Title: CAPSAICIN: A LONG ACTING PAIN FIBER SPECIFIC LOCAL ANESTHETIC

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Introduction. Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the primary pungent component of hot peppers, produces an acute painful local irritation at the site of topical or subcutaneous administration. This irritation is followed by a profound desensitization to further nociceptive stimuli which can last indefinitely and encompass all body surfaces. [1] Parenteral administration of capsaicin to adult animals also results in a specific depletion of substance P (SP) from primary afferent neurons. [2] The undecapaptide, SP, is thought to be a nociceptive neurotransmitter which may mediate slow dull pain in some C fibers. In this study we characterized the specific sensory modalities affected by capsaicin, determined the relationship between analgesia and depletion of SP, and demonstrated the potential for regional block of chronic pain with capsaicin.

Methods. Hartley guinea pigs were treated with capsaicin (50 mg/kg s.c.). At various times after treatment (1 day-10 weeks) peripheral sensory function was assessed. After sensory testing, animals were killed and SP content of dorsal root ganglia (DRG) and dorsal spinal cord (DC) was determined by a specific RIA. Ability to sense thermal nociceptive stimuli was assessed by determining the latencies to escape from a 60° hot plate and to a skin flinch when a 500 watt lamp was directed at the bare skin of the back. Chemogenic nociception was assessed by determining the response when 1% zingerone solution (25µl) was applied to the eye. The ability to sense mechanical nociceptive stimuli was determined by pricking the skin of the back with a 30 g needle or by the presence or absence of vocalization when a hindfoot was compressed. A separate group of animals was treated with morphine sulfate (10 mg/kg i.p.) and served as positive controls. To investigate the site at which capsaicin acts to produce analgesia, a front footpad of guinea pigs was injected with 8 µg of capsaicin (20 µl) under light ether anesthesia. The contralateral foot served as a vehicle-treated control. At various times after treatment (2 hours-10 days) the response of each foot to a heated probe (100°C) was assessed. Untreated animals removed their feet from the hot probe within 1 sec. Contact with the probe for more than 1 sec was considered an analgesic response. In addition, the ability of each foot to sense noxious chemical agents was determined by injecting 10 µl of 1 N acetic acid into the footpad. Mechanical nociception was assessed by pricking each foot with a 30 g needle. After sensory testing, SP content of ipsilateral and contralateral dorsal root ganglia C_4-C_7 was determined as described above. In a separate experiment, a front footpad of guinea pigs was injected with 20 µl of a 1% etidocaine solution containing 8 µg of capsaicin. The contralateral foot was injected with 20 µl of 1% etidocaine only and the response of each foot to various sensory stimuli was assessed as described above.

Results. Animals treated with capsaicin (50 mg/kg s.c.) demonstrated obvious signs of discomfort immediately after capsaicin injection which subsided within one hour. Within one day of treatment, animals demonstrated modality-specific analgesia which lasted in excess of 10 weeks (Table 1). Capsaicin treatment also depleted SP from DRG and DC by 80 and 45%, respectively ($p < .05$). However, SP depletion was not detectable until two days after capsaicin treatment.

TABLE 1

Sensory function 10 weeks after treatment with capsaicin (50 mg/kg s.c.)

Mean ± SEM or % responding

	Control	Capsaicin	P
Hot plate	4.7 ± 0.6 sec	all > 20 sec	<.01
Skin flinch	10.1 0.7 sec	all > 30 sec	<.01
Zingerone	100%	0%	<.01
Pin prick	100%	100%	-
Paw press	83%	91%	-

Animals treated with 8 µg of capsaicin by unilateral injection into a front footpad demonstrated localized chemogenic and thermal analgesia surrounding the site at which capsaicin was injected. Analgesia occurred in the capsaicin-treated foot within two hours of injection and was still present 10 days after treatment. No statistical change in SP content of ipsilateral or contralateral DRG C_4-C_7 was detected at any time measured (2 hours-10 days) after capsaicin treatment. Combining etidocaine with capsaicin blocked the acute nociceptive effects of capsaicin injection, but had no effect on prolonged capsaicin analgesia.

Discussion. The data indicate that capsaicin is capable of specifically altering the function of afferent neurons involved in the perception of chemogenic and thermal nociception. Depletion of SP from primary afferent neurons does not appear to be the mechanism by which capsaicin induces analgesia since peripheral local injection of capsaicin does not induce SP depletion in DRG of the corresponding dermatome. Finally, combining etidocaine with capsaicin prevents the acute noxious actions of capsaicin leaving only a modality-specific analgesia of extremely long duration (> 10 weeks). Because capsaicin produces a long-lasting regional analgesia, its use in chronic pain treatment deserves extensive study.

REFERENCES

1. Hayes AG and Tyers MB: Effects of capsaicin on nociceptive heat, pressure and chemical thresholds and substance P levels in the rat. Brain Research 189:561-564, 1980.

2. Jessel MG, Iversen LL and Cuello AC: Capsaicin-induced depletion of substance P from primary sensory neurones. Brain Research 152:183-188, 1978.