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Transdermal iontophoretic delivery of [^{3}H]GHRP in rats

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Abstract

In this study, we demonstrate transdermal iontophoretic delivery of radiolabeled growth hormone-releasing peptide ([^{3}H]GHRP, [^{3}H]SK&F 110 679) from an iontophoretic patch delivery device in rats. [^{3}H]SK&F 110 679 was adsorbed on a hydrophilic microporous membrane, which was positioned on a support in the device and sealed in place. A silver/silver chloride electrode system was used for iontophoresis and a potential of 4.5 V (rectangular pulse, 40 kHz, 30% duty cycle) was applied using an Advance depolarizing pulse iontophoresis system (ADIS-4030). Current-dependent appearance of [^{3}H]SK&F 110 679 equivalents in blood, bile and urine did not depend on membrane loading between 1.8 and 8 mg adsorbed on the membrane. Blood levels of [^{3}H]SK&F 110 679 equivalents persisted for at least 2 h after the current was turned off, indicative of depot formation in the skin. Fractions of bile and urine were analyzed by reversed-phase high-performance liquid chromatography (HPLC). The radiochemical profiles were dominated by a single species, coeluting with intact [^{3}H]SK&F 110 679. A flux of at least 0.8–1.2 ug/h per cm^2 was achieved, indicating that, with appropriate optimization of the patch device, therapeutic levels of SK&F 110 679 in man may be attainable by transdermal iontophoresis. © 1997 Elsevier Science B.V.

Keywords: Growth hormone-releasing peptide; ^{3}H-GHRP; Iontophoresis; Peptide delivery; Transdermal delivery

1. Introduction

Most therapeutic peptides and proteins are susceptible to enzymatic degradation and undergo extensive first-pass hepatic metabolism following

Abbreviations: ADIS, Advance depolarizing pulse iontophoresis system; GH, growth hormone; GHRP, growth hormone-releasing peptide; i.p., intraperitoneal; i.v., intravenous; PBS, phosphate-buffered saline; PVA, polyvinyl alcohol; s.c., subcutaneous; SC, stratum corneum.

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oral administration. In addition, these molecules are usually hydrophilic in nature and of relatively large molecular weight. Hence, their oral bioavailability is often low. There has been an intensive effort to develop alternative delivery strategies. Much emphasis has been placed on finding viable delivery routes other than injections. Novel delivery routes include nasal (Hayashi et al., 1991; Edman and Bjork, 1992), pulmonary (Patton and Platz, 1992; Smith et al., 1994) and transdermal delivery (Hadgraft and Guy, 1989). One of the advantages of these alternative routes is that first-pass hepatic elimination is avoided.

The concept of transdermal delivery is now well accepted and there are a number of drugs on the market that are delivered from a transdermal patch. Passive delivery of compounds through the skin is limited to small, lipophilic and potent compounds. Transdermal iontophoresis has gained increasing recognition in recent years for the delivery of charged molecules (Okabe et al., 1986; Meyer et al., 1988; Chien et al., 1990; Iwakura and Morimoto, 1991; Ishii et al., 1992; Kumar et al., 1992; Singh and Maibach, 1994).

In this paper, we describe the transdermal delivery of growth hormone-releasing peptide (GHRP, SK&F 110 679) from an iontophoretic patch delivery device in rats. GHRP (L-histidyl-D-tryptophyl-L-alanyl-L-tryptophyl-D-phenylalanyl-L-lysinamide) is a hexapeptide analogue of met-enkephalin that stimulates the secretion of growth hormone (GH) when administered in a variety of animal species (Bowers et al., 1984). Synthesis and secretion of GH is regulated by two peptides, growth hormone-releasing hormone (GHRH) and somatostatin, which inhibits GH secretion. The mechanism of action of GHRP is not entirely understood. Data from animal and human studies suggests that GHRP may be a somatostatin antagonist (Cheng et al., 1989; Clark et al., 1989; Bowers et al., 1990).

The physicochemical characteristics of GHRP (positively charged with good water solubility in the acetate salt form), the absence of metabolism in the skin following subcutaneous administration (Davis et al., 1994) and the low dose requirement, make this molecule an attractive candidate for transdermal iontophoresis. Finally, GH secretion in man occurs in a pulsatile fashion throughout the day (Winer et al., 1990). An iontophoretic device could be programmed for pulsatile delivery of GHRP.

2. Materials and methods

2.1. Radiolabeled SK&F 110 679

Radiolabeled SK&F 110 679 was synthesized by the Radiochemistry Department at SmithKline Beecham Pharmaceuticals. [^{3}H]SK&F 110 679 (labeled at the 5- and 7-positions of the D-tryptophan residue) with a specific activity of 14.9 Ci/mmol and a radiochemical purity of 97.4% was used in the studies with the 2.5 cm^2 patch. The specific activity of [^{3}H]SK&F 110 679 on the 2.5 cm^2 patch was 320 dpm/ng. [^{3}H]SK&F 110 679 (labeled in the imidazole portion of the histidine moiety) with a specific activity of 0.281 Ci/mmol and a radiochemical purity of 97% was used in the studies with the 5 cm^2 patch. The specific activity of [^{3}H]SK&F 110 679 on the 5 cm^2 patch varied between 80 and 710 dpm/ng.

2.2. Iontophoretic patches

All materials used in the patches were provided by the Advance Co. of Japan. A silver/silver chloride electrode system was chosen for iontophoresis since it prevents electrolysis of water and thereby electrolytic degradation of SK&F 110 679 on the anodal surface. Electroosmotic flow during iontophoresis may dry out the area of the skin under the anodal patch, which may result in uneven contact between patch and skin and, with constant voltage iontophoresis, a consequent change in current. In preliminary experiments, we found that this indeed was the case. The drying of the skin (with the consequent change in current) could be prevented by water addition during iontophoresis. Clearly, the patch design needs to be further optimized for future studies.

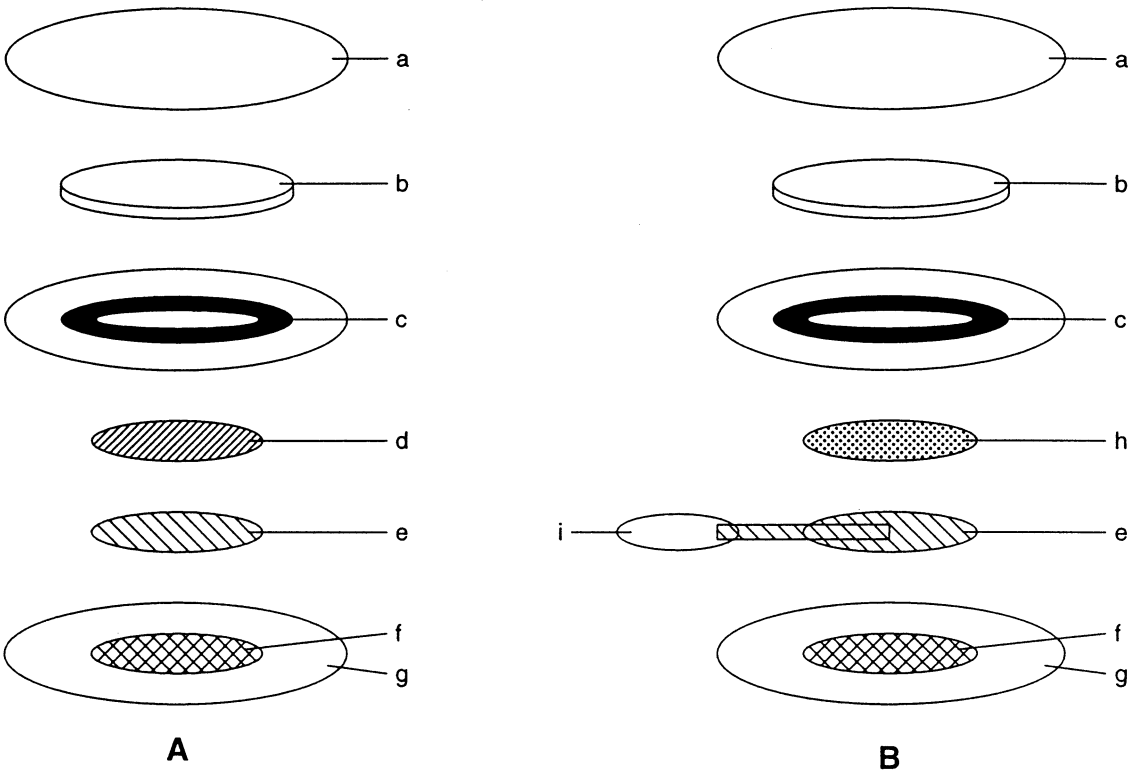

Fig. 1. Anodal patch. (A) The 2.5 cm^2 anodal patch consists of: (a) polyethylene backing, (b) PVA gel, (c) silver sheet ring electrode, (d) hydrophilic microporous membrane, (e) cellulose membrane, (f) drug membrane, in direct contact with the skin, (g) adhesive (for attachment to the skin). (B) The 5 cm^2 patch consists of: (a) polyethylene backing, (b) PVA gel, (c) silver sheet ring electrode, (h) anion exchange membrane (preventing backflow of SK&F 110 679 and therefore adsorption on the silver electrode), (e) cellulose membrane, (i) polyethylene-lined water compartment connected to drug membrane by cellulose membrane (for wetting), (f) drug membrane, in direct contact with the skin, (g) adhesive (for attachment to the skin).

2.2.1. Anodal patches

Fig. 1 shows a diagram of the anodal patches used in this study. With patch A (2.5 cm^2 patch), water addition to the polyethylene backing reservoir was performed manually during iontophoresis, with a hypodermic needle and syringe. Patch B (5 cm^2) contained a system for automatic and continuous water addition. The 2.5 cm^2 patch (A) consists of a polyethylene backing, PVA gel disk containing saline to provide electrolytes necessary to carry the current, silver sheet ring electrode, hydrophilic microporous and cellulose membranes for support, and drug membrane. The 5 cm^2 patch consists of a polyethylene backing, PVA gel disk containing saline to provide electrolytes necessary to carry the current, silver sheet ring electrode, anion exchange membrane (to prevent backflow of SK&F 110 679 and therefore adsorption on the silver electrode), cellulose membrane (for support and wetting of the drug membrane), polyethylene-lined water compartment connected to the drug membrane by the cellulose membrane (for wetting), and drug membrane.

2.2.2. Cathodal patch

The AgCl/Ag electrode was prepared by printing Ag/AgCl ink onto a polyethylene film. The cathodal patch consists of a PVA gel contained in a polyethylene foam ring, a silver chloride/silver electrode, and a polyethylene film (Fig. 2).

2.2.3. Power source

The Advance depolarizing pulse iontophoresis system (ADIS-4030) was used, which generates a pulsed voltage output of rectangular wave form (Okabe et al., 1986). The device features adjustable voltage output from 0 to 50 V, an adjustable current limit from 0 to 20 mA at a frequency of 5–50 kHz and a 10–50% duty cycle. In our experiments, we used a constant voltage of 4.5 V at 40 kHz with a 30% duty cycle. During iontophoresis the current was monitored with the ADIS device as well.

The [^{3}H]SK&F 110 679-containing membrane was prepared by slowly distributing 150 μl of a solution of [^{3}H]SK&F 110 679 in ethanol on a hydrophilic microporous membrane in aliquots of 10–15 μl, taking care to cover the entire surface. The membrane was allowed to airdry overnight. With the 2.5 cm^2 patch, the [^{3}H]SK&F 110 679-containing membrane was placed in the device onto the cellulose membrane and was sealed in place with a ring of surgical adhesive tape (3M). With the 5 cm^2 patch, the water reservoir was filled immediately before the experiment with 1 ml of distilled water containing 0.1% Tween 80, using a syringe with a 26 gauge needle. The compartment was then sealed with 3M tape. The [^{3}H]SK&F 110 679-containing membrane was placed in the device onto the cellulose membrane and was sealed in place with a ring of surgical adhesive tape. The water for wetting the cellulose membrane was then released from the reservoir by puncturing the adhesive backing, cellulose membrane and underside of the water compartment with a 26 gauge needle. Wetting of the cellulose membrane was complete in a few minutes. A total of 1 ml of 0.1% Tween 80 in water was sufficient for 4 h of iontophoresis.

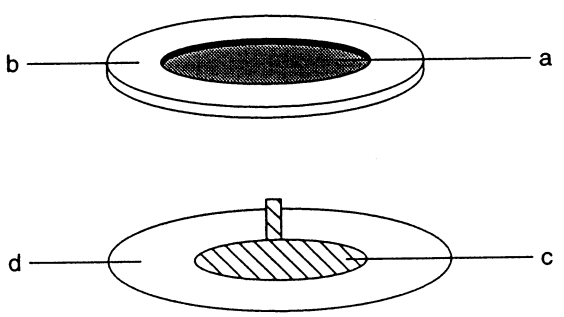

Fig. 2. Cathodal patch. (a) PVA gel, (b) polyethylene foam ring, (c) silver chloride/silver electrode, (d) polyethylene film.

2.3. Transdermal delivery of [^{3}H]SK&F 110 679 in rats

Male Sprague–Dawley rats were obtained from Charles River-Raleigh Breeding laboratories. Rats were housed in plastic boxes with wood bedding and received Rodent Lab Chow # 500 (Purina Mills, St. Louis, MO) and water ad libitum. Animal cages were in unidirectional airflow rooms (25 $\pm$ 2°C, relative humidity 50 $\pm$ 10%) on a 12 h light/dark cycle. Studies were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Fasted rats (about 8–10 weeks old and weighing about 320–355 g) were anesthetized with pentobarbital (60 mg/kg, i.p.). Anesthesia was maintained throughout the course of the experiment by femoral vein infusion of pentobarbital at 8.0 mg/kg per h. Rats were placed on a thermal pad to maintain body temperature at 38°C. For blood sampling, a catheter was placed in one of the jugular veins. For placement of the iontophoretic device, the abdominal region was shaved carefully to avoid any abrasions to the skin. In one set of experiments, animals were prepared for bile and urine collection as follows. A midline incision of 3–4 cm was made and the bile duct was cannulated and exteriorized from the inguinal area. The incision was closed with wound clips. Bile was collected quantitatively. Bile flow was about 1 ml/h. After collection of the final blood and bile samples, the bladder was exposed and urine collected in a syringe. At the end of the experiment, animals were euthanized with an overdose of pentobarbital. Radioactivity in blood, bile and urine samples was determined using a Packard Tri-Carb Sample Oxidizer from the Packard Instrument Company (Downers Grove, IL).

2.4. HPLC for radiochemical profiling

Radiochemical profiling of bile and urine was accomplished by gradient reversed-phase high-performance liquid chromatography (HPLC) with on-line flow radiochemical detection. HPLC was performed with a Waters Programmable System Controller, two model 510 pumps and a model 710B WISP (Waters autosampler). The chromatographic eluate was monitored for radioactivity using a Raytest Ramona-90 flow radiochemical detector. Data were collected and analyzed on a personal computer running NINA Chromatographic Software (Nuclear Interface). The flow cell volume of the Ramona was 500 μl. Scintillant (Beckman Ready Flow III) was pumped with an LPC 1000 (Scientific Systems) at a flow rate of 3 ml/min. Biliary and urinary excreta were resolved on a Beckman Ultrasphere C8 column (5 μm, 4.6 mm $\times$ 15 cm) with a Brownlee (Applied Biosystems) RP300 guard column (7 μm, 4.6 mm $\times$ 3 cm). Elution proceeded at 1 ml/min with a 30 min linear gradient from 95% solvent A (0.1% trifluoroacetic acid) to 100% solvent B (0.1% trifluoroacetic acid, 39.9% H_2O, 60% acetonitrile). For profiling experimental rat bile and urine, equal sample volumes from all of the rats in the 1.8, 3.8 and 8 mg dosing groups and from respective collection time intervals, were combined prior to analysis.

3. Results and discussion

An iontophoretic patch (2.5 cm^2 loaded with 2 mg [^{3}H]SK&F 110 679), was placed on the abdominal region of anesthetized rats, with the [^{3}H]SK&F 110 679-containing membrane and drug delivery electrode (silver anode) on the right hand side and the counter electrode (silver/silver chloride) on the left hand side of the rat's abdomen. Blood sampling started immediately following placement of the device. After 1 h, the electrodes were connected to an Advance depolarizing pulse iontophoresis system (ADIS-4030). A potential of 4.5 V was applied for 2 h, resulting in an average current density of about 1 mA/cm^2. Fig. 3 shows ng equivalents [^{3}H]SK&F 110 679 appearing in the blood as a function of time. No radioactivity was transported into the systemic circulation during the first 60 min following placement of the device. When current was applied, radioactivity started accumulating in the blood. After about 1 h of current application, a steady-state level of about 25 ng equivalents [^{3}H]SK&F 110 679 per ml of blood was achieved.

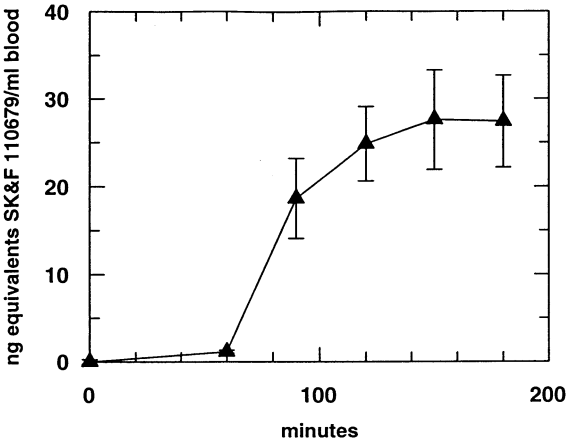

Fig. 3. Iontophoretic delivery of [^{3}H]SK&F 110 679 from a 2.5 cm^2 patch in rats. The patch was placed on the abdominal region and blood samples were taken from a jugular catheter during the entire experiment. Blood sampling started immediately following placement of the device. A potential difference of 4.5 V was imposed between the electrodes 1 h after placement, resulting in a current density of about 1 mA/cm^2. This current density was maintained for 2 h. The values shown are averages $\pm$ S.E. for six animals.

Bioavailability of unlabeled SK&F 110 679 following subcutaneous (s.c.) administration is 90–100%. Following intravenous (i.v.) or s.c. administration, [^{3}H]SK&F 110 679 is excreted predominantly in the bile (60–70% of the dose) and to a large extent as intact peptide (Davis et al., 1994). In order to identify possible breakdown products and metabolites following iontophoretic delivery of [^{3}H]SK&F 110 679 across the skin, experiments were performed in bile duct cannulated rats. In these experiments, the surface area of the drug membrane was increased to 5 cm^2 and the membrane was loaded with 1.8, 3.8 or 8 mg [^{3}H]SK&F 110 679. The device was placed as described above. Care was taken to place the device at least 1 inch from the incision. Blood sampling

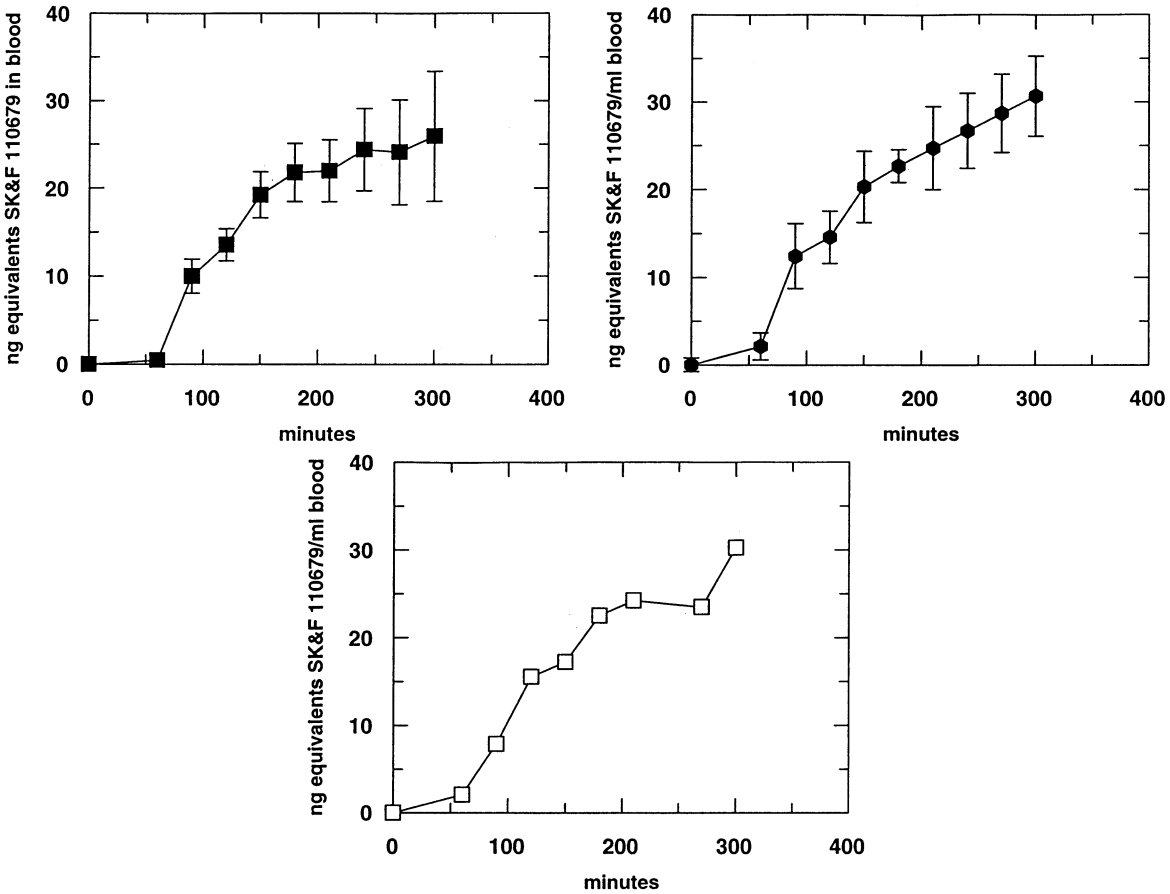

Fig. 4. Iontophoretic delivery of [^{3}H]SK&F 110 679 from a 5 cm^2 patch in rats: effect of patch loading. The patch was placed on the abdominal region, blood samples were taken from a jugular catheter throughout the entire experiment. Blood sampling started immediately following placement of the device. A potential difference of 4.5 V was imposed between the electrodes 1 h after placement, resulting in a current density of 0.15–0.20 mA/cm^2. This current density was maintained for 2 h. After 2 h, the electrodes were disconnected from the power source, but the device was left in place on the abdomen. Blood sampling continued for another 2 h. (■) Device containing 1.8 mg [^{3}H]SK&F 110 679; (●) device containing 3.8 mg [^{3}H]S&F 110 679; (□) device containing 8 mg [^{3}H]SK&F 110 679. For the 1.8 and 3.8 mg devices, the numbers shown are averages ± S.E. from four animals. For the 8 mg device, the number shown is the average of two animals.

and bile collection started immediately following placement of the device. After 1 h, an applied potential of 4.5 V was imposed between the electrodes, resulting in a current density of about 0.2 mA/cm^2. After 2 h, the electrodes were disconnected from the power source, while the device was left in place on the abdomen. Blood sampling and bile collection continued for another 2 h. At the end of this time period, urine was collected as well. Fig. 4 shows ng equivalents [^{3}H]SK&F 110 679 per ml of blood as a function of time and of [^{3}H]SK&F 110 679 in the device. Very little or no radioactivity was transported into the systemic circulation during the first 60 min following placement of the device. When current was applied, radioactivity started accumulating in the blood. There was no significant difference in transport of radiolabel following application of devices with 1.8, 3.8 and 8 mg [^{3}H]SK&F 110 679. After 2 h of current application, a level of about 27 ng equivalents [^{3}H]SK&F 110679 per ml of blood was achieved in all cases. Interestingly, the radioactiv-

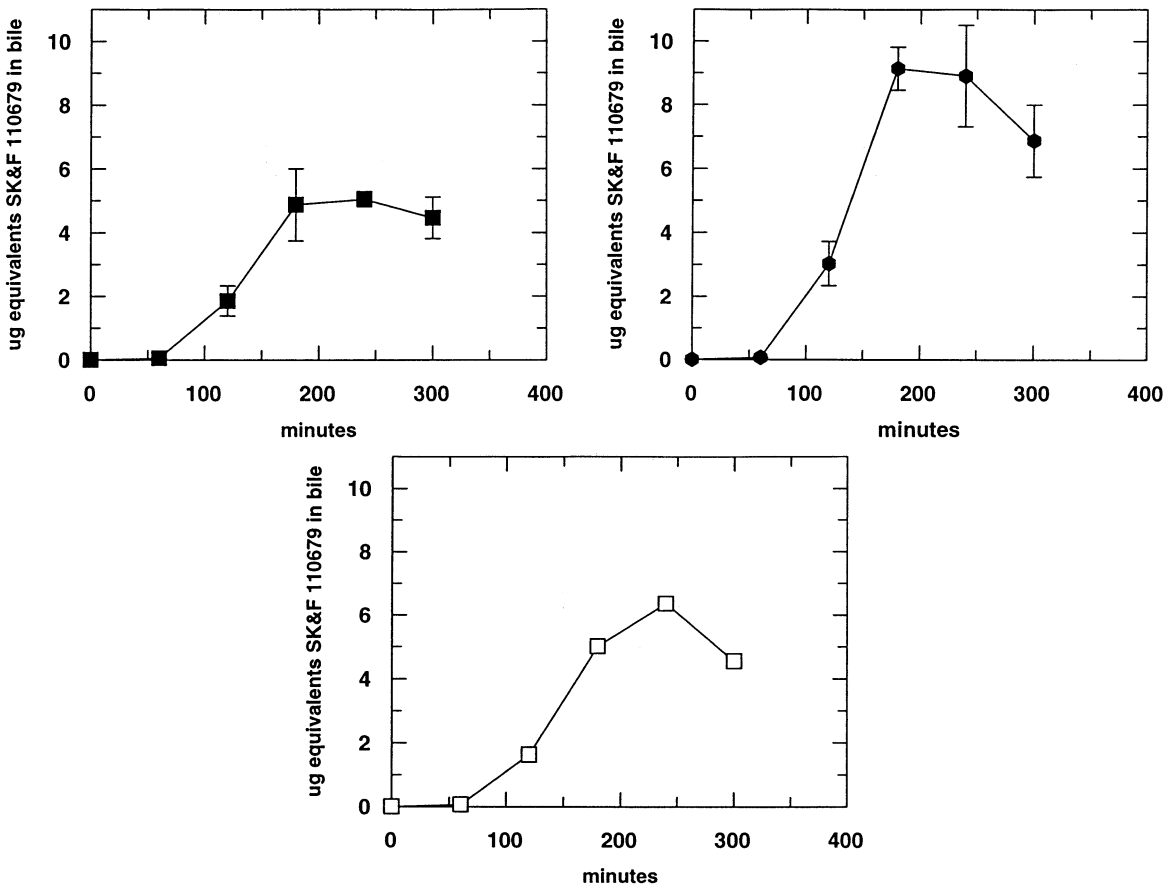

Fig. 5. Cumulative biliary excretion of [^{3}H]SK&F 110 679. The patch (5 cm^2) was placed on the abdominal region, bile samples were collected at 60 min intervals during the entire experiment. Bile collection started immediately following placement of the device. A potential difference of 4.5 V was imposed between the electrodes 1 h after placement, resulting in a current density of 0.15–0.20 mA/cm^2. This current density was maintained for 2 h. After 2 h, the electrodes were disconnected from the power source, but the device was left in place on the abdomen. Bile collection continued for another 2 h. (■) Device containing 1.8 mg [^{3}H]SK&F 110 679; (●) device containing 3.8 mg [^{3}H]SK&F 110 679; (□) device containing 8 mg [^{3}H]SK&F 110 679. For the 1.8 and 3.8 mg devices, the numbers shown are averages ± S.E. from four animals. For the 8 mg device, the number shown is the average of two animals. The animals are the same as those used for the study in Fig. 4.

ity in the blood was maintained at this level even after the power source was disconnected. Fig. 5 shows ug equivalents [^{3}H]SK&F 110 679 appearing in the bile. Very little could be detected in the bile during the first 60 min following placement of the device. Radioactivity started appearing in the bile after current was applied and reached a level of 5 ug equivalents [^{3}H]SK&F 110 679 in the bile sample collected between 120 and 180 min with the 1.8 and 8 mg device, and of 9 ug equivalents [^{3}H]SK&F 110 679 with the 3.8 mg device. These levels did not decrease significantly over the next 2 h following disconnection of the power source. Table 1 shows total radioactivity collected in bile and urine.

To profile radioactivity from bile and urine, fractions of bile and urine collected from all animals at the 2, 3, 4 and 5 h time periods were pooled and analyzed by reversed-phase HPLC with flow radiochemical detection (Fig. 6). In these analyses, radioactivity peaks resolved by reversed-phase HPLC were quantitated as per-

Table 1
Total radioactivity and SK&F 110 679 excreted in bile and urine during the course of the experiment

	Loading dose (mg)	Bile	Urine	Total	Delivery rate[a] (ug/h)
Total μCi excreted[b]	1.8	4.86 ± 0.80	1.23 ± 0.36	6.09	
	3.8	9.14 ± 1.64	0.95 ± 0.45	10.09	
	8	5.86	1.05	6.91	
Total μg SK&F 110 679 excreted[c]	1.8	12.9 ± 2.0	3.0 ± 0.5	15.9	4.0
	3.8	20.4 ± 3.8	2.1 ± 0.5	22.5	5.6
	8	13	2.6	15.6	3.9

[a] Minimal rate of systemic delivery of SK&F 110 679 during 4 h period following initiation of iontophoresis.
[b] Normalized to a specific activity of 710 dpm/ng SK&F 110 679.
[c] Calculated using the profiling factor from HPLC (Table 2).
For the 1.8 and 3.8 mg devices, the numbers shown are averages ($\pm$S.E.) from four animals. For the 8 mg device, the number shown is the average of two animals.

centage of LC run by integration. HPLC column recovery was complete. In both bile and urine, the radiochemical profile was dominated by a single species eluting at about 20 min. This species accounted for at least 73% of radioactivity analyzed (Table 2). The remaining radioactivity eluted in non-quantifiable peaks throughout the chromatographic analyses.

Reference standard [^{3}H]SK&F 110 679 was known to elute at about 20 min when analyzed using the same chromatographic conditions. Experimental bile and urine samples were thus mixed with pure [^{3}H]SK&F 110 679 and analyzed in a single chromatographic run to see if the primary component in bile and urine coeluted with intact [^{3}H]SK&F 110 679. When approximately equal amounts of radioactivity were coinjected, a single radioactive peak of approximately doubled integrated area was observed (data not shown). Due to the different matrices, bile versus urine, there was a small difference in elution times. Thus, the primary radioactive species in bile and urine coeluted with intact [^{3}H]SK&F 110 679. This species has previously been identified as intact parent compound by continuous flow fast atom bombardment/mass spectrometry (FAB/MS) of bile and urine samples from rats dosed s.c. or i.v. with [^{3}H]SK&F 110 679 (Davis et al., 1994).

The radiochemical HPLC profile of [^{3}H]SK&F 110 679 in bile and urine following transdermal iontophoresis is indistinguishable from that following s.c. or i.v. injection (Davis et al., 1994). At the end of the sampling period, the ratio of radioactivity in bile and urine was also very similar to that following s.c. administration. It therefore appears that the fate of [^{3}H]SK&F 110 679 delivered by transdermal iontophoresis is not different from the fate of s.c. injected material and that the primary component in bile and urine samples represents intact SK&F 110 679. Table 1 shows the total amount of intact SK&F 110 679 recovered from bile and urine, as demonstrated by HPLC.

SK&F 110 679 has a short intravenous half-life in the rat, 3.6 min for the initial phase of the decline (% $\lambda_1 = 62$) and under 30 min for the secondary phase (Davis et al., 1994). Davis et al. observed an apparent terminal half-life of 71 min following s.c. administration of SK&F 110 679 to rats, reflecting slow absorption from the injection site. Since in our experiments, radioactivity in blood and bile does not decline for at least 2 h after discontinuation of the current, it must be that there is continued input of [^{3}H]SK&F 110 679 into the systemic circulation. This could be from a depot of [^{3}H]SK&F 110 679 formed in the skin during iontophoresis. Skin depot formation following iontophoretic delivery has been reported for other molecules as well, e.g. verapamil (Wearly et al., 1989), insulin (Kari, 1986; Siddiqui et al., 1987) and the LHRH analogue, nafarelin (Delgado-Charro and Guy, 1995). Based on the observation that iontophoretic transport of na-

farelin results in a reversal of the permselectivity of the skin, it was argued that depot formation of this molecule is due to complexation with fixed negative charges in the skin. Since SK&F 110 679 is positively charged when passing through the skin, it may bind to and be retarded by negatively charged proteins and lipids. With respect to this, it is interesting to note that SK&F 110 679 can form an electrostatic complex with a negatively charged phospholipid, phosphatidylglycerol, spread as a monolayer at an air/water interface (Issaurat and Teissie, 1988).

Since the device was left in place after discontinuation of the current, the continued input of [^{3}H]SK&F 110 679 could also be (in part) due to an increase in the rate of passive transport of [^{3}H]SK&F 110 679 across the skin. A 3 h pretreatment with current at 0.36 mA/cm^2 results in a significant increase in the rate of passive transport of the tripeptide threonine–lysine–proline across nude rat skin in vitro and in vivo (Green et al., 1992). The iontophoresis-induced increase in rate of passive transport through the skin may be dependent on the size of the molecule that is being transported. Pre-iontophoresis was shown not to affect the subsequent passive transport of the decapeptide LHRH analogue, nafarelin, through hairless mouse skin in vitro (Delgado-Charro and Guy, 1995). Also, the rate of transport of the LHRH analogue, [D-Trp^6, Pro^9–NHeT]GnRH, through hairless mouse skin in vitro, decreases by more than 95% immediately following discontinuation of the current (Miller et al., 1990). In addition, the flux of the nonapeptide, arginine–vasopressin, across hairless rat skin in vitro returned to normal within 1.5 h after termination of iontophoresis (Lelawongs et al., 1989).

A significant GH response in man (> 10 ug/ml serum) is achieved following i.v. infusion dosing of SK&F 110 679, at a rate of 0.3 ug/kg·h or 21 ug/h in a 70 kg adult (DeBell et al., 1991). Maximal GH response occurred 50–120 min after initiation of the infusion. Here we show that in rats

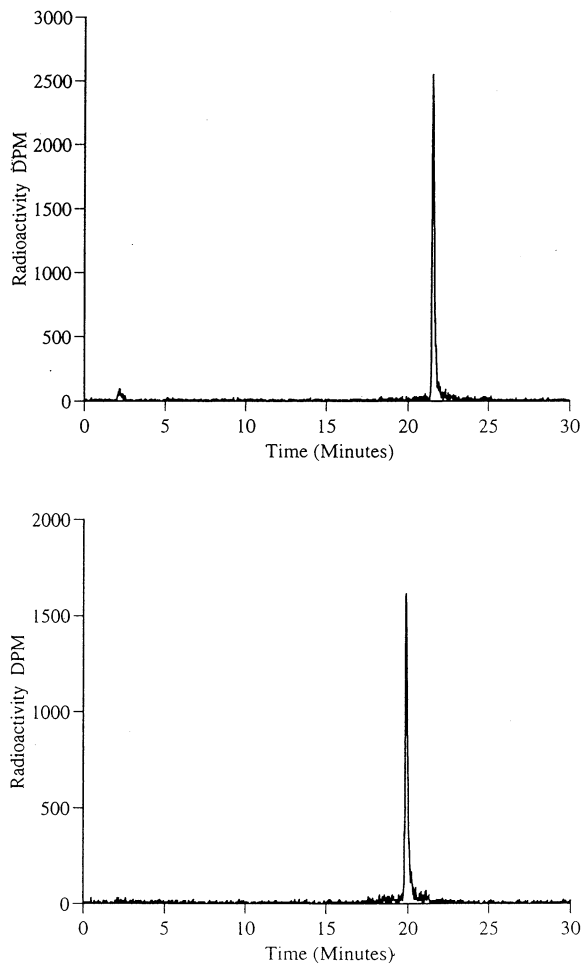

Fig. 6. HPLC radiochromatograms of pooled rat bile and urine from the 1.8 mg group. A 50 ul sample was applied to the column. Top panel, bile; bottom panel, urine.

Table 2
Percent of radioactivity excreted in bile or urine which coeluted with intact [^{3}H]SK&F 110 679

	Pool[a]	% Radioactivity coeluting with intact [^{3}H]SK&F 110 679[b]
Bile	1.8 mg group	84
	3.8 mg group	73
	8 mg group	74
Urine	1.8 mg group	78
	3.8 mg group	76
	8 mg group	77

[a] Equal volumes of bile or urine collected at 2, 3, 4 and 5 h were pooled. The 8 mg group consisted of two animals, while the other groups had four animals each.
[b] Percentage of total eluted radiochemical determined by integration of HPLC peak areas as described in the text (mean of duplicate analyses of pooled samples).

a minimum of 4–6 ug/h (0.8–1.2 ug/h per cm^2) is delivered during the 4 h period following the initiation of iontophoresis (Table 1). Although little is known about the relative rates of transdermal iontophoretic transport across rat versus human skin, it appears that, with appropriate optimization of the delivery system (i.e. increased patch size), therapeutic levels of SK&F 110 679 in man may be attainable by transdermal iontophoresis.

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