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RAPID ABSORPTION FROM THE URINARY BLADDER OF A SERIES OF *n*-ALKYL CARBAMATES: A ROUTE FOR THE RECIRCULATION OF DRUGS

J.W. BRIDGES, N.S.E. SARGENT* & D.G. UPSHALL*

Institute of Industrial and Environmental Health* and Safety,
University of Surrey, Guildford and the Chemical Defence Establishment*,
Porton Down, Nr. Salisbury, Wilts

1 The rate of loss of a series of *n*-alkyl carbamates from the lumen of the urinary bladders of female rats has been studied.

2 The rate of loss obeys first order kinetics and was not affected by water flux across the bladder wall nor by binding of the carbamates to it.

3 The rate of loss of octyl carbamate was reduced by about 76% by the presence of 5% Tween 80. Histological evidence indicates that this may be due to the formation of a thin luminal lining which may be adsorbed Tween 80 or mucopolysaccharide material.

4 The absorption rate of the carbamates was limited by their hydrophilicity but reached a plateau for the more lipophilic homologues with a half life for loss of approximately 10 min.

5 The implications of these results with regard to the recirculation of unmetabolized drugs and hydrolysed conjugates of drugs, the systemic absorption of intravesically applied cancer chemotherapeutic agents and bladder wall permeability to carcinogens are discussed.

Introduction

Previous work has shown that the urinary bladders of rabbits, dogs and humans are slightly permeable to inorganic ions such as I^-, Na^+, Cl^-, K^+, H^+, Br^- and PO_4^{3-} (Read & Care, 1954; Maluf, 1955; Englund, 1956; Hlad, Nelson & Holmes, 1956; Andrysek & Schuck, 1959; Rapoport, Nicholson & Yendt, 1960). Organic molecules such as glycine, glucose and tryptophan and some of its metabolites are extensively reabsorbed from the urinary bladder of the mouse within 24 h of administration (Bryan, Morris & Brown, 1965; Morris & Bryan, 1966).

Yeates (1960), using a series of sulphonamides, found that there was a molecular weight limit of 200 beyond which these compounds were not absorbed from the bladder; the influence of other molecular features such as lipophilicity and dissociation constant on absorption were not considered.

Although both 5-fluorouracil and the bis-pyridinium oxime HS-6 are small hydrophilic molecules the former is not absorbed from the bladder (Bessman, Johnson & Goldin, 1975) whilst the latter is well absorbed following its intravesical instillation (Kepner & Wolthuis, 1978).

Little or no absorption of high molecular weight compounds such as doxorubicin hydrochloride (Banks, Pontes, Izbicki & Pierce, 1977), neomycin, polymyxin B, bacitracin (Chamberlain & Needham, 1976) cytosine arabinoside or adriamycin (Bessman, *et al.*, 1975) occurs.

Borzelleca (1963; 1965) demonstrated that nicotine is absorbed from rat and rabbit bladders and that the extent of this absorption is dependent on the degree of ionisation of nicotine in accordance with the pH-partition hypothesis.

Jones & Swinney (1961) and Bessman, *et al.* (1975) reported that thiotepa (triethylene thiophosphoramide) was absorbed from the urinary bladders of humans and rats and the latter workers showed that the rate of absorption of thiotepa increased as the asymmetric unit membrane (Vergara, Longley & Robertson, 1969; Hicks & Ketterer, 1969; 1970; Warren & Hicks, 1970) became de-differentiated after feeding the rats with the bladder carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide.

Systematic studies on the influence of factors such as lipophilicity and molecular connectivity index on bladder absorption have not been described previously. The present studies were initiated by the realisation that urethane (ethyl carbamate) was being absorbed from the bladder subsequent to its clearance by the kidneys. The series of aliphatic carbamates selected has previously been used to elucidate the absorption characteristics of the rat intestine; thus a

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direct comparison of the absorptive properties of the intestine and bladder can be made.

Methods

Ethyl[^{14}C]-carbamate (sp. act. 31.4 μCi/μmol; purity >98.9%) was obtained from Fluorochem Ltd., Glossop, Derby. The other ^{14}C-labelled carbamates were synthesized in the Chemistry Division, C.D.E. Porton by condensation of [^{14}C]-urea with the appropriate *n*-aliphatic primary alcohol, sp. act. 0.5 to 1.65 μCi/μmol; purity >99% (Wood, 1977).

Carbamates were made up to a concentration of 5 μmol/ml, 0.2–0.4 μCi/ml in 0.17 M citric acid-disodium hydrogen phosphate buffer pH 6.4 (Analar grade; BDH) with various solubilizing additives as shown in Tables 1 and 2. Tween 80 was obtained from Hopkin & Williams, propan-1,2-diol (Analar grade) from BDH and the detergent Metapol from Durham Chemicals Distributors Ltd.

Water flux rates in the presence of various carbamate solutions were estimated as follows: non-radiolabelled carbamates were dissolved in 0.17 M citrate-phosphate buffer pH 6.4 and to these were added tracer amounts of tritiated water ([^{3}H]-H_2O) and [^{14}C]-polyethylene glycol 4000 ([^{14}C]-PEG 4000) (Radiochemical Centre Ltd., Amersham) in an activity ratio, $^{3}H/^{14}C$, of approximately 5.

Female Wistar albino rats (180 to 230 g) guaranteed free of the nematode bladder parasite *Trichosomoides crassicuda* (Clayson & Cooper, 1970) were

Table 1 Relationship between partition coefficient (P) and first-order atom molecular connectivity index ($^{1}\chi$) of several carbamates and their absorption from the bladder

Carbamate	*Dissolved in*	*Conc. (mM)*	K_a *min*$^{-1}$	$T_{\frac{1}{2}}$*(min)*	*n*	*c*	*P*	$^{1}\chi$	*% dose bound to bladder wall after 30 min*
Ethyl	Citrate-phosphate	5	−0.0236 ±0.0078	29.4 ±7.3	5	4.49 ±0.12	0.7	2.414	1.29 ± 0.23
Propyl	Citrate-phosphate	5	−0.0354 ±0.0019	19.6 ±1.0	4	4.44 ±0.05	2.3	2.914	1.39 ± 0.74
Butyl	20% Propan-1,2-diol in citrate-phosphate	5	−0.0639 ±0.0014	10.8 ±0.2	4	4.66 ±0.12	7.1	3.414	0.64 ± 0.37
Pentyl	20% Propan-1,2-diol in citrate-phosphate	5	−0.0516 ±0.0063	13.4 ±1.4	4	4.59 ±0.08	22.5	3.914	0.23 ± 0.09
Hexyl	20% Propan-1,2-diol in citrate-phosphate	5	−0.0750 ±0.0126	9.2 ±1.3	4	4.60 ±0.04	70.8	4.414	0.76 ± 0.36
Octyl	5% Tween 80 in citrate-phosphate	5	−0.0151 ±0.0026	45.9 ±6.7	4	4.51 ±0.02	700	5.414	1.26 ± 0.20
Decyl	5% Tween 80 in citrate-phosphate	5	−0.0086 ±0.0019	80.6 ±14.6	4	4.58 ±0.02	7000	6.414	1.55 ± 0.27
Ethyl	20% propan-1,2-diol in citrate-phosphate	5	−0.0293 ±0.0059	23.7 ±4.0	3	4.55 ±0.08			—
Ethyl	5% Tween 80 in citrate-phosphate	5	−0.0324 ±0.0087	21.4 ±4.5	3	4.55 ±0.11			—
Butyl	Citrate-phosphate	5	−0.0588 ±0.0052	11.8 ±1.0	5	4.66 ±0.08			0.73 ± 0.19
Octyl	Citrate-phosphate	0.5	−0.0621 ±0.0142	11.2 ±2.1	4	4.33 ±0.07			1.23 ± 0.28
Butyl	20% Propan-1,2-diol in citrate-phosphate	0.5	−0.0698 ±0.0199	9.9 ±2.2	3	4.52 ±0.03			—
Butyl	20% Propan-1,2-diol in citrate-phosphate	50	−0.0626 ±0.0115	11.1 ±1.7	3	4.54 ±0.08			—
Butyl	20% propan-1,2-diol in citrate-phosphate in presence of 50 mM propyl carbamate	5	−0.0765 ±0.0232	9.1 ±2.1	4	4.68 ±0.16			—

Carbamates used and the conditions under which they were studied are shown, together with rates of loss from the bladder (K_a, min^{-1}), half life of loss ($T_{\frac{1}{2}}$, min), number of experiments (*n*), intercept an the *y*-axis (c) and % dose bound to the bladder wall after 30 min. Results are means ± s.d.

used. Anaesthesia was induced by ether and maintained with intraperitoneal pentobarbitone sodium, 60 mg/ml (May & Baker Ltd). A midline incision was made on the abdomen, both ureters were ligated with cotton and the abdomen closed with suture clips except for a small length over the bladder. The urethra was cannulated with PP25 polythene tubing (Portex), and the bladder was emptied by gentle pressure on the bladder wall. This cannula was then removed and replaced with another which was secured by a cotton ligature around the urethra.

Solutions within the bladder lumen were kept well stirred both by removing small amounts into the urethral cannula and rapidly pushing them back in again and by the muscular contractions of the bladder wall.

Solutions (always 1 ml/kg body weight) were instilled into the bladder and samples withdrawn into preweighed plastic scintillation vials (Sterilin Ltd.), and reweighed. The volume of the sample was determined from the weight difference assuming the specific gravity of the sample to be 1.00. Scintillation counting medium was made up as follows: toluene: metapol, 2:1, plus 0.55% w/v 2,5-diphenyloxazole (PPO, Koch-Light Ltd). For double labelled counting 0.05% w/v 1,4-di-2-(4-methyl-5-phenyloxazolyl) benzene (di Me POPOP: Koch-Light Ltd.) was also added; 4 ml of this medium was added to each vial which was then counted in an LKB Wallac 1210 Ultrobeta programmable liquid scintillation counter. Counting efficiency was determined by an automatic external standard using a quench curve established by counting known amounts of tritium or ^{14}C activity in the presence of increasing amounts of carbon tetrachloride.

Blood levels of ^{14}C were determined following the intravesical instillation of 5 mM [^{14}C]-butyl carbamate in 20% propan-1,2-diol in 0.17 M citrate-phosphate buffer pH 6.4 (1 ml/kg). Blood was sampled from the right carotid artery and immediately centrifuged at 2000 *g* for 2 min. Plasma samples (0.1 ml) were added to 1 ml NCS solubiliser (Amersham-Searle) in glass vials and counted as above, after allowing for the attenuation of chemiluminescence by storing the samples in the cold and dark for at least 3 h.

The degree of binding to the bladder wall was determined by removing the entire bladder (approximately 75 mg) at the end of the 30-min absorption period and washing it rapidly (10 to 15 s) twice in ice-cold 0.9% w/v NaCl solution (saline), blotting it dry and solubilizing in 1 ml Soluene 100 (Packard Ltd). The samples were bleached with 0.2 ml isopropanol (BDH Ltd.) and 0.1 ml 100 volume hydrogen peroxide. Samples were counted and then 10 µl standard [^{14}C]-hexadecane (Radiochemical Centre Ltd) was added to each vial and recounted to estimate the counting efficiency.

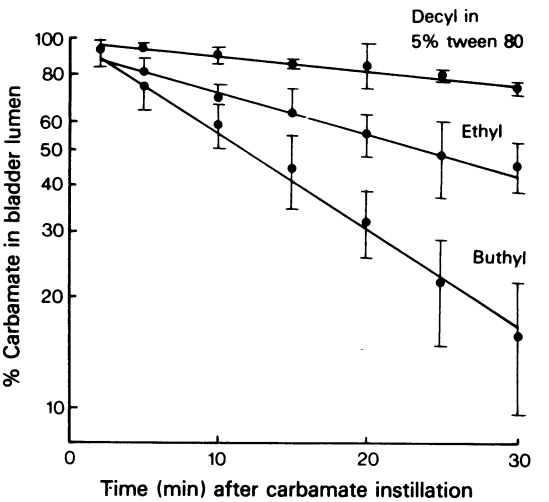

Figure 1 Typical semi-logarithmic plots showing the rate of loss of ethyl, butyl and decyl (in the presence of 5% Tween 80) carbamates from the bladder lumen. Ordinate scale; % carbamate remaining in bladder lumen; abscissa scale; time (min) after instillation of carbamate solution into the bladder lumen. Mean values are shown; vertical lines indicate s.d.

To examine the possible effect of Tween 80 on the bladder wall, a solution of 5% Tween 80 in 0.17 M citrate-phosphate buffer pH 6.4 (1 ml/kg) was instilled intravesically into each of three rats. Three control rats received 0.17 M citrate-phosphate buffer alone. After 30 min the bladders were cut out, carefully blotted dry (avoiding touching the mucosa) and sectioned in half longitudinally with a scapel blade. One half from each rat was fixed in 10% formyl saline for 6 days, progressively dehydrated and embedded in wax; 6 µm sections were cut in a microtome, floated on warm water and dried on slides in an oven at 37 C. Sections were dewaxed in xylene, rehydrated in dilute alcohol followed by water and stained in either haematoxylin and eosin or periodic acid–Schiff reagent.

Partition coefficients were determined by Houston (1973) using octan-1-ol and 0.1 M phosphate buffer pH 7.4 at 37°C. The value for decyl carbamate was determined by linear extrapolation of a plot of the number of carbon atoms in the alkyl side chain against log partition coefficient for the series methyl to *n*-octyl carbamate.

The first order atom molecular connectivity indices, $^{1}\chi$, were determined according to Kier & Hall (1977).

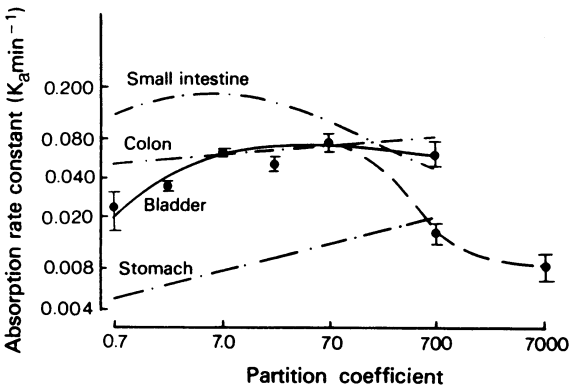

Figure 2. Plot of log partition coefficient (abscissa scale) against log first order diffusion coefficient, K_a, (ordinate scale) for the straight chain carbamates in the stomach, small intestine, colon and urinary bladder. Mean values are shown; vertical lines indicate s.d. The dashed line branching from the solid line for the bladder plot follows the absorption rate constants for octyl and decyl carbamates in the presence of 5% Tween 80.

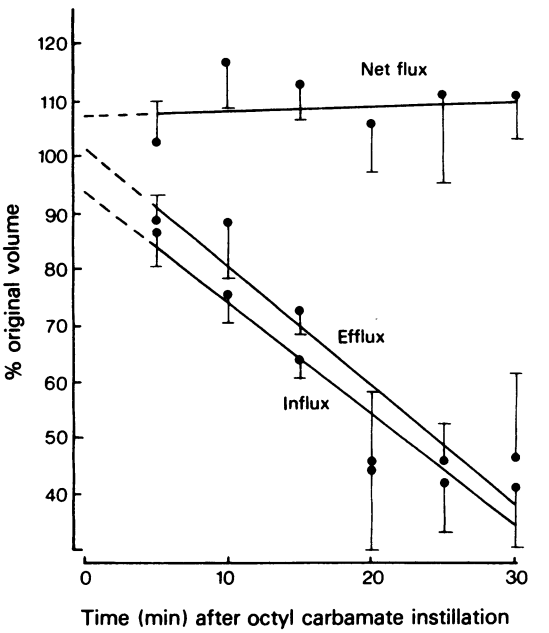

Figure 3. Typical plots of the rates of water influx, efflux, and net flux across the bladder wall, in this case under the influence of intravesical 5 mM octyl carbamate in 5% Tween 80 in 0.17 M citrate-phosphate buffer pH 6.4. Mean values are shown; vertical lines indicate s.d.

Results

First order rate constants for the loss of the carbamates from the bladder lumen were calculated by linear regression analysis by the method of least squares of a graph of:

$$\log_e y = c - K_a t \quad \text{(see Figure 1)}$$

where y = % original carbamate concentration remaining in bladder after time, t, c = intercept on the y-axis and K_a = rate of loss of carbamate from the bladder lumen.

In Figure 2 the relationship between partition coefficient and rate constant for loss of carbamates from the bladder is shown and compared with carbamate absorption from the stomach (Houston, 1973), colon (Wood, 1977) and small intestine (Houston, 1973; Wood 1977). The data points and standard deviations of these earlier determinations have been omitted for the sake of clarity.

Contrary to the conclusions of Hicks (1966) it has been found that water readily passes across the bladder wall in both directions. The presence of carbamate did not appear to affect net water flux to any significant extent (see Table 2 and Figure 3).

The rates of water flux are presented as percentage original bladder volume (1 ml/kg) transported per minute and were calculated as follows: Efflux of [^{3}H]-H_2O is indicated by loss of ^{3}H relative to changes in [^{14}C]-PEG 4000, which is a non-absorbed non-diffusible indicator, i.e.:

$$\frac{(^3\text{H}/^{14}\text{C})\, t = t}{(^3\text{H}/^{14}\text{C})\, t = 0}$$

(N.B. Influx of water will dilute ^{3}H and ^{14}C to an equal extent and so not affect the ratio).

Influx of water: the specific activity of the instilled solution is not affected by efflux of [^{3}H]-H_2O so any change in specific activity must be due to an influx of H_2O diluting the [^{3}H]-H_2O.

The net volume change or flux is proportional to

$$\frac{1}{[^{14}\text{C-PEG 4000}]_{t=t}}$$

therefore the fractional volume change

$$= \frac{[^{14}\text{C}]_{t=0}}{[^{14}\text{C}]_{t=t}}$$

The % original volume in Table 2 is the mean ±s.d. for all the values

$$\frac{[^{14}\text{C}]_{t=0}}{[^{14}\text{C}]_{t=t}} \times 100$$

for each carbamate solution tested. Preliminary experiments showed that for the first 40 to 50 min water flux rates obey zero order rate kinetics but this becomes a pseudo first order rate as equilibrium is approached between ^{3}HOH in the plasma and bladder.

The presence of 5% Tween 80 (a non-ionic surfactant: polyoxyethylene sorbitan mono-oleate) reduced the rate of loss of octyl carbamate by approximately 76% ($P < 0.001$) but did not affect the rate of loss of ethyl carbamate (Table 1).

Examination of Figure 2 reveals that the rate of loss of the more hydrophilic carbamates is limited but that with increasing lipophilicity the rate of loss becomes constant.

Discussion

The first-order rate of loss of the carbamates from the bladder, which was preserved over a 100 fold difference in the concentration of butyl carbamate and was unaffected by the further addition of a 10 fold molar excess of propyl carbamate, demonstrated that carbamate disappearance occurs by simple diffusion. This is also the case for carbamate loss from the stomach, small intestine and colon (Houston, 1973; Houston, Upshall & Bridges, 1974; 1975; Wood, Upshall & Bridges, 1978).

Houston (1973) observed that the gastric absorption of octyl carbamate was reduced by 5% Tween 80. This concentration of Tween 80 is well in excess of its critical micellar concentration, and 98% of the octyl carbamate present was incorporated into the micelles under these conditions (Houston, 1973). Houston (1973) surmised that the Tween 80 effect on the permeability of the gastric mucosa might be more significant than its influence in retarding octyl carbamate availability to the mucosa. The fact that periodic acid–Schiff reagent stained the luminal edge of the bladder epithelium much more intensely in the presence than in the absence of Tween 80 supports this notion of a direct effect of Tween 80 on absorptive surfaces. The increased staining may be due to the reaction of Tween 80 adsorbed onto the epithelial surface with the periodic acid–Schiff reagent or stimulation of the production of mucopolysaccharides of the epithelium by Tween 80. Either of these possibilities would be expected to reduce the rate of loss of a hydrophobic molecule such as octyl carbamate but would have a minimal effect on the rate of loss of a hydrophilic molecule such as ethyl carbamate, as is the case.

It is possible to understand how a detergent may alter the permeability of the membrane if the detergent molecules are seen as being orientated so that their lipophilic components are located towards or embedded in the luminal membrane with the hydrophilic part of the molecule directed towards the lumen of the bladder. In this way compounds would have to traverse an additional hydrophilic barrier in order

Table 2 Determination of rates of water influx, efflux and net flux across the bladder epithelium in the absence and presence of carbamates

Compound	*Dissolved in*	*Concentration (mM)*	*Influx (%/min)*	*Efflux (%/min)*	*Net flux (%/min)*	*% Original volume*	n
Control	0.17 M citrate-phosphate only	—	1.12 ± 0.64	0.99 ± 0.76	0.16 ± 0.51	100.3 ±11.4	4
Ethyl carbamate	Citrate-phosphate	5	1.40 ± 0.09	1.35 ± 0.21	0.30 ± 0.26	110.2 ±10.3	3
Butyl carbamate	20% Propan 1,2-diol in citrate-phosphate	5	1.63 ± 0.36	1.58 ± 0.38	0.90 ± 0.53	104.1 ±13.1	4
Octyl carbamate	5% Tween 80 in citrate-phosphate	5	1.98 ± 0.27	2.09 ± 0.45	0.06 ± 0.51	109.0 ±11.2	4
Butyl carbamate	Citrate phosphate	5	1.21 ± 0.48	0.93 ± 0.52	0.70 ± 0.21	109.1 ±12.2	4
Octyl carbamate	Citrate-phosphate	0.5	2.04 ± 0.27	2.03 ± 0.67	0.16 ± 0.70	109.9 ±8.9	3

The % of original volume found at the end of each experiment and the number of experiments performed (*n*) are shown. Results are means ± s.d.

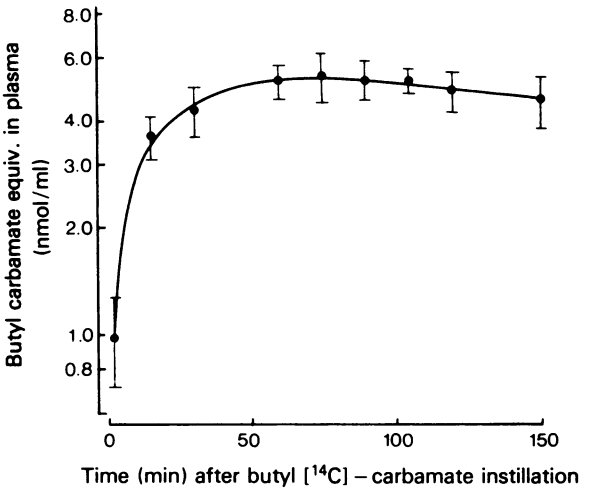

Figure 4. Graph showing the rate of appearance of butyl carbamate equivalents in the plasma after intravesical instillation of [^{14}C]-butyl carbamate (5 μmol/kg). Mean values are shown; vertical lines indicate s.d.; $n = 5$.

to cross the membrane and so the absorption rate of lipophilic compounds may be retarded.

Comparison of the rates of diffusion of carbamates across the parts of the gastrointestinal tract with that of the bladder shows that the bladder wall is at least as permeable as the small intestine and colon to these straight chain carbamates and this is supported by the rapid appearance of ^{14}C in the plasma following intravesical instillation of [^{14}C]-butyl carbamate (Figure 4).

The first-order atom molecular connectivity index and the partition coefficients both gave very similar relationships with the first-order rate constant.

It is clear from these results that there exists a considerable potential for the recirculation of both highly lipophilic and relatively polar drugs. Furthermore sulphate or glucuronic acid drug conjugates may be hydrolysed by sulphatase and β-glucuronidase present in the bladder wall (Clayson & Cooper, 1970) to less polar molecules which may then be reabsorbed. The possibility of exchange of compounds between the ureter and the ureteral vein should not be overlooked since there exists along certain lengths of the ureter a likely counter current exchange system.

To avoid systemic side effects following intravesical instillation of drugs, particularly cancer chemotherapeutic drugs, it seems advisable either to use the more hydrophilic high molecular weight agents (Editorial, 1977) or our findings would suggest the alternative of modifying lipophilic drugs to make them more hydrophilic and hence slow their absorption from the bladder. Ethyl carbamate (urethane), which is a carcinogen, is well absorbed from the bladder and it is likely that many other proximate and ultimate carcinogens also pass readily into the mucosal epithelium (Kadlubar, Miller & Miller, 1977) where metabolism within the bladder mucosal epithelium may occur leading to either detoxication or intoxication (Uehleke, 1966; Brill, 1977).

The drug metabolizing capabilities of the epithelial mucosa of the bladder are currently being investigated.

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