Drug Effects on Urinary Bladder Tone during Spinal Morphine-induced Inhibition of the Micturition Reflex in Unanesthetized Rats

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In an unanesthetized chronic rat model involving the placement of one catheter in the bladder for cystometrography and one catheter in the intrathecal (IT) space for drug injections, 10 μg morphine sulfate injected intrathecally (IT) produced long-lasting inhibition of the volume-evoked micturition reflex. During inhibition of the micturition reflex, intravesical pressure rose with infusion until a continuous emission of urine (dribbling) was observed. Such a level of intravesical pressure (overflow pressure) was significantly greater than the premorphine bladder opening pressure (+56%). During dribbling, no periodic vesical contractions were observed, and the effects of a variety of agents on bladder tone were assessed. Significant (P < 0.05) increases in vesical pressure over that produced by morphine were observed after intraperitoneal (ip) injection of carbachol (+86%), bethanechol (+55%), norepinephrine (+53%), methoxamine (+88%), and ST-91, an α-adrenergic agonist (+70%). The increased vesical pressure was not accompanied by an increase in the rate of urine expression. Intraperitoneal injection of serotonin produced no effects on intravesical pressure or urine expression. Significant decreases in the otherwise elevated intravesical pressure were observed after ip injection of isoproterenol (+30%) and phenolamine (+21%), with a small change in the rate of urine expression. In contrast, ip injection of apomorphine (dopamine agonist) resulted in significant decreases in vesical pressure (+49%) and near maximal emptying of the bladder. Apomorphine produced no effects on it morphine-induced antinociception as assessed by the tail flick response. Regarding potential treatments of spinal morphine-induced urinary retention, the present study suggests that: 1) cholinomimetic and α-adrenergic agonist agents might be harmful; 2) β-adrenergic agonist and α-adrenergic blocking agents might be useful; and 3) dopaminergic agonist agents might be the drugs of choice. (Key words: Analgesics, narcotic; morphine. Anatomy: intrathecal space; urinary tract. Anesthetic techniques: intrathecal morphine. Complication: urinary retention. Cystometrography. Dopaminergic nervous system: apomorphine. Parasympathetic nervous system: bethanechol; carbachol. Serotonin. Sympathetic nervous system: isoproterenol; norepinephrine; methoxamine; phenolamine; ST-91.)

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The direct effects of opiates mediated by receptors in Rexed's laminae 1, 2, and 5 of the dorsal horn of the spinal cord have been demonstrated in animals.1–3 Based on the loss of binding following rhizotomy, the receptors are thought to be located in part on primary afferent terminals. The presence of opioid receptors in the spinal cord led to the lumbar intrathecal (it) injection of small doses of morphine resulting in intense prolonged analgesia of the hind limbs in several unanesthetized animal models.4,5 Such observations led to the iit and epidural injections of small doses of morphine in humans for pain relief.6,7 Unfortunately, unwanted side effects, such as urinary retention, may arise. In young male volunteers receiving 2–10 mg of epidural morphine, up to 90–100% incidence of retention can be expected.8,9 In a prospective study on the effects of epidural morphine for postoperative pain relief in 1085 patients, 42% incidence of retention has been reported.10 Urinary retention in itself is not usually a serious complication, but untoward consequences might be expected if vesical catheterization should lead to urinary infection, following surgical intervention.11

To study the spinal pharmacology of the micturition responses in the unanesthetized animal, we developed a chronic rat model involving the placement of one catheter in the bladder for cystometrography and one catheter in the IT space for drug injections.12 On this model, it morphine induced complete inhibition of the micturition reflex. During micturition blockade, we examined the effects of certain conventional neurotransmitters and derivatives on bladder tone.

Materials and Methods

Surgical Procedure

Animal preparation and the reliability of the in vivo chronic unanesthetized rat bladder model have been reported elsewhere.12 Briefly, adult male Sprague-Dawley rats (250–300 g) were anesthetized with halothane 2% in air. Bladder catheters made of polyethylene-100 (PE-100) tubing were heated at the bladder end to create a collar. A 1.5-cm abdominal incision was made on midline rostrally from the pubic bone. The vertex of the bladder was then incised, and the tip of the catheter was passed into the bladder. The bladder wall
Fig. 1. Typical cystometrogram carried out in an unanesthetized male rat during continuous saline infusion (250 μl/min). The top tracing indicates the bladder pressure (cm H₂O), and the lower tracing, the volume of urine in the collection cup (ml), as a function of time (min). The left tracing was made at a rate of 5 mm/min. The right tracing from the same rat was made at a five-fold faster rate to show the temporal relationship between the notch (BOP) observed in the rising phase of the bladder contraction and the expression of urine (vertical dashed line). BP = baseline pressure; BOP = bladder opening pressure; PP = peak pressure; V = volume of urine expressed per bladder contraction.

was tightly sutured around the collar of the catheter. The catheter was then tunneled subcutaneously to exit through the skin in the back of the neck caudad to the site of intrathecal catheterization. To prevent urine leakage and infection, the external tip of the catheter was closed with a stainless steel pin. Abdominal muscles and skin were sutured in two planes.

Intrathecal catheters were made of polyethylene-10 (PE-10) tubing. Catheterization of the subarachnoid space was described previously. Briefly, rats were mounted in a stereotaxic instrument. A midline incision was made at the level of the superficial neck muscles beginning at the occipital crest and extending caudally about 2 cm. Subsequent retraction of the underlying muscle layer exposed the atlanto-occipital membrane. The membrane was incised with a 22-G needle and then gently retracted with a small hook. The tip of the PE-10 catheter was inserted into the subarachnoid space and then carefully advanced in a caudal direction for 8–9 cm. The caudad end of the catheter was located at the level of the lumbar enlargement. The external tip emerged through the skin in the occipital region and was closed with a stainless steel pin. Neck muscles and skin were sutured in two planes. Animals were allowed to recover for a few days. Amikacin sulfate (2.5 mg/kg) was injected intramuscularly once daily to prevent urinary infection in animals with chronically implanted bladder catheters.

CISTOMETROGRAPHY

The unanesthetized animal was placed in a hemicylindrical restraining cage narrow enough to prevent front-to-back rotation and large enough to permit the animal to adjust itself in a normal posture. Under the rear of the animal was a collecting funnel whose neck opened into a lever arm-mounted cup connected to a strain gauge for measurement of urine volume expressed per bladder contraction. The bladder catheter was connected to a pump for continuous saline infusion (250 μl/min) and to a transducer for monitoring bladder pressure. Given an average volume of 1 ml per bladder contraction, such a rate of infusion induces bladder contractions every 4 min. Transducer and strain-gauge outputs were recorded simultaneously on a two-channel pen writer. The following parameters of the micturition reflex can be measured: baseline pressure (BP), bladder opening pressure (BOP), peak pressure (PP), and volume of urine expressed per bladder contraction (V) (fig. 1). After it injection of morphine, animals displayed a rise in intravesical pressure. At a critical pressure level (overflow pressure, OVP), continuous emission of urine (dribbling) occurred (fig. 2).

Compared to previously reported models, the present model has four major advantages: 1) absence of the inhibitory effect of anesthetics on the micturition reflex; 2) possible assessment of bladder contraction-sphincter relaxation coupling due to the absence of catheter in the urethra; 3) chronic catheterization allows several injections over several days; and 4) possi-

Fig. 2. Cystometrogram carried out in an unanesthetized male rat before and after it injection of morphine 10 μg. Morphine produced complete blockade of the micturition reflex 25 min following injection. Blockade lasted 2 h. P = pressure; V = volume of urine; OVP = overflow pressure. Chart speed = 5 mm/min.
Table 1. Comparative Effects of Systemically Injected Drugs on Bladder Emptying in Presence or Absence of Spinal Morphine

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Bladder Body Response</th>
<th>Internal Sphincter Response</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic drugs</td>
<td>Contraction</td>
<td>Relaxation†</td>
<td>Bladder emptying</td>
</tr>
<tr>
<td>Without spinal morphine*</td>
<td>Contraction</td>
<td>Contraction</td>
<td>Increase in overflow pressure with no bladder emptying</td>
</tr>
<tr>
<td>With spinal morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sero-tonic drugs</td>
<td>Contraction</td>
<td>Relaxation†</td>
<td>Bladder emptying</td>
</tr>
<tr>
<td>Without spinal morphine</td>
<td>Contraction</td>
<td>No effect</td>
<td>No bladder emptying</td>
</tr>
<tr>
<td>With spinal morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenergic drugs</td>
<td>Contraction</td>
<td>Relaxation†</td>
<td>Bladder emptying</td>
</tr>
<tr>
<td>α-Agonist</td>
<td>Contraction</td>
<td>Contraction</td>
<td>Increase in overflow pressure with no bladder emptying</td>
</tr>
<tr>
<td>Without spinal morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With spinal morphine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>α-Antagonist and β-agonist</td>
<td>Relaxation</td>
<td>Relaxation</td>
<td>Decrease in intravesical pressure during bladder contraction</td>
</tr>
<tr>
<td>Without spinal morphine</td>
<td>Further relaxation (?)</td>
<td>Relaxation</td>
<td>Decrease in overflow pressure with no bladder emptying</td>
</tr>
<tr>
<td>With spinal morphine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dopaminergic drugs‡</td>
<td>Contraction</td>
<td>Relaxation†</td>
<td>Bladder emptying</td>
</tr>
<tr>
<td>Without spinal morphine</td>
<td>Contraction</td>
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</tr>
<tr>
<td>With spinal morphine</td>
<td></td>
<td>Bladder emptying</td>
<td></td>
</tr>
</tbody>
</table>

* Effects in the absence of spinal morphine derive from unpublished data collected by P. A. C. Durant, P. C. Lucas, and T. L. Yaksh on the same rat model.
† In this context, relaxation means that the micturition reflex is unaltered, i.e., bladder contraction is coupled to sphincter relaxation.
‡ Apomorphine (dopamine agonist) has been shown to be effective by the iv route as well (unpublished data).

ble comparison between central (spinal) and peripheral drug effects.

Drug Administration

After establishing a baseline of 4–6 stable micturition responses, agents were administered. For it administration, agents were prepared such that the final dose was administered in a volume of 10 μl. This volume was delivered by hand-driven syringe pump followed by 10 μl of saline to flush the catheter. Dye studies have shown that such a volume spreads in the cerebrospinal fluid from the midthoracic to sacral levels. Drugs administered intraperitoneally (ip) were delivered in a volume of 0.2 ml/100 g.

To induce blockade of the micturition reflex, morphine sulfate 10 μg was injected it. One group of animals was injected with morphine only. This group served as a reference for duration of micturition blockade and analgesia.

In the other groups, animals received one of the following agents during it morphine-induced inhibition of the micturition reflex: carbachol chloride (100 μg, ip), bethanechol chloride (300 μg, ip), serotonin creatinin sulfate (1,800 μg, ip), norepinephrine hydrochloride (300 μg, ip), isoproterenol hydrochloride (100 μg, ip), methoxamine hydrochloride (3 mg, ip), ST-91 chloride (300 μg, ip), phenylamine hydrochloride (1 mg, ip), or apomorphine hydrochloride (100 μg and 300 μg, ip; 30 μg and 100 μg, it). All doses (the highest doses for apomorphine) correspond to the maximally effective doses of those agents given in the absence of spinal morphine (unpublished observations). Bladder body and internal sphincter responses to those agents are summarized in table 1. All doses refer to the salt. ST-91, an ε2-selective adrenergic agonist, is a polar analog of clonidine. Thus, ST-91 exerts mainly peripheral effects after systemic administration. Apomorphine has been chosen as dopaminergic agonist agent because its effects are significantly more potent than that of dopamine.

All drugs were freshly dissolved in saline before use. Apomorphine was dissolved in 50% dimethylsulfoxide solution with 0.01% L-ascorbic acid as an antioxidant. In other experiments, those vehicles have been shown to be without effect on the micturition reflex.

Nociceptive Test

To assess antinociception in the morphine group and in the morphine-apomorphine groups, the tail flick test was used. The tail flick response was thermally evoked by laying the tail of the rat over a slit, through which the light of a 300 W quartz bulb was focussed. Time between stimulus presentation and the rapid removal of the tail from the slit was defined as the response latency. To prevent tissue damage, the trials were terminated.
after 6 s. Analgesia was assessed 5, 20, 60, 120, 180, 240, and 300 min following its injection of morphine.

**STATISTICS**

In the group of animals that received morphine only, premorphone BOP values were compared to postmorphine OVP values with the paired *t* test. For each animal, the morphrine rate of urine expression was computed. In addition, the volume of saline infused into the bladder and the volume of urine expelled between the injection of morphine and the beginning of dribbling were computed. The difference between the infused volume and the volume expelled was considered as the residual volume. For example, in figure 2, the morphrine rate of infusion was calculated to be 0.24 ml/min, the time between morphine injection and beginning of dribbling was 28.5 min, and the volume expelled between morphine injection and dribbling was calculated to be 5.7 ml. Thus, the residual volume was (0.24 ml × 28.5) - 5.7 ml = 1.14 ml.

In groups that received an additional agent during it morphine-induced micturition blockade, pre-drug and post-drug OVP values were compared by the paired *t* test. In each animal, pre-drug OVP value was assessed when the intravesical pressure was stable for at least 10 min. Post-drug OVP value was measured at the time of maximal effect. In addition, during dribbling, volumes of urine expressed during the 10-min periods preceding drug administration and that following drug administration at the time of maximal effect were compared by the paired *t* test. In the apomorphine groups, to estimate the percent of the residual volume expressed during the 10-min period following apomorphine injection, the rate difference (table 2) was divided by the residual volume.

To determine if apomorphine produced any effect on antinociception, the areas under the time-response curves (AUC) in the morphine group and in the morphine-apomorphine groups were measured by the trapezoidal rule. Briefly, each AUC is the sum of the individual trapezoids in which the heights are the response latencies minus the predrug baseline latencies and the bases, the time intervals between measurements. Comparison of the AUCs between the morphine group and the morphine-apomorphine (300 μg, ip) group was made by the paired *t* test (same animals used 3 days apart). Comparison of the AUCs between the morphine group and the morphine-apomorphine (100 μg, it) group was made by the unpaired *t* test.

**Results**

**EFFECTS OF IT MORMINE ON BLADDER TONE**

Immediately following its injection of morphine 10 μg, a few irregular bladder contractions were routinely observed. Complete blockade occurred by 16 ± 8 min (mean ± SD, *n* = 7) following morphine injection, and was characterized by an initial rise in intravesical pres-
sure during which no urine was expressed. When the intravesical pressure reached a critical level (OVP), continuous emission of urine was observed (fig. 2). During dribbling, the rate of urine expression was equivalent to the rate of saline infusion (2.5 ml/10 min). In this unanesthetized model, complete blockade was long-lasting (274 ± 100 min, mean ± SD, n = 4) and naloxone-reversible (TL Yaksh, unpublished observations). During dribbling, OVP values (50 ± 9 cm H₂O) were significantly greater than premorphine BOP values (32 ± 5 cm H₂O, mean ± SD, n = 7, P < 0.01), and the residual volume in the bladder was 1.44 ± 0.48 ml (mean ± SD).

During this period, tail flick response latencies rose to a maximum of 6 s in all animals. Reappearance of the micturition reflex corresponded temporally with the return of the nociceptive response.

**DRUG EFFECTS DURING IT MORPHINE-INDUCED MICTURITION BLOCKADE**

During it morphine-induced inhibition of the micturition reflex, the effects of certain conventional neurotransmitters and derivatives on the micturition reflex were assessed. Typical responses are shown in figures S–6. Quantitative results are summarized in table 2.

**Cholinomimetic Agents:** Carbachol and bethanechol produced significant, long-lasting (>30 min) increases in intravesical pressure (+86% and +55%, respectively). No evidence of sphincter relaxation was observed during the increased vesical pressure. Thus, as shown in figure 3, no significant increases in rate of urine expression was observed, even during the peak of bladder contraction.

**Serotonin:** Serotonin produced no statistically significant changes in overflow pressures and rates of urine expression.

**Adrenergic Receptor Agonist and Antagonist Agents:** Noradrenephrine produced rapid (within 5 min) significant long-lasting (>30 min) increases in vesical pressure (mean change: +53%). No changes in rates of urine expression were observed.

Methoxamine, an α₁-selective adrenergic agonist, produced significant long-lasting increases in vesical pressure (mean change: +88%) with no changes in rates of urine expression. In four of six animals, peak pressure was observed around 20–24 min following methoxamine injection. Peak pressure values ranged between 98 and 110 cm H₂O. During the peak, no increase in urine expression was observed.
ST-91, an α2-selective adrenergic agonist, produced significant increases in vesical pressure (mean change: +70%) with no changes in rates of urine expression. In two of six animals, a peak pressure was observed 17 min following ST-91 injection. During the peak, no urine was expressed.

Isoproterenol, a non-selective β-adrenergic agonist, produced immediate long-lasting (>30 min) significant decreases in vesical pressure (mean change: −50%), with no changes in rates of urine expression (fig. 4).

Phentolamine, an α-adrenergic blocking agent, produced significant decreases in vesical pressure (mean change: −21%) with no changes in rates of urine expression.

Dopaminergic Receptor Agonist Agent: Shortly after ip administration of apomorphine (100 µg and 300 µg), periodic emission of urine was observed and associated with a reduction in intravesical pressure (−41 and −49%, respectively). In the 100 µg group, small bladder contractions were observed during emission of urine. In the 300-µg group, sustained contractions of the bladder were observed. During the 10-min period following ip injection of apomorphine (100 µg and 300 µg), most of the residual volume was expelled from the bladder (56% and 77%, respectively). At both doses, onset of action ranged between 2 and 6 min after injection. The mean duration of action was 6 min in the 100 µg group and 31 min in the 300 µg group (fig. 5).

Apomorphine it (30 and 100 µg) produced moderate changes in vesical pressures (−12% and −23%, respectively) and rates of urine expression (+6% and +48%, respectively) (fig. 6). In those two groups, 7% and 48% of the residual volume were expelled from the bladder during the 10-min period following it injection of apomorphine, respectively. Most of the animals that received apomorphine displayed typical stereotyped (sniffing and licking) behavior.

With regard to the effect of apomorphine on the it morphine-induced antinociception, the AUC values in the morphine group (548 ± 299 s × min, mean ± SD, n = 7) were not different from the values in the morphine-apomorphine 300 µg ip group (609 ± 308 s × min, mean ± SD, n = 7) and from those in the morphine-apomorphine 100 µg it group (719 ± 358 s × min, mean ± SD, n = 6).

Discussion

INNERVATION OF THE RAT URINARY BLADDER

In mammals, afferent impulses from the bladder travel up the pelvic nerves via Aδ and C fibers to the sacral cord to form the afferent limb of the micturition reflex. The pelvic (mainly parasympathetic) and hypogastric (mainly sympathetic) nerves form the efferent limb.

In rats and humans, a rich and uniform plexus of cholinergic fibers is present in all layers of the detrusor muscle and trigone. In the bladder neck, cholinergic nerves continue into the proximal urethra. In contrast to the uniform distribution of parasympathetic post-ganglionic fibers, termination of adrenergic fibers shows prominent species variations and marked re-

Fig. 5. Cystometrogram carried out during it morphine-induced micturition blockade. Apomorphine (APO) ip produced near complete emptying of the bladder, i.e., intravesical pressure dropped to baseline level with emission of a large volume of urine. P = pressure; V = volume. Details as in figures 1 and 2.

Fig. 6. Cystometrogram carried out during it morphine-induced micturition blockade. Apomorphine it produced significant decreases in overflow pressure. P = pressure; V = volume. Details as in figures 1 and 2.
SPINAL MORPHINE AND URINARY RETENTION IN RATS

The adrenergic innervation of the rat bladder is scanty; the proximal third is totally devoid of adrenergic fibers, the middle third contains small groups of fibers posteriorly and laterally, and the distal third, i.e., the base, displays more abundant adrenergic fibers that are still more prominent posteriorly, i.e., in the trigone and lateral part of the detrusor muscle. Control of the detrusor muscle by adrenergic sympathetic fibers may be direct or indirect by inhibiting parasympathetic ganglionic transmission. In rats, a rich adrenergic nerve supply has been identified in the smooth muscle layer of the urethra. However, in the bladder and urethra, the distribution of adrenergic receptor-subtypes is not uniform. The β-adrenergic receptors are predominant in the detrusor and the α-adrenergic receptors in the trigone and proximal urethra. Thus, during the collecting phase, the detrusor relaxes through activation of the β-adrenergic receptors by the released norepinephrine to retain urine, and the trigone area contracts through that of the α-adrenergic receptors to close the outlet. Bladder expansion gives rise to activity in sacral parasympathetic outflow and leads to bladder contraction and sphincter relaxation.

The central limb of the bladder innervation is less well understood. Classic studies by Barrington emphasized the role of brainstem centers in the micturition reflex. Bulbospi nal projections containing norepinephrine, serotonin, and, possibly, dopamine are thought to reach the sacral spinal cord. The role of those descending pathways in modulation of the micturition reflex is still unknown.

DRUG EFFECTS ON BLADDER FUNCTION

Intrathecal Morphine: In mammals, activation of the parasympathetic pathways to the detrusor muscle and inhibition of somatic input to the external urethral sphincter are the essential neuronal events initiating release of urine. In rats, enkephalin fibers are found interspersed among preganglionic parasympathetic neurons in the sacral parasympathetic nucleus. In addition, enkephalin fibers parallel the localization of primary visceral afferents found in the pelvic nerve. In cats, firing in vesical parasympathetic postganglionic nerves is inhibited by it injection of enkephalins. In the present study, massive inhibition of primary afferent processing by it injected morphine produced detrusor relaxation, possibly by interaction with parasympathetic outflow to the bladder. Similarly, the tonic bladder is a common occurrence after destruction of the sensory nerve fibers from the bladder to the cord (crushing injuries, tabes dorsalis). In addition, the present study suggests that it-injected morphine may produce an increase in tone in the external urethral sphincter, possibly by disinhibition of the somatic input to the sphincter (OVP values significantly greater than pre-morphine BOP values: +56%). It is worth noting that, in multiple sclerosis, all patients with clinical evidence of upper motor neuron lesions at the lumbar and sacral levels display an increase in external sphincter tone. In addition, it has been demonstrated that the striated muscle has the potential of producing a serious outlet obstruction if it becomes spastic.

Agents Increasing Bladder Tone: Agents known to induce bladder emptying (carbachol, bethanechol, nor epinephrine, methoxamine, and ST-91) after systemic administration produced significant increases in vesical pressure with no changes in the rate of urine expression during it morphine-induced urinary retention. Failure of sphincter relaxation coincident with a detrusor contraction is termed detrusor-urethral sphincter dyssynergia. This condition has been identified in patients with various neurologic problems, including spinal injury, multiple sclerosis, and diabetes. In the present circumstance, the failure to increase the rate of urine expression at least transiently in the face of increased vesical pressure actually suggests that the drugs either concurrently increased sphincter tone or that active contraction of the bladder in the absence of an active sphincter relaxation mechanically increased the resistance to urine passage. In addition, the present study shows that synergism between bladder contraction and sphincter relaxation appears to require the integrity of primary afferent input.

Carbachol, as acetylcholine, retains substantial nicotinic activity, particularly on autonomic ganglia. Bethanechol acts selectively on the bladder smooth muscle (muscarinic effect). Bethanechol has been recommended as a possible treatment for urinary retention after epidural morphine. However, under these circumstances, it would appear that cholinergic-evoked contraction will require passing urine through a dysnergic sphincter. Indeed, bethanechol has been shown to be virtually useless in humans, and to do no more than increase bladder discomfort and distress, suggesting contraction of the bladder through a constricted sphincter.

In rats, serotonergic receptors are present on bladder smooth muscle (5-HT₂ subtype) and on pelvic ganglia. In mammals, the bladder, more than any other tissue, acquires serotonin from circulating blood platelets. Thus, serotonin-induced bladder stimulation might be nerve-independent. In addition, in patients with neurogenic bladder dysfunction, inhibition of serotonin uptake by clomipramine has been shown to promote bladder emptying. In the present study, however, high doses of systemic serotonin produced virtually no effects on the bladder.
In the present study, norepinephrine, methoxamine, and ST-91 produced significant increases in vesical pressure. The α-adrenergic receptor subtype being predominant in the trigone and proximal urethra, such effects are likely mediated through direct activation of α-adrenergic receptors. However, it is worth noting that norepinephrine and ST-91 produced those effects at significantly lower doses than methoxamine.

Agents Relaxing Bladder Tone: In most mammals, including rats and humans, the density of α-adrenergic receptors is greater than that of β-adrenergic receptors in the bladder outlet. However, β-adrenergic agonists, even in low concentrations, have been shown to reduce the maximal micturition pressure and the basal flow resistance through the outlet in cats, dogs and rats (Table 1). In the present study, an immediate drop in vesical pressure (~30%) was observed after ip isoproterenol, with not even a transient change in the rate of expression of urine. Following the course of the argument outlined for agents which contract, these observations suggest that the decrease in vesical tone was accompanied by a decrease in sphincter tone. Clearly, had sphincter tone remained constant, the rate of urine expression should have been at least transiently depressed in the face of a decreased vesical tone. Likewise, had bladder tone remained constant, the rate of urine expression should have been at least transiently increased in the face of a decreased sphincter tone.

Systemic administration of phenolamine, given alone, causes a mild fall in outflow resistance in rats (~8%; PAC Durant and TL Yaksh, unpublished observations) and in humans (~52%). In patients, during postoperative epidural morphine analgesia, systemic administration of phenoxybenzamine has been shown to decrease the time of first voiding and the incidence of bladder catheterization. Dyssynergia of the internal sphincter has been successfully treated with adrenergic blocking agents. In the present study, phenolamine administration produced a 21% reduction in OVP values, suggesting significant reduction in flow resistance through the bladder outlet.

Apomorphine: In cats, bulbocapnine, an apomorphine derivative, has been shown to produce complete emptying of the bladder during ether anesthesia. Those effects were prevented by section of the lumbar sympathetic chain. In addition, bulbocapnine has been shown to antagonize the α-adrenergic-induced inhibition of parasympathetic ganglionic transmission. The proposed mechanisms of action of apomorphine and bulbocapnine are direct central antagonism of noradrenergic and dopaminergic inhibitory neurons, and interference with sympathetic outflow. Thus, such agents can mimic the so-called uninhibited neurogenic bladder; i.e., hyperexcitability of the sacral centers induced by lesions of the inhibitory descending pathways. In addition, pharmacologic block of the sympathetic innervation has been shown to reduce urethral flow resistance, increase frequency of urination, and reduce bladder capacity. Apomorphine, given alone, has been shown to produce dose-dependent activation of bladder emptying with the agent more effective when given by the it than the ip route (PAC Durant and TL Yaksh, unpublished observations). In the present study, apomorphine (ip, 300 µg) produced significant drops in vesical pressure (~49%) with near maximal emptying of the bladder (~77% of the residual volume).

Though the mechanisms underlying these results are not completely understood, the dopamine agonist is unique in that it had an apparent effect on mechanisms which control sphincter tone (external, internal, or both). Figure 5 shows a stepwise emission of urine with a concomitant drop in intravesical pressure to baseline level. Such observations can be explained either by a sustained relaxation of the sphincter with a concomitant series of bladder contractions, or by a series of sphincter relaxations which allowed the distended bladder to express its contents. The former hypothesis is more likely because, had series of sphincter relaxations occurred, a stepwise increase in volume of urine with a concomitant stepwise decrease in bladder pressure should have been observed. In addition, apomorphine injected in the absence of spinal morphine at a dose of 300 µg has been shown to induce sustained bladder contractions during continuous saline infusion in the bladder (PAC Durant and TL Yaksh, unpublished observations).

These observations also provide insight into the effects of spinal opiates on the micturition reflex. Spinal morphine blocks the periodic volume-evoked contractions of the bladder. Failure to void is thus not dependent on the sphincter tone. On the other hand, the failure to express urine, even in the face of increased vesical pressure, indicates that opiates also act to block the vesical somatic reflex upon which external sphincter relaxation depends. Such observations indicate that spinal morphine induces urinary retention by two independent mechanisms involving bladder contractility and sphincter tone.

ANALGESIA

Narcotic agents potentiate or antagonize some of the pharmacological effects of apomorphine. For instance, subcutaneous administration of apomorphine potentiates the analgesic effects of subcutaneous morphine in a dose-dependent manner in rats and mice. Very small doses of subcutaneous apomorphine antagonize the locomotor stimulant effect of morphine in rats. In addition, it apomorphine produces significant anal-
CONCLUSIONS AND EXTRAPOLATION TO HUMAN BEINGS

Three guidelines for potential treatments of it morphine-induced urinary retention emerge from the present study: 1) cholinomimetic and α-adrenergic agonist agents might be harmful; 2) β-adrenergic agonist and α-adrenergic blocking agents might be useful; and 3) dopaminergic agonist agents by producing near complete bladder emptying might be the drugs of choice. However, before considering clinical trials, further investigations in other species are necessary. In addition, dopaminergic agents that do not induce vomiting should be tested. Lastly, given the paucity of effective pharmacotherapy in managing the dysuric bladder in a variety of pathological conditions, similar investigations on bladder motility to be carried out in the intact animal should be done in animals after destruction of primary afferent fibers from the bladder or after lesion of the sacral cord.

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