Effect of capsaicin on the micturition reflex in normal and chronic spinal cord-injured cats

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Effect of capsaicin on the micturition reflex in normal and chronic spinal cord-injured cats. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R786–R794, 1999.—The effect of capsaicin (10–80 mg/kg sc) on reflex activity of the urinary bladder was examined in anesthetized normal as well as anesthetized and awake chronic spinal cord-injured (SCI) cats. In normal cats, capsaicin elicited a transient increase in the frequency of isovolumetric bladder contractions and reduced the volume threshold for inducing micturition, but did not depres the amplitude of bladder contractions or the reflex firing on bladder nerves. In anesthetized SCI cats, capsaicin depressed reflex bladder activity and firing on bladder nerves. In awake SCI cats, capsaicin initially decreased the volume threshold for inducing micturition; however, after a delay of 3–6 h the volume threshold increased and intravesical voiding pressure decreased. This effect persisted for 4–12 days. It is concluded that capsaicin-sensitive C fiber bladder afferents are not involved in initiating reflex micturition in normal cats, but play an essential role in triggering automatic micturition in chronic SCI cats. The results are consistent with the clinical data indicating that C fiber bladder afferents contribute to bladder hyperactivity and incontinence in patients with neurogenic bladder dysfunction.

urinary bladder; spinal cord injury; C fiber afferents; detrusor hyperreflexia

The emergence of a C fiber afferent-evoked reflex in SCI cats is dependent on peripheral and central changes in the reflex pathways (8, 9, 30). First, C fiber afferents are unresponsive to bladder distension in normal cats (17) and therefore their peripheral receptor properties must be altered so that they can respond to bladder distension in chronic SCI animals. Second, the central synaptic connections of C fiber afferents, which are weak in normal animals, must be strengthened after spinal injury to account for the development of strong micturition reflexes and the emergence of a hyperreflexic bladder in SCI preparations (10, 11).

The present experiments were undertaken to evaluate further the role of C fiber bladder afferents in micturition in normal and chronic SCI cats. We attempted to chemically disrupt C fiber afferent functions by administering capsaicin, a neurotoxin, which is believed to act selectively on small diameter afferent neurons (23). The data indicate that capsaicin-sensitive mechanisms are relatively unimportant for the control of micturition in normal cats but play an essential role in initiating micturition in chronic SCI cats. Preliminary accounts of the results have appeared in an abstract (4).

MATERIALS AND METHODS

Fifteen adult female and four male cats (2–3.5 kg) were used in this study. All experiments on normal animals were conducted in α-chloralose-anesthetized preparations (60 mg/kg iv) after induction with halothane (2–3%). Chronic SCI cats were studied in both anesthetized (α-chloralose) and unanesthetized preparations. In anesthetized preparations, a tracheal cannula was inserted to facilitate respiration. Blood pressure was monitored via a catheter in the common carotid artery. Fluids or drugs were administered by a catheter in the femoral or cephalic vein. Some animals breathed spontaneously, whereas others were paralyzed with pancuronium bromide (0.1–0.2 mg/kg iv) and artificially respirated. Body temperature and expired CO2 were maintained within normal limits by external heating devices and by adjusting the rate and depth of respiration, respectively.

Urinary bladder activity was monitored by a catheter (PE-100 tubing) inserted into the bladder through the urethra. The catheter was filled with saline solution and connected to a strain gauge pressure transducer to measure intravesical pressure. In some preparations, the urethra or the urethral orifice was ligated to prevent bladder emptying and thereby record isovolumetric bladder contractions. In other experiments, the bladder was allowed to empty around the catheter. Cystometrograms (CMGs; i.e., bladder pressure-volume curves) were performed by infusing saline into the

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bladder through the catheter at a moderate rate (1.23–2.47 ml/min) using an infusion pump. CMGs were also performed on unanesthetized SCI animals, which were restrained in a plastic cage during the experiment. The animals were briefly (5–10 min) anesthetized with halothane to insert the urethral catheter and then allowed to recover for 1 h before beginning recordings. Before the experiment, the animals were acclimated to the cage during several trial sessions. In general, the animals appeared comfortable and remained quiescent during the recording sessions.

Spinal cord transections were performed using aseptic surgical techniques under halothane anesthesia. The cord was exposed by a laminectomy at the T10–T12 segmental level, and then the cord and dura were cut leaving a wide gap (3–4 mm) between the cut ends. Animals were treated prophylactically with antibiotics (ampicillin 150 mg/kg im) for 1 wk, and the bladder was expressed manually three to four times per day until automatic micturition developed. Animals were studied 2–6 mo after spinal transection. Experimental protocols were approved by The University of Pittsburgh Animal Care and Use Committee.

Electrical recordings on vesical postganglionic nerves were performed in chloralose-anesthetized cats as described previously (7, 12). In brief, the bladder and its innervation were exposed by a midline abdominal incision, and postganglionic nerves on the surface of the bladder were prepared for monophasic, multunit recording with bipolar silver electrodes. The pelvic nerve was exposed and placed on bipolar electrodes for stimulation of afferent and preganglionic efferent axons with rectangular pulses (0.05-ms duration) of varying intensities (0.5–50 V), frequencies (0.5–30 Hz), and patterns (single shocks or trains, 30–100 Hz, 20–100-ms train duration). Abdominal skin flaps were tied to a metal frame to form an abdominal pool, and the area was covered with warm mineral oil. Cutaneous afferent receptors in the perigenital area were stimulated by gently stroking the skin with a cotton swab.

Neural activity was recorded with high-gain preamplifiers and displayed on an oscilloscope or averaged on a digital computer and plotted on a paper recorder. Bladder pressure, blood pressure, expired CO2, and asynchronous neural activity monitored with a window discriminator/ratemeter were displayed on a rectilinear paper recorder.

Drugs

Capsaicin (Sigma) was dissolved in a solution containing 10% ethanol, 20% Tween 80, and 70% distilled water. When animals were pretreated before the experiment with capsaicin, the neurotoxin was administered subcutaneously in divided doses under halothane anesthesia (2–3% in oxygen). Anesthesia was maintained for at least 1 h after the injection.

RESULTS

Spinal Intact Cats

Effect of capsaicin on bladder activity. The acute and chronic effects (4-day pretreatment) of capsaicin (5–100 mg/kg sc) on CMGs and rhythmic isovolumetric bladder contractions were studied in 10 chloralose-anesthetized cats with intact spinal cords (Fig. 1).
Untreated animals exhibited a wide range of bladder capacities (10–30 ml) and bladder contraction amplitudes (30–60 cmH2O). Similar responses were noted in animals \(n = 3\) pretreated 4 days before the experiment with a large dose of capsaicin (50–60 mg/kg sc).

The acute administration of capsaicin during the experiment in doses extending to the lethal level, mean 40 mg/kg (range 20–100 mg/kg sc), did not depress the frequency, amplitude, or duration of rhythmic bladder contractions recorded under isovolumetric conditions in the distended bladder (15–50 ml) (Fig. 2). The volume threshold for inducing the micturition reflex was also not increased by acute capsaicin administration. Rather it was decreased for a period of several hours (Fig. 1B). Similarly, during the initial period (20–40 min) after capsaicin injection, bladder activity recorded isovolumetrically was facilitated in some animals (Figs. 1 and 2). Baseline bladder pressure also increased (5–15 cmH2O). After the initial period of stimulation, subsequent doses of capsaicin did not elicit an increase in bladder activity.

Effect of capsaicin on reflex activity in vesical postganglionic nerves. Electrical recordings on vesical postganglionic nerves revealed asynchronous firing in concert with large-amplitude bladder contractions and synchronous discharges occurring at short (15–25 ms) and long (90–140 ms) latencies in response to electrical stimulation of the pelvic nerve (Fig. 3A). The short-latency responses represent peripheral responses (PR), i.e., postganglionic firing elicited by stimulation of the...
preganglionic pathways to the bladder, whereas the long-latency discharges reflect central reflex responses (CR) elicited by stimulation of afferent axons in the pelvic nerve. Both responses were blocked by ganglionic blocking agents (hexamethonium, 1–5 mg/kg iv), indicating that they represented firing in postganglionic nerves. Capsaicin (10–80 mg/kg sc) did not alter the early or late occurring discharges on bladder postganglionic nerves.

**Chronic SCI Cats**

CMGs in unanesthetized animals. Repeated CMGs were performed in three chronic SCI cats (2 males, 1 female) 2–6 mo after spinal cord transection and after the development of automatic micturition. Intravesical pressure was measured via a catheter inserted into the bladder through the urethral orifice. Several CMGs were performed during each recording session, and several recording sessions were conducted before the administration of capsaicin. The micturition volume thresholds varied considerably between the three animals (10–65 ml) but were reasonably consistent in the same animal. In two animals, low doses of capsaicin (5–10 mg/kg) initially stimulated bladder activity. This effect persisted for several hours after the injection of the drug. Injection of the capsaicin vehicle had no detectable effect. As shown in Fig. 4, the more delayed effect of capsaicin (10–50 mg/kg sc) was a significant

![Fig. 4](http://ajpregu.physiology.org/) Time course of changes in bladder activity during CMGs before and after injection of increasing doses of capsaicin in an unanesthetized chronic spinal cat. A: CMG before capsaicin injection. Capsaicin was then administered 3 times in doses of 15, 15, and 20 mg/kg sc at 5, 7, and 9 days, respectively, after original CMG. B: CMG performed 2 days after capsaicin (15 mg/kg sc). C: CMG performed 2 days after capsaicin (total dose 30 mg/kg sc). D: Increase in volume threshold and decrease in contraction amplitude 5 days after capsaicin injection (total dose 50 mg/kg sc). E: bladder activity 12 days after last capsaicin injection. Arrows, beginning of saline infusion; * in A, B, and C, voiding of large volumes. After largest dose of capsaicin (D and E), only small volumes of fluid were voided during low-amplitude bladder contractions.
increase in the volume threshold (mean, 77%; range 36.5–140%), a decrease in the amplitude of bladder contractions (mean, 49%; range 37.6–60%) (Fig. 5), and a marked decrease in volume of fluid voided. The minimum effective dose of capsaicin ranged from 10 to 30 mg/kg sc. The depressant effect of capsaicin was observed within 3–6 h after administration and persisted for 4–12 days. In one animal, bladder contraction amplitude recovered but the micturition volume threshold remained elevated for the duration of the study (1 mo). After capsaicin administration it was necessary to manually empty the bladders at regular intervals (6–8 h) because they were usually distended with urine. This indicates that capsaicin induces urinary retention. Before capsaicin treatment the bladders were less distended, presumably because they emptied by reflex voiding.

Effect of capsaicin on bladder activity in anesthetized animals. Isovolumetric bladder contractions were recorded in four chronic SCI animals under chloralose anesthesia (Figs. 6 and 7). The amplitudes of the bladder contractions were less (50%) than those recorded in unanesthetized animals just before anesthesia. Two of the animals had received capsaicin treatment 30–45 days before the experiment. Rhythmic bladder contractions in the four animals were markedly reduced in amplitude by capsaicin (5–35 mg/kg sc) (Fig. 6D). A complete block of rhythmic contractions occurred in doses between 10 and 50 mg/kg (Fig. 7C). Excitatory effects (Fig. 6B) with low doses (5–15 mg/kg) of capsaicin were noted in two of four animals before the onset of the depression. The amplitude and frequency of rhythmic, isovolumetric contractions were reduced within 15–20 min after the injection of capsaicin and remained depressed for the remainder of the experiment (1–4 h). Injection of additional fluid into the bladder did not reverse the depressant effect. However, tactile stimulation of the perigenital region still excited the bladder (Fig. 8) when rhythmic bladder contractions were abolished. The bladder contractions elicited by electrical stimulation of preganglionic axons

Fig. 5. Time course of changes in amplitude of bladder contractions after vehicle (V) or small doses (10 mg/kg sc) of capsaicin in an unanesthetized chronic spinal cord-injured animal. Vehicle pretreatment did not depress bladder activity. First 2 doses of capsaicin led to a significant decrease in contraction amplitude followed by partial recovery over course of several days. Decrease in bladder contraction amplitude occurred again with a second administration of capsaicin. Vertical calibration: amplitude of bladder contractions in cmH2O; horizontal calibration: time in days. C, capsaicin administration (10 mg/kg sc).

Fig. 6. Effects of increasing doses of capsaicin on rhythmic bladder contractions under isovolumetric conditions in an anesthetized chronic spinal cord-injured cat. A: rhythmic bladder contractions before administration of capsaicin. B: increase in frequency of bladder contractions 20 min after capsaicin injection (10 mg/kg sc). C: irregular and relatively small bladder contractions 3 h after capsaicin injection (total 15 mg/kg sc). D: suppression of bladder activity 6 h after capsaicin injection (25 mg/kg sc). Capsaicin injections were given 1, 2, and 5 h after control recordings shown in A. Vertical calibration: intravesical pressure in cmH2O; horizontal calibration: time in min.
in the pelvic nerve were not depressed by capsaicin (Fig. 8B).

Effect of capsaicin on reflex activity in vesical postganglionic nerves. Electrical stimulation of the pelvic nerve in chronic SCI animals (n = 4) at intensities sufficient to activate Aδ-fibers (0.75–4 V) did not evoke central reflexes. However, stimulation at higher intensities sufficient to activate C fiber afferents (5–30 V) elicited long-latency (180–220 ms), prolonged discharges (CR; 100–150 ms), as well as short-latency, peripheral ganglionic responses (PR; Fig. 9, A and B). Capsaicin (5–25 mg/kg sc) produced a rapid onset (15–25 min) depression of the late central reflex (Fig. 9, B and C) without altering the early peripheral ganglionic response (Fig. 9, C–E). The depression remained for the duration of the experiment (2–3 h).

DISCUSSION

The present experiments revealed that the effects of capsaicin on the urinary bladder of the cat are markedly influenced by spinal cord injury. In cats with an intact neuraxis, capsaicin administered systemically had primarily a facilitatory effect on reflex bladder activity, whereas in chronic SCI cats capsaicin had a prolonged depressant effect. These responses are consistent with the selective actions of capsaicin on small diameter afferents (23) and current concepts regarding the organization of micturition reflex pathways in normal and chronic SCI animals (7–10, 26).

The excitatory effects of capsaicin in the normal animal are most reasonably attributed to stimulation of C fiber afferents in the bladder (23). These afferents are of a high threshold type that do not respond to bladder distension but do respond to noxious stimulation such as chemical irritation (17). These afferents have been named silent C fibers (17, 18, 23). Activation of nociceptive afferents by the application of local irritants to the bladder facilitates the micturition reflex and produces bladder hyperactivity (2, 5, 21, 24, 28, 32). This hyperactivity must occur at least in part by facilitation of the central reflex pathways. Because capsaicin is known to excite and then desensitize C fiber afferents (23, 25), its facilitatory effects on the bladder are likely to be elicited by a similar mechanism. Activation of myelinated Aδ-af fferents that comprise the afferent limb of the micturition reflex pathway in normal animals might also contribute to the response, because some of these afferents can be excited by capsaicin (23).

Large doses of capsaicin in normal animals produced a prolonged facilitation of bladder activity and eventually desensitization of the response to subsequent doses of capsaicin. However, bladder reflexes were not blocked. This indicates that Aδ-afferents in the cat, unlike those in the rat (5, 23, 25), are resistant to the toxic effects of...
capsaicin. In the rat, large doses of capsaicin blocked micturition for 12–18 h (5).

In chronic SCI cats that had developed automatic micturition, capsaicin depressed the micturition reflex. This was evident as an increase in the volume threshold for inducing micturition, a decrease in the amplitude of micturition contractions, as well as a depression of reflex activity on bladder postganglionic nerves and rhythmic bladder contractions in anesthetized animals. The depressant effects were preceded by a transient facilitation of bladder activity in 50% of the animals. The dose of capsaicin to elicit excitation was low (5–10 mg/kg sc) in both normal and chronic SCI animals, whereas the dose to suppress bladder activity in chronic SCI animals was higher (5–35 mg/kg sc). This is consistent with the findings that low concentrations of capsaicin excite and high concentrations desensitize or block C fiber afferent nerves.

It is clear that the effects of capsaicin in chronic SCI cats were affected by chloralose anesthesia. In anesthetized animals capsaicin could completely block the micturition reflex, whereas in unanesthetized cats capsaicin reduced the micturition reflex and increased the bladder volume threshold for inducing micturition but never completely blocked reflex activity. This difference is most reasonably attributable to a synergistic interaction between the anesthetic and capsaicin. Anesthetics are known to suppress the micturition reflex and to have a greater effect in chronic SCI animals than in animals with intact neuraxes (6, 31). Furthermore, in the present study, when bladder activity was recorded in the same cat before and after the administration of chloralose, it was noted that the anesthetic reduced the amplitude of reflex bladder contractions. Thus autonomic synapses in the spinal cord already partially depressed by anesthesia may be more susceptible to a reduction of afferent input induced by capsaicin.

The present experiments indicate that capsaicin administered systemically may act at multiple sites to reduce bladder activity. On the basis of the extensive literature (23, 24) regarding the selective neural actions of capsaicin, it seems reasonable to assume that the toxin depresses C fiber afferent input to the spinal cord from tension receptors in the bladder wall. It is clear that capsaicin does not affect the effenter pathway to the bladder, because it did not alter 1) the postganglionic nerve action potentials or the bladder contractions evoked by preganglionic nerve stimulation, 2) the reflex bladder contractions and postganglionic nerve firing elicited by tactile stimulation of myelinated somatic afferent nerves in the perineum, or 3) bladder reflexes in normal cats. Because the same parasympathetic effenter pathway mediates the micturition reflex in normal cats as well as the C fiber bladder reflex in chronic SCI cats, a selective effect of capsaicin on the latter must be due to an action on the effenter limb of the pathway. However, on the basis of data from experiments in which the effenter axons in the pelvic nerve were electrically stimulated, it seems reasonable to propose that the depression of the evoked reflexes by capsaicin must have been due to the action of the toxin on the effenter axons in the peripheral nerves and dorsal roots or on the central effenter terminals in the spinal cord. An alternate explanation is that the electrically evoked reflexes depend on facilitation produced by tonic affenter activity arising in the bladder. Depression of this putative tonic activity by capsaicin would then indirectly reduce the evoked reflexes. This mecha-
nism seems less likely because the C fiber-evoked bladder reflex in chronic SCI cats (11) can be elicited when the bladder is empty, and therefore the activation of this reflex pathway does not appear to depend on facilitation by tonic bladder afferent input. Capsaicin might have multiple effects on C fiber bladder afferents, including 1) initial stimulation followed by acute desensitization of the afferent terminals and block of afferent firing, 2) depletion of neuropeptide transmitters in the afferents, and 3) degeneration of the afferent terminals in the bladder wall or in the spinal cord (23, 24). The effect of capsaicin to produce an initial stimulation of the bladder consisting of a decrease in the micturition volume threshold during CMGs and an increase in the frequency and amplitude of rhythmic bladder contractions under isovolumetric conditions supports the view that capsaicin stimulates C fiber afferents and that these afferents can facilitate voiding function in the cat. The more prolonged depressive effects of capsaicin on micturition are likely to be due either to loss of transmitter stores and/or afferent terminal degeneration. Neuropeptides such as substance P, vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase activating peptide have been identified in bladder afferents and/or implicated in bladder reflex mechanisms (9, 10). VIPergic afferents have attracted considerable attention in regard to bladder reflexes in paraplegic cats, because VIP-containing afferents form a very prominent projection to the sacral parasympathetic nucleus (20) and VIP is localized specifically to C fiber afferents at the sacral level of the spinal cord of cats (27). In addition, in SCI cats the intrathecal injection of VIP elicits a strong excitatory effect on bladder reflexes that is not seen in normal cats (10). Thus it has been proposed (8, 10) that plasticity in VIPergic, C fiber bladder afferent pathways may underlie the emergence of the C fiber micturition reflex in chronic SCI cats.

In normal cats it appears that the C fiber-evoked bladder reflex is relatively unimportant in the control of micturition because capsaicin treatment did not suppress bladder activity. This is consistent with the observation that C fiber bladder afferents in the cat are silent and do not respond to bladder distension (17). However, in the rat a subpopulation of C fiber bladder afferents does respond to mechanical stimuli (28, 29). Thus capsaicin does alter voiding function in rats with an intact neuraxis even though micturition is triggered primarily by Aδ bladder afferents (5, 23–26). After spinal cord injury in the rat, Aδ bladder afferents continue to play a major role in the initiation of micturition (26). Therefore capsaicin treatment in paraplegic rats does not block voiding as noted in the cat but does reduce bladder hyperreflexia and bladder sphincter dyssynergia (3, 6).

Clinical studies in which capsaicin was tested on patients with neurogenic bladder hyperactivity have demonstrated a number of similarities between cats and humans. For example, in patients with multiple sclerosis (14, 15) or traumatic injuries of the spinal cord exhibiting detrusor hyperreflexia and urge incontinence (13), intravesical administration of a concentrated (1–2 mM) capsaicin solution increased bladder capacity and reduced urinary frequency, urgency, and incontinence. The effect of capsaicin was prolonged, persisting many weeks to months, indicating that it is likely due to degeneration of afferent fibers in the bladder wall. This observation led to the proposal that neurogenic bladder hyperactivity in humans is also triggered by C fiber afferents (8, 9, 13–15).

Damage to central neural pathways also unmasks other types of reflexes mediated by C fiber bladder afferents. The introduction of cold water into the bladder of patients with spinal cord injury or multiple sclerosis induces reflex voiding (16). Cold stimulation has no effect in neurologically normal patients but does trigger voiding in neonates. This suggests that the cold-evoked reflex is a primitive spinal reflex pathway that is expressed in the immature spinal cord, disappears during postnatal development, and then reappears after damage to the spinal cord (16). Electrophysiological studies in cats have revealed that cold temperatures activate C fiber afferents in the bladder (22). Because intravesical capsaicin treatment suppresses cold-induced bladder reflexes in patients with neurogenic bladder dysfunction it seems reasonable to believe that these reflexes in humans as in cats are triggered by C fiber afferents.

In summary, the present experiments have revealed that systemic or intravesical administration of capsaicin can suppress bladder hyperactivity and C fiber afferent-evoked parasympathetic reflexes to the urinary bladder of the chronic SCI cat. Capsaicin did not block Aδ-afferent-evoked supraspinal reflexes in cats with an intact neuraxis. It is concluded that in the cat as well as humans (13–15) that spinal cord injury causes a marked reorganization of the reflex pathways controlling the urinary bladder, leading to the emergence of primitive spinal reflex mechanisms that are triggered by an unusual type of "silent" C fiber afferent. Thus automatic micturition in paraplegic cats is likely to be a useful model system for testing new therapies for the treatment of neurogenic disorders of the lower urinary tract.

Perspectives

Considerable attention has been focused on capsaicin-sensitive C fiber afferents because they are important targets in the treatment of pain (24). However, these afferents can also trigger autonomic reflexes and induce visceral dysfunction. The ability of bladder nociceptive afferents to induce hyperactive voiding is not surprising, when one considers that the most effective response of the bladder to infection or to irritant substances in the urine would be increased voiding frequency. Thus C fiber-evoked bladder reflexes are most reasonably viewed as primitive defense mechanisms to trigger bladder emptying. Why neurological diseases, such as multiple sclerosis, or spinal cord injury cause the emergence of spinal C fiber-mediated voiding reflexes is not known. However, this may occur in response to elimination of bulbospinal pathways
followed by reorganization of synaptic connections in the cord. It is also known that ion channel expression in bladder afferent neurons is changed after spinal cord injury (30). This increases neuronal excitability and might allow nociceptive afferents to respond to nonnoxious bladder activity. It has been speculated that this afferent plasticity occurs indirectly as a result of uncoordinated bladder-sphincter activity, which increases urethral outlet resistance, followed by bladder hypertrophy and increased levels of neurotrophic factors in the bladder. The latter in turn can induce changes in neuronal properties. Regardless of the mechanism underlying the emergence of C fiber-evoked changes in neuronal properties, this information is valuable and simple supplement to routine cystometric investigation.

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