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Transport of deslorelin, an LHRH agonist, is vectorial and exhibits regional variation in excised bovine nasal tissue

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Abstract

The nasal route is a non-invasive alternative route for the delivery of a number of macromolecules, including peptides, proteins and vaccines. The purpose of this study was to determine the regional variation in excised bovine nasal tissue permeability to deslorelin, a nonapeptide luteinizing hormone releasing hormone (LHRH) agonist, and to further elucidate its mechanisms of transport. To this end, this study determined the permeability of deslorelin across different regions of freshly excised bovine nasal mucosa, including the medium turbinate anterior (MTA), medium turbinate posterior (MTP) and the inferior turbinate posterior (ITP) regions. At 37°C, mucoal-to-serosal (m-s) transport of deslorelin across excised bovine nasal mucosa exhibited regional variation, with the % cumulative transport in 6 h being in the order: MTA ($0.2 \pm 0.06\%$) < MTP ($1.6 \pm 0.1\%$) < ITP ($2.85 \pm 0.3\%$). In addition, at 37°C, deslorelin transport across all these nasal regions was vectorial and the mucosal-to-serosal:serosal-to-mucosal (m-s:s-m) transport ratios across MTA, MTP and ITP regions were 1.5, 5.4 and 3.7, respectively. At low temperature (4°C) and at 37°C in the presence of 2,4-dinitrophenol, an energy depletor, the m-s deslorelin transport across the MTP region decreased to 0.32 ± 0.12 and $0.13 \pm 0.05\%$, respectively, and the directionality was abolished. Sodium fluorescein transport also exhibited regional variation but no directionality. Histology and scanning electron microscopy studies indicated non-ciliated columnar epithelium in the MTA region and ciliated respiratory epithelium in the MTP and ITP regions. The thickness of the various regions, as visualized using histology, was in the order: MTA > MTP > ITP. Thus, deslorelin transport across excised bovine nasal mucosa is vectorial, temperature- and energy-dependent and exhibits regional variation. The regional differences in s-m transport are likely due to differences in the passive transport. Differences in m-s:s-m flux ratios may be due to differential expression of carriers.

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Introduction

In recent years, the nasal route has emerged as a convenient route for the delivery of peptide and protein drugs that have poor oral availability (Illum 2003). Since the nasal route is non-invasive and makes self-medication practical, it improves patient compliance when compared with the parenteral route (Pontiroli et al 1989a). Indeed, currently some peptide drugs, including calcitonin, buserelin, nafarelin and desmopressin, are available as nasal sprays. However, protein and peptide delivery through the nasal route is considerably less effective than through the parenteral route and the bioavailability of therapeutic peptides administered nasally is often less than 5% (Illum 2002). The bioavailability of therapeutic peptides delivered nasally is often limited by presystemic elimination due to enzymatic degradation and by poor mucosal membrane permeability (Sarkar 1992). A better understanding of the rate-limiting barriers is essential to develop more efficacious strategies to overcome these barriers.

The long-term goal of our study is to investigate the nasal route for the delivery of deslorelin. Deslorelin is a nonapeptide with an amino acid sequence: pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-ProNHEt. It is a luteinizing hormone-releasing hormone (LHRH) agonist that is 144 times more potent than the native LHRH (Vale et al 1976). Deslorelin has potential therapeutic benefit in the treatment of several gynaecological disorders,

such as endometriosis and uterine fibroids. Also, it is useful in the treatment of precocious puberty and breast and prostate cancers (Schally et al 1984; Schally 1999). Previously in our laboratory we demonstrated that deslorelin is degraded by various mucosal tissues, including the nasal tissue (Kompella & Dani 1996, 1997; Dani & Kompella 1998). Furthermore, we elucidated the pathways and kinetics of deslorelin degradation in Calu-1, a human airway epithelial cell line (Koushik et al 2003).

The focus of this study is on the investigation of transport mechanisms of deslorelin across nasal epithelia. Much of the information available on nasal absorption of peptides has been derived from bioavailability studies of nasally administered peptides or model compounds (Raehs et al 1988; Pontiroli et al 1989b). The data obtained rely on the determination of plasma (or serum) levels or on pharmacodynamic effects. However, these approaches cannot clearly identify the rate-limiting barriers in the absorption process. A valuable approach to gain insight into the mechanisms involved in the nasal absorption of peptides is the use of well-defined in-vitro permeation studies (Merkle et al 1998). Suitable donor–receiver permeation experiments employing excised nasal mucosae of various species, such as rabbit or cattle, or nasal cell culture systems, have been developed (Cremaschi et al 1998; Merkle et al 1998; Wadell et al 1999; Schmidt et al 2000).

In our studies, we have used excised bovine nasal tissue as an in-vitro model for assessing nasal deslorelin permeability. The histology, viability, transepithelial electrical resistance (TEER) and aminopeptidase activity of the bovine nasal mucosa make it a suitable model to study the absorption of therapeutically relevant peptides (Schmidt et al 1998, 2000). Previous studies have indicated that different regions of the nasal tissue may be involved in the active absorption of peptide drugs (Cremaschi et al 1991, 1996). Also, by identifying regions with high permeability or specialized transport processes, it was hypothesized that drugs can be targeted and their systemic delivery enhanced (Chien & Chang 1987; Vidgren & Kublik 1998). To realize such possibilities in the long-run, this study assessed deslorelin transport across different regions of the excised bovine nasal tissue, identified a region that exhibits maximum directionality and studied the temperature-dependence, and energy-dependence of deslorelin transport across this region.

Materials and Methods

Chemicals

Deslorelin was kindly provided by Balance Pharmaceuticals, Inc. (Santa Monica, CA). Trifluoroacetic acid (TFA), sodium fluorescein, 2,4-dinitrophenol and all chemicals required for buffer preparation were obtained from Sigma (St Louis, MO). Acetonitrile of HPLC grade was obtained from Fisher Scientific (Pittsburg, PA). The composition of the assay buffer (isotonic, pH 7.4) used in transport studies was reported previously (Bandi & Kompella 2002).

Isolation of excised bovine nasal mucosa

Bovine nasal mucosa was obtained from freshly slaughtered cattle at the local slaughter-house (J & J meats, Elkhorn, NE). The nasal tissue was isolated and prepared for experiments as described previously (Schmidt et al 2000). The skin covering the nose was removed and the frontal part of the nasal conchae was dissected. The mucosal tissue was then carefully stripped from the cartilage using a pair of tweezers and immediately used for experiments. Tissues used for experiments typically had an area of 3–4 cm^2. Different regions of the bovine nasal tissue, including the medium turbinate anterior (MTA) (up to 2.5 inches from the frontal tip of nares), medium turbinate posterior (MTP) (beyond 2.5 inches past the tip of nares) and the inferior turbinate posterior (ITP) (beyond 2.5 inches past the tip of nares; this region is below the MTP region and facing the floor of the nasal cavity, i.e. the inferior maetus) regions, were used for the transport studies.

Transport studies

Modified Ussing chambers (Navicyte, Reno, NV) were used to mount the nasal tissue for permeation studies. The tissue was exposed to 1.5 mL of assay buffer with drug on one side (donor side) and assay buffer without the drug on the other side (receiver side). The fluid volume was 1.5 mL on each side and the exposed tissue area was 0.64 cm^2. In this study, transport studies were conducted in both mucosal-to-serosal (m-s) and serosal-to-mucosal (s-m) directions. The chambers were maintained at a constant temperature (37°C or 4°C) with an external circulating water bath. Gas-flow controllers and air manifolds were used to ensure constant gas flow (5% CO_2/20% O_2/75% N_2) into the tissue bathing fluids. The mucosae were initially equilibrated with pre-warmed assay buffer for 15 min. Following this, the solution from donor chambers (mucosal and serosal for m-s and s-m transport studies, respectively) was aspirated and immediately replaced with deslorelin or fluorescein solutions and buffer was added to the receiver chamber. Samples (250 μL) were collected from the receiver chamber at various intervals up to 6 h and replaced with pre-warmed buffer. Deslorelin and fluorescein transport in both directions was assessed at 37°C and 4°C. Also, the effect of 2,4-dinitrophenol was determined on directional transport of deslorelin and fluorescein at 37°C. In these studies, 2,4-dinitrophenol (100 μM) was added only to the donor chamber. That is, for m-s transport studies, 2,4-dinitrophenol was added to the mucosal side and for the s-m transport studies, it was added to the serosal side. The samples were placed in polypropylene tubes, capped and stored at −20°C until analysis. Samples of the same volume were also taken from the peptide-containing solution.

The apparent permeability coefficient (P_{app}) was calculated using equation 1.

$$P_{app} = (dM/dt)/(A*C_d) \quad (1)$$

In equation 1, dM/dt is the slope of the cumulative amount of deslorelin transported vs time, A is the area (0.64 cm^2) available for transport and C_d is the initial donor drug concentration. Permeation data were corrected for dilution of the receiver solution with sample volume replenishment.

Sample analysis

Fluorescein transport across excised bovine nasal tissue was analysed and quantified using a spectrofluorometer (Shimadzu, RF 5000 U). An excitation wavelength of 488 nm and an emission wavelength of 510 nm was used. Band widths of 3 or 5 nm were used for the analysis of samples after dilution, as required.

The deslorelin transported was quantified by high-performance liquid chromatography using a Waters HPLC system comprising of a Waters 600 S controller, Waters TM 616 solvent delivery pump and a Waters 717 plus auto injector. The deslorelin was detected using a Waters 996 PDA detector set at a wavelength of 220 nm or a Waters 474 scanning fluorescence detector with an excitation of 280 nm and an emission of 350 nm and the peak areas were integrated using Millennium software (version 2.15.01). The mobile phase consisted of 30% acetonitrile and 70% of 0.1% TFA in distilled water delivered at a rate of 1 mL min^{-1}. A microsorb C-18 column (250 × 4 mm) with a particle diameter of 5 μm and a pore size of 100 Å from Rainin Instruments (Emeryville, CA) was used.

Scanning electron microscopy (SEM) and histology

Different regions (MTP, MTA and ITP) of the bovine nasal epithelium were isolated as described above. The tissues were fixed in a mixture of 2.5% formaldehyde and 2.5% glutaraldehyde in pH 7.4 PBS for 12 h at 4°C. The tissues were then dried using a critical point dryer (HCP-2; Hitachi, Tokyo, Japan), sputter-coated with gold–palladium under an argon atmosphere using a gold sputter module in a high-vacuum evaporator and examined using SEM set at 15 kV (JSM-5510; JEOL USA, Peabody, MA).

For histological examination, approximately 1-cm segments of tissue were used. The tissues were fixed similarly, dehydrated in ethanol, and the blocks were embedded in paraffin. Samples (about 5–7 μm thick) were sectioned for microscopic examination. Three consecutive tissue sections were mounted on a glass slide and stained with hematoxylin and eosin. The tissues were examined using a light microscope. All experiments were carried out in triplicate.

Data presentation and statistical analysis

Unless otherwise stated, each experiment was carried out in triplicate using tissues from different animals. Data in all cases are expressed as mean ± standard deviation. Comparison of mean values between the different treatments was carried out using two-way analysis of variance followed by Tukey's post-hoc analysis using SPSS (version 8.0) software. The level of significance was set at $P < 0.05$.

Results

Deslorelin transport across excised bovine nasal tissue exhibits regional variation and directionality

The transport of deslorelin (1 mg mL^{-1}) across medium turbinate anterior (MTA), medium turbinate posterior (MTP) and inferior turbinate posterior (ITP) regions of the excised bovine nasal tissue was assessed in the mucosal-to-serosal (m-s) and serosal-to-mucosal (s-m) directions. The cumulative m-s transport of deslorelin at the end of 6 h was in the order MTA < MTP < ITP (Figure 1A). Also, the s-m transport exhibited a similar trend. Furthermore the deslorelin transport was vectorial (Figure 1B) with the m-s:s-m transport ratios being in the order

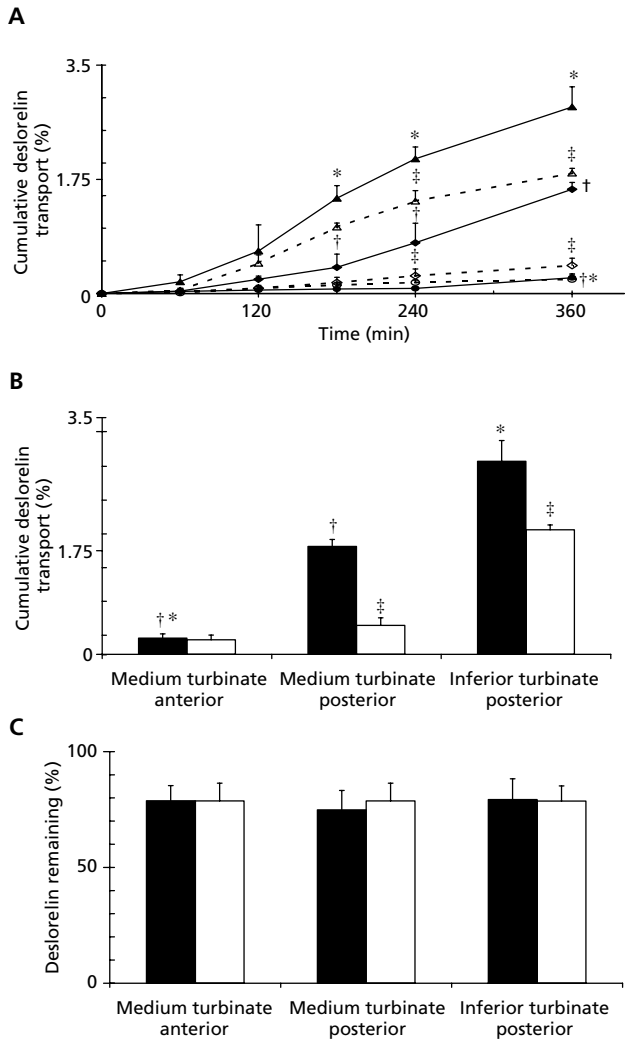

Figure 1 A. Time course of deslorelin transport in the mucosal-to-serosal (solid lines; filled symbols) and serosal-to-mucosal (broken lines; open symbols) directions across medium turbinate anterior (MTA) (circles), medium turbinate posterior (MTP) (diamonds) and inferior turbinate posterior (ITP) (triangles) regions of excised bovine tissue. B. Percent cumulative deslorelin transported at the end of 6 h across MTA, MTP and ITP regions in the mucosal-to-serosal (closed bars) and serosal-to-mucosal (open bars) directions. C. Percentage of deslorelin remaining in donor chamber at the end of 6 h of transport across MTA, MTP and ITP regions in the mucosal-to-serosal (closed bars) and serosal-to-mucosal (open bars) directions. Data are expressed as mean ± s.d., n = 4–6 animals. *$P < 0.05$ compared with MTP; †$P < 0.05$ compared with ITP; ‡$P < 0.05$ compared with mucosal-to-serosal transport in the same region.

Table 1 Comparison of mucosal-to-serosal:serosal-to-mucosal (m-s:s-m) ratios of deslorelin and fluorescein cumulative transport across different regions of excised bovine nasal tissue

Region	Medium turbinate anterior	Medium turbinate posterior	Inferior turbinate posterior
Deslorelin m-s:s-m transport ratio	$1.5 \pm 0.234^{\dagger}$	$5.4 \pm 0.67^{*}$	$3.72 \pm 0.72^{*\dagger}$
Fluorescein m-s:s-m transport ratio	1.12 ± 0.27	1.27 ± 0.18	0.89 ± 0.16

Data are expressed as mean ± s.d., n = 3 animals. $^{*}P < 0.05$ compared with fluorescein for the same region. $^{\dagger}P < 0.05$ compared with medium turbinate posterior region.

MTA < ITP < MTP (Table 1). The MTP region, which exhibited the highest m-s:s-m ratio, was further evaluated for the temperature and energy dependence of deslorelin transport. The percentage of deslorelin remaining in the mucosal chamber at the end of 6 h was not significantly different and was 78.8 ± 6.8, 74.87 ± 8.4 and 79.3 ± 8.9% for MTA, MTP and ITP, respectively (Figure 1C). Also, no difference was observed between mucosal and serosal donor concentrations.

Fluorescein transport across bovine nasal tissue exhibits regional variation but no directionality

The transport of sodium fluorescein, a hydrophilic solute that is predominantly or solely transported via the paracellular route, was assessed across the MTA, MTP and ITP regions of bovine nasal mucosa. The % cumulative sodium fluorescein transport was different across different regions and was in the order: MTA (2.8 ± 0.1%) < MTP (4.2 ± 0.5%) < ITP (9.9 ± 1.6%) (Figure 2A). However, the transport was not vectorial (Figure 2B) and the m-s:s-m ratios were 1.12 ± 0.27, 1.27 ± 0.18 and 0.89 ± 0.16 for the MTA, MTP and ITP regions, respectively (Table 1).

Deslorelin transport across bovine nasal tissue is directional and temperature- and energy-dependent

The cumulative amount of deslorelin transported across the MTP region of bovine nasal mucosa in the m-s direction (23.3 ± 1.5 μg) at 37°C was significantly higher than that transported in the s-m direction (Figure 3A). However, at 4°C, there was no significant difference between the m-s and s-m transport. At 37°C the m-s deslorelin permeability was about twice the s-m permeability (Figure 3A). Thus, vectorial transport of deslorelin was abolished at 4°C. Furthermore, upon the addition of 2,4-dinitrophenol (100 μM), an energy inhibitor, the m-s and s-m transport of deslorelin did not significantly differ from each other at the end of 6 h (Figure 3A). However, fluorescein transport across MTP was not temperature or energy dependent (Figure 3B). Overall, these results indicate that deslorelin transport across the MTP region is vectorial and energy dependent.

Bovine nasal tissue characterization

Observation of the MTA, MTP and ITP bovine nasal mucosal regions by scanning electron microscopy revealed that while MTP and ITP were ciliated columnar epithelia typical of respiratory epithelium (Figure 4B, C), the

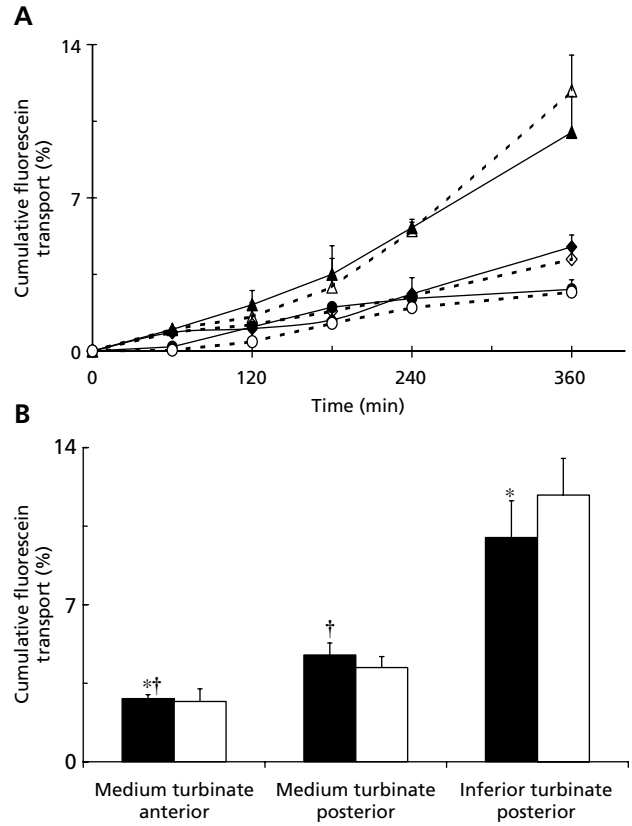

Figure 2 A. Time course of fluorescein transport in the mucosal-to-serosal (solid lines; filled symbols) and serosal-to-mucosal (broken lines; open symbols) directions across medium turbinate anterior (MTA) (circles), medium turbinate posterior (MTP) (diamonds), and inferior turbinate posterior (ITP) (triangles) regions of excised bovine tissue. B. Percent cumulative fluorescein transported at the end of 6 h across MTA, MTP and ITP regions in the mucosal-to-serosal (closed bars) and serosal-to-mucosal (open bars) directions. Data are expressed as mean ± s.d., n = 3 animals. $^{*}P < 0.05$ compared with MTP; $^{\dagger}P < 0.05$ compared with ITP; $^{\ddagger}P < 0.05$ compared with mucosal-to-serosal transport in the same region.

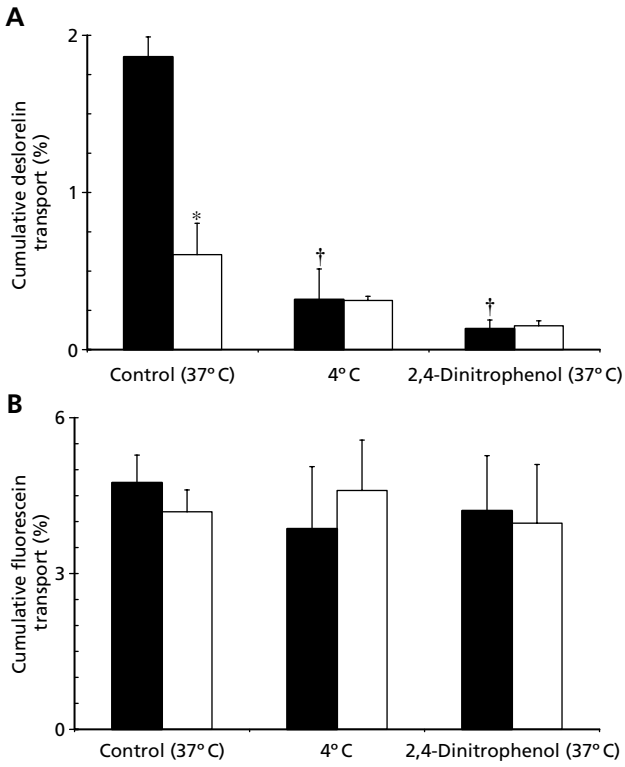

Figure 3 Effect of low temperature (4 °C) and 100 μM 2,4-dinitrophenol (37 °C) on the mucosal-to-serosal (closed bars) and the serosal-to-mucosal (open bars) transport of deslorelin (A) and fluorescein (B) across the medium turbinate posterior region of excised bovine nasal tissue. Data are expressed as mean ± s.d., n = 4 (deslorelin) or 3 (fluorescein). *$P < 0.05$ compared with mucosal-to-serosal transport at the same condition; †$P < 0.05$ compared with control mucosal-to-serosal transport.

MTA region was devoid of cilia and appeared to consist of non-ciliated columnar/simple columnar epithelium (Figure 4A). Based on the histological cross sections of similar magnification (10×), the thickness of the various regions appears to be in the order: MTA > MTP > ITP (Figure 5).

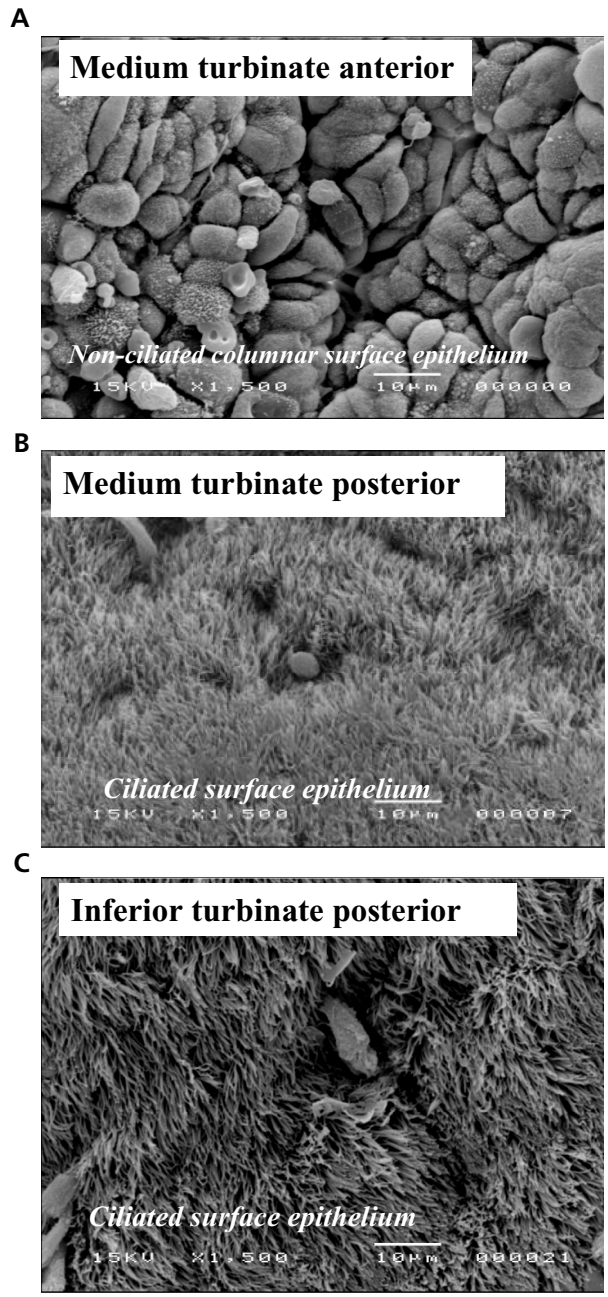

Figure 4 Scanning electron microscopy pictures of the mucosal surface of the medium turbinate anterior, medium turbinate posterior and inferior turbinate posterior regions of excised bovine nasal mucosa. Note the absence of cilia in the medium turbinate anterior region.

Discussion

Thus far, the mechanism of transport of LHRH analogues such as nafarelin or buserelin across the nasal epithelia remains unknown and it is assumed that paracellular transport is the main mechanism of absorption of these peptides. In this study we have two important findings — first, deslorelin transport across bovine nasal tissue exhibits a regional variation and second, deslorelin transport is vectorial, with preferential transport in the m-s direction, and is dependent upon temperature and energy.

The different turbinate regions of the bovine nasal tissue were used in our studies. The physiological function of turbinates is to warm and humidify the inhaled air (Chien & Chang 1987). From a drug delivery viewpoint, turbinates are important as they increase nasal surface area and are highly vascularized, providing for increased intranasal absorption. Although there are three turbinate regions, inferior, medium and superior, the superior turbinate is of little significance for drug absorption (Critchley et al 1994) because it occupies the least surface area and is deep on the roof of the nasal cavity and therefore inaccessible to nasally

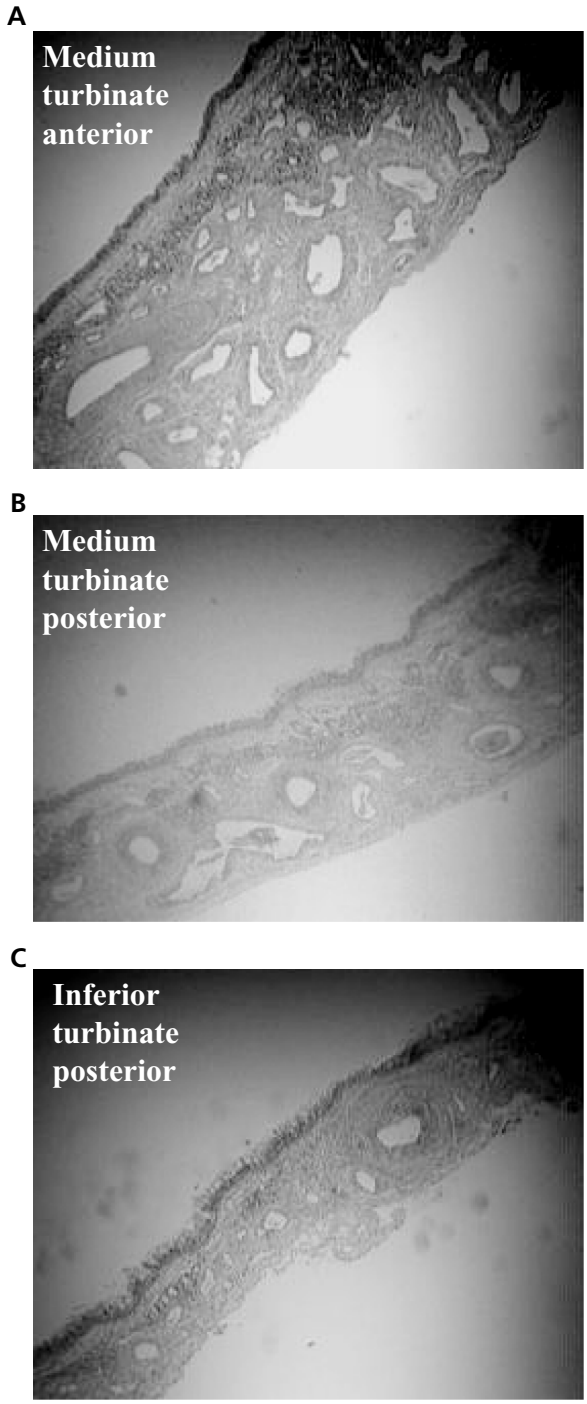

Figure 5 Light microscopic pictures of cross-sections of the medium turbinate anterior (MTA), medium turbinate posterior (MTP) and inferior turbinate posterior (ITP) regions of excised bovine nasal mucosa. All images were taken at 10× magnification. The tissue thickness appears to be in the order: MTA > MTP > ITP.

administered drugs. Therefore, we used the medium and inferior turbinate regions, both of which are of importance in drug absorption.

We observed that deslorelin transport across excised bovine nasal tissue exhibited regional variation (Figure 1). To investigate whether this regional variation is due to differences in passive transport, we assessed the transport of sodium fluorescein, a polar solute transported primarily by the paracellular route through the tight junctions between the cells. Consistent with its predominantly passive diffusion in nasal tissue, the fluorescein transport did not exhibit vectorial transport. However, it exhibited regional variability in transport similar to s-m transport of deslorelin (Figure 2A). This suggested that at least part of the regional variation observed with deslorelin could be due to differences in paracellular permeability of deslorelin. Another reason for the difference in transport could be the differences in metabolism of deslorelin in the different regions of the nasal tissue. Indeed, it was observed that the expression of amino and carboxypeptidases was different in different regions of the rabbit nasal cavity (Vaarala et al 2001). However, determination of the deslorelin remaining at the end of 6 h following exposure to different regions of the nasal tissue indicated no such differences in the degradation of deslorelin (Figure 1C). Previously, Schmidt et al (2000) used measurement of transepithelial electrical resistance (TEER), mannitol flux and aminopeptidase activity to determine the viability and metabolic activity of excised bovine nasal tissue. These studies indicated that the isolated bovine nasal tissues began losing viability and activity beyond 4 h of isolation. We have not assessed these parameters in our study. With loss of cell viability, barrier integrity is known to be compromised. However, we observed no significant increases in the fluxes of fluorescein and deslorelin by the end of the transport studies, as indicated by linear cumulative amount versus time plots (Figures 1 and 2). Thus, a substantial loss of barrier integrity or cell viability is unlikely in these studies. Even if there are some differences in viability by the end of the experiment, the comparison of various tissues under similar conditions is clearly reflective of vectorial transport of deslorelin, which exhibits regional variation in the nasal tissue, unlike fluorescein. It should be noted that the tissue integrity and metabolic activity in excised tissue studies may not be the same as in-vivo. The techniques of isolation and the time elapsed since tissue isolation can compromise these properties. To minimize such changes, the intact noses were brought to the laboratory and the time between the sacrifice of animals and the mounting of the tissues was maintained at under 2 h.

An examination of the tissue surfaces by SEM indicated that the anterior portion of the medium turbinate was non-ciliated (Figure 4).We found that the transport of deslorelin across this non-ciliated anterior portion of the nasal epithelium is low. Indeed, the distribution of the drug dose between ciliated and non-ciliated zones within the nasal cavity is relevant for both effective topical therapy of the nasal cavity and for possible systemic drug delivery by the intranasal route. It has been demonstrated that with most of the commercial nasal pumps most of the drug is deposited in the anterior region of the nose by inertial impaction, and there is little nasal penetration of the drug (Cheng et al 2001). Also, from our studies it is clear that permeability of

deslorelin increases as one goes into the deeper regions of the nose from MTA to MTP or ITP. A number of parameters, including spray angle and droplet size, are important in influencing the deposition pattern in the nasal airway (Newman et al 1988). Larger droplets and a wider spray angle increases deposition in the anterior region of the nasal airway, which then prevents more material from depositing in the deeper turbinate regions where most of the systemic absorption occurs. Therefore, modifying the deposition pattern could be a useful strategy in increasing peptide nasal bioavailability. Another problem with nasal delivery is the high inter-individual variability in the bioavailability of nasally administered peptides. A number of reasons, including differences in deposition, mucociliary clearance and enzymatic degradation, have been proposed to explain this (Arora et al 2002). Indeed, regional differences in absorption secondary to depositional differences within the nasal cavity may contribute to this variability.

Since the m-s:s-m transport ratio of deslorelin was the highest for the MTP region, we investigated the energy and temperature dependency of deslorelin transport across this region. We found that at low temperature (4°C) deslorelin m-s transport was decreased by 75% and the directionality was lost. It has been shown that dinitrophenol can block energy-dependent transport processes in Caco-2 and LLC-PK1 cells (Ito et al 1993; Dantzig et al 1994). We have not determined the effect of 2,4-dinitrophenol on the viability of excised bovine nasal tissue in our studies. However, previous studies indicated that 100 μM 2,4-dinitrophenol does not affect TEER significantly for rat nasal tissue, rabbit nasal tissue, rabbit intestinal tissue and Caco-2 cell monolayers (Cremaschi et al 1991; Ma et al 1999; Gabel et al 2001; Ohtake et al 2003). Previous studies in our laboratory indicated that 2,4-dinitrophenol, when used at 100 μM, does not affect the TEER of cultured monolayers of Calu-3, an in-vitro model for respiratory epithelium (Koushik et al 2004). Our results show that dinitrophenol decreases the m-s transport, whereas the s-m transport was not significantly decreased (Figure 3A). All this evidence indicates the involvement of a specialized process in the transport of deslorelin across nasal tissue.

Previous studies have indicated the contribution of specific active transport processes in the absorption of peptides across nasal mucosa. Indeed, the transport of insulin, [1,7 Asu] eel-calcitonin, and ACTH have been proposed to occur through transepithelial receptor-mediated transcytosis processes across nasal epithelium (Cremaschi et al 1991, 1996, 1998, 2001). Furthermore, a non-specific endocytosis has been shown for the permeation of human calcitonin across excised bovine nasal tissue (Lang et al 1998). However, this is the first study to suggest an active process for the permeation of an LHRH agonist across nasal epithelium.

Although excised bovine nasal tissue is a very useful in-vitro model to study therapeutic peptide transport, extrapolation of the data obtained to human subjects should be done with caution. There are drastic differences in the anatomy of the bovine and human nasal cavity and the permeability differences observed between regions of the bovine tissue may not completely translate to human tissue (Duchateau 1987). Furthermore, the mucociliary clearance rate, which is the main factor determining residence time in the nasal cavity, differs between the bovine and human nasal cavities (Merkus et al 1998). Nevertheless, the findings of this study indicate regional differences in the transport of peptide drugs in the nasal cavity. These observations are likely to be applicable to human tissue, since we have recently observed vectorial transport of deslorelin in Calu-3 cell monlolayers (Koushik et al 2004), a human-derived cell culture model for respiratory epithelia.

Conclusions

In conclusion, our results indicate a regional variation in the transport of deslorelin across the nasal epithelium. The deslorelin transport across nasal epithelium is vectorial, with the mucosal-to-serosal transport being greater than the serosal-to-mucosal transport, and is temperature and energy dependent. The regional variation could be due to differences in the paracellular permeability of deslorelin or the expression of transporters involved in deslorelin transport.

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