin at 250  $\mu\text{g}/\text{Kg}$  i.v. facilitated the discharge by 128%  $\pm$  12% (M.S.P.C.) on completion of the injection, and 15 minutes after completion of the injection, the heat-evoked discharge was facilitated only by 2%  $\pm$  5% (M.S.P.C.). Capsaicin at 500  $\mu\text{g}/\text{Kg}$  i.v. increased the discharge by 142%  $\pm$  12% (M.S.P.C.) on completion of the injection, and 15 minutes after completion of the injection, the heat-evoked discharge was facilitated by 3%  $\pm$  5% (M.S.P.C.). Fig. 6 shows the results.



**Fig. 4** Effect of 125  $\mu$ g/Kg of capsaicin i.v. on the L<sub>7</sub> ventral root spontaneous discharge (voltage of 1 mv/cm)



**Fig. 5** Effects of 125, 250, and 500 µg/Kg of capsaicin i.v. on C-fiber reflexes (1 mv/cm, train of four pulses, 15 V intensity, 2 msec duration)



**Fig. 6** The effects of 125, 250, and 500 µg/Kg of capsaicin i.v. on heat-evoked discharge (voltage of 1 mv/cm)

## DISCUSSION

The acute effects of capsaicin on nociception can be explained by interaction with the central terminals of the primary sensory neurons containing substance P (5, 6). The injection of capsaicin has shown disruption of the thermoregulation of the hypothalamus (7), a region which is known to be rich in substance P (8), and excites nociceptive neurons in the medial thalamus in a selective and opiate-sensitive manner (1). The electrophysiological data suggest that all neurons excited by afferent fibers among A $\delta$  and C fibers are activated by substance P released by capsaicin. Capsaicin may act directly on the neurons in the sensory ganglia, the axons emanating from these cells and their terminals in the dorsal horn, or their sensory endings in the periphery. The present results showed that capsaicin had short acting effects by intravenous systematic administration. The duration of action was within 5 ~ 20 minutes. Acute capsaicin administration has shown increased firing in ventral root discharge. In our data, the C-fiber reflex was facilitated by 125  $\mu$ g/Kg i.v. of capsaicin. The present results indicate that the effect of capsaicin on heat-evoked discharge elicited primarily by A $\delta$  fiber activation, is more distinct than that on the C-fiber reflex. Therefore, we concluded that A $\delta$  fiber has a higher sensitivity to capsaicin than C-fiber.

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