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International Journal of Pharmaceutics 251 (2003) 195–203
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Sucrose cocoate, a component of cosmetic preparations, enhances nasal and ocular peptide absorption

Fakhrul Ahsan [1], John J. Arnold, Elias Meezan, Dennis J. Pillion *

Department of Pharmacology and Toxicology, School of Medicine, University of Alabama at Birmingham, 1670 University Boulevard, Birmingham, AL 35294-0019, USA

Received 5 September 2002; received in revised form 31 October 2002; accepted 31 October 2002

Abstract

Sucrose cocoate (SL-40), an emulsifier employed in emollient, skin-moisturizing cosmetic formulations, contains a mixture of sucrose esters of coconut fatty acids in aqueous ethanol solution. In order to determine its potential utility in enhancing nasal and ocular drug delivery, absorption studies were performed in anesthetized Sprague-Dawley male rats with calcitonin and insulin, two distinct therapeutic peptides. Administration of a nasal insulin formulation containing 0.5% sucrose cocoate caused a rapid and significant increase in plasma insulin levels, with a concomitant decrease in blood glucose levels. When insulin was administered ocularly in the presence of 0.5% sucrose cocoate, a smaller increase in plasma insulin levels, and a decrease in blood glucose levels, were observed. Administration of a nasal calcitonin formulation containing 0.5% sucrose cocoate caused a rapid increase in plasma calcitonin levels and a concomitant decrease in plasma calcium levels. Mass spectrometric analyses were used to characterize the nature of the sucrose fatty acid esters in the mixture. The most abundant sucrose ester in sucrose cocoate was sucrose monododecanoate, with smaller amounts of sucrose monodecanoate and sucrose monotetradecanoate. In vivo experiments confirmed that this ester was an effective enhancer of nasal peptide drug absorption.

Keywords: Nasal absorption; Sucrose cocoate; Insulin; Calcitonin; Ocular absorption; Sucrose fatty acid esters

1. Introduction

Sucrose cocoate (SL-40) is a mixture of fatty acid sucrose esters, produced through the chemical esterification of coconut oil with sucrose. Coconut oil, a vegetable oil found commonly in foods, contains fatty acid chains of different lengths esterified to glycerol. The fatty acid chains are typically unbranched and contain an even number of carbon atoms between 10 and 20, with the majority primarily being 12 carbons. The relative abundances of the various fatty acids in coconut oil are presented in Table 1 (Ensminger et al., 1983). Sucrose fatty acid esters are typically manufactured without ethoxylation, using a

* Corresponding author. Tel.: +1-205-934-4570; fax: +1-205-934-7048
E-mail address: dpillion@uab.edu (D.J. Pillion).
[1] Present address: Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX 79106, USA.

0378-5173/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0378-5173(02)00597-5

Table 1
Approximate fatty acid composition of coconut oil (adapted from Ensminger et al. (1983))

Fatty acid	Percent of total (%)
Saturated fatty acids (%)	
Capric (C_{10})	7.6
Lauric (C_{12})	44
Myristic (C_{14})	18
Palmitic (C_{16})	9.5
Stearic (C_{18})	5
Unsaturated fatty acids (%)	
Oleic (C_{18})	8.2

method that controls the degree of esterification. The resultant products can include a sucrose monoester, a diester, or a combination of both.

Sucrose cocoate has been used extensively as a pharmaceutical excipient in cosmetic and dermatological products. With an HLB (hydrophilic and lipophilic balance) value of 15, it has properties as a skin emollient and moisturizer. Further, sucrose fatty acid esters are classified as food grade emulsifiers and texturizers in foods, and as components in protective coatings for oral products (49th report of the Joint FAO/WHO Expert Committee on Food Additives, 1999). The properties of these chemicals make sucrose cocoate an attractive candidate to serve as a possible absorption enhancer in nasal and ocular drug formulations.

In this study, we have measured the effects of sucrose cocoate on the absorption of two distinct peptide drugs, insulin and calcitonin, following nasal and ocular delivery. Two drugs were chosen for study in order to identify if any changes in drug transport were due to selective changes in the nasal permeability to either peptide. We further performed in vivo and mass spectrometric studies in order to characterize the active absorption-enhancing components of sucrose cocoate. The long-term goal of the investigation is to evaluate the potential of utilizing this mild emulsifier in formulations of peptide drugs that can be applied topically to the eye or nose, to circumvent the need for subcutaneous injections of the peptide drugs.

2. Materials and methods

2.1. Materials

Sucrose cocoate in aqueous ethanol (SL-40) was obtained as a kind gift from Croda Inc. (Century Drive, Parsipanny, NJ). Sucrose monodecanoate and sucrose monododecanoate were purchased from Calbiochem (La Jolla, CA) and Anatrace Corporation (Maumee, OH). Sucrose monotridecanoate and sucrose monotetradecanoate were synthesized by CytRx Corporation (Norcross, GA) as previously described (Pillion et al., 2002). Regular human insulin (Humulin®, 100 U/ml) and salmon calcitonin (Miacalcin®, 2200 U/ml) were obtained from Eli Lilly & Company (Indianapolis, IN) and Novartis Pharmaceuticals Corp. (East Hanover, NJ), respectively.

2.2. Preparation of nasal and ocular formulations

On the day of an experiment, sucrose cocoate solutions were prepared in normal saline at 1% (w/v). The nasal and ocular formulations were prepared by mixing either regular human insulin (Humulin®, 100 U/ml) or salmon calcitonin (Miacalcin®, 2200 U/ml) with the appropriate amounts of sucrose cocoate and saline to achieve a final mixture that contained either 25 U/ml of insulin or 110 U/ml of calcitonin.

2.3. Nasal and ocular absorption studies in rats

Nasal and ocular absorption studies were performed in Sprague-Dawley male rats obtained from Charles River Laboratories (Charlotte, NC). Rats were anesthetized by intramuscular injection of a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) and anesthesia was maintained with additional xylazine/ketamine as needed throughout the experiment. The xylazine/ketamine mixture causes impaired insulin release and results in hypoinsulinemia and hyperglycemia, as reported previously (Ahsan et al., 2001a). The number of rats used in each experiment ranged between 3 and 6.

Nasal formulations were instilled into the left nares, 0.02 ml per rat, using a pipetter (Pipetman,

Gilson, France) with a disposable plastic tip. In the intravenous studies, the right femoral vein of anesthetized rats was ligated and insulin (0.5 U) was delivered as a single bolus dose. Extreme care was taken to avoid any leakage from the vein during this process. The nasal, ocular and intravenous insulin formulations were administered 40–60 min after the initial dose of anesthetic agent, to allow time for the blood insulin levels to decrease and blood glucose levels to increase (250–400 mg/dl). The total amount of insulin delivered nasally or ocularly to each rat, was 0.5 U except for the study described in Fig. 5. In order to facilitate cross-comparison with previously obtained data, the amount of insulin utilized in nasal absorption studies with 0.06% sucrose cocoate described in Fig. 5 was increased to 2 U and delivered in two applications containing 1 U each in 0.02 ml, administered at time 0 and at 5 min. Ocular formulations (0.02 ml per rat) were administered to the left eye of anesthetized rats, also using a pipetter, 40–60 min after the initial dose of anesthetic agents. The solutions were instilled slowly, one drop at a time, to avoid spillage of the formulation.

Blood glucose levels were measured in blood collected from the tip of the rat tail using a glucose meter (Glucometer Elite, Bayer Corp., Elkhart, IN) at time 0 and at 5–20 min intervals for 120 min following insulin delivery. Concomitantly, blood samples were collected from the tip of the tails of anesthetized animals in plastic microfuge tubes containing 5 μl of heparin (1000 U/ml) for determination of plasma insulin. Plasma specimens were isolated following centrifugation and stored at −20 °C. A human insulin specific radioimmunoassay kit (Linco Research Inc., St. Charles, MO) was used to measure exogenous human insulin in the rat blood at various times after insulin delivery.

The amount of calcitonin delivered nasally to the rat was 2.2 U. In some experiments, the amount of calcitonin administered ocularly to the rat was increased to 22 U. Blood samples were again collected from the tip of the tails and immediately placed on ice. Within 1 h, plasma specimens were separated following centrifugation and stored at −20 °C until assayed for calcitonin and calcium content. A salmon calcitonin specific radioimmunoassay kit (DSL Inc., Webster, TX) was used to measure salmon calcitonin levels in the plasma specimens collected at various times after nasal or ocular administration of calcitonin. Calcium was measured in 0.01-ml aliquots of plasma using a colorimetric method (Sigma Chemical Co., St. Louis, MO).

The animal studies were conducted according to the principles outlined in the 'Guide for the Care and Use of Laboratory Animals,' Institute of Laboratory Animal Resources, National Research Council.

2.4. Mass spectrometry

Mass spectrometry (MS) was carried out in the UAB Comprehensive Cancer Center Mass Spectrometry Shared Facility. Analyses were performed on an API III triple quadrupole mass spectrometer by either the flow injection method or by RP-HPLC MS using electrospray MS in the negative mode (Cao et al., 2000). Tandem MS (MS/MS) daughter ion spectra were obtained by passing the (M−H)-ion selected with the first quadrupole into the second quadrupole containing argon gas and analyzing the fragment ion with the third quadrupole.

2.5. Statistical analysis

The area under the curve (AUC) values were calculated by the trapezoidal method. AUC values obtained in the presence and absence of sucrose cocoate were compared for differences using an unpaired Student's test (SigmaStat software). Statistical significance was assigned to tests that displayed P values < 0.05. The correlation coefficient, r, was also calculated using the same software.

3. Results

3.1. Mass spectrometry

MS was used to evaluate the composition of SL-40 and to compare it to a sample of the synthetic

alkyl sucrose ester, sucrose monododecanoate (Anatrace Corporation; Maumee, OH). MS of a sample of sucrose monododecanoate in the negative ion mode identified the parent ion ($m = 523$) and its chloride ($m = 559$) and formate ($m = 569$) adducts (Fig. 1A). MS of SL-40 in the negative ion mode (Fig. 1B) gave a prominent signal for sucrose monododecanoate ($m = 523$) and its formate adduct ($m = 569$). Much smaller signals were observed in the SL-40 profile for negative ions $m = 495$ and $m = 541$, which presumably represented sucrose monodecanoate (C_{10}) and its formate adduct, respectively. Small signals were also observed at $m = 551$ and $m = 597$, which represented sucrose monotetradecanoate (C_{14}) and its formate adduct (Fig. 1B). These results were in agreement with the saturated fatty acid composition of the coconut oil from which SL-40 is derived (Table 1). The identity of sucrose monododecanoate as the predominant sucrose ester in sucrose cocoate was confirmed by examining the daughter ion profile produced by fragmentation of the parent ion ($m = 523$) obtained by MSMS (Fig. 2). Among the daughter ions produced were fragments representative of the carbohydrate moiety, e.g. fragments of glucose and fructose ($m = 89$, $m = 59$), intact glucose and fructose ($m = 179$) and sucrose itself ($m = 341$). Additionally, fragments arising from the alkyl chain ($m = 71$, $m = 113$) or comprising the entire chain, i.e. the monododecanoate moiety ($m = 199$), were observed. The negative ion MSMS spectrum of the parent sucrose monododecanoate (sucrose monolaurate) ion was in agreement with that previously reported for this compound (de Koster et al., 1993). Hence, the characteristics of the major peak observed in the spectrogram of sucrose cocoate are consistent with the properties predicted for sucrose monododecanoate.

3.2. Nasal and ocular insulin absorption

Nasal formulations containing 0.5 U insulin formulated in saline without sucrose cocoate failed to elicit an increase in plasma insulin (Fig. 3A). The administration of nasal formulations containing insulin plus 0.125, 0.25 or 0.5% sucrose cocoate caused rapid and transient increases in plasma insulin levels (Fig. 3A). Insulin levels increased from less than 10 μU/ml prior to administration of nasal formulations to greater than 200 μU/ml ($P < 0.05$), with a T_{max} of 10 min. A comparison of the AUC_{0-60} values for plasma insulin obtained with increasing concentrations of sucrose cocoate is presented as an insert to Fig. 3A. These results

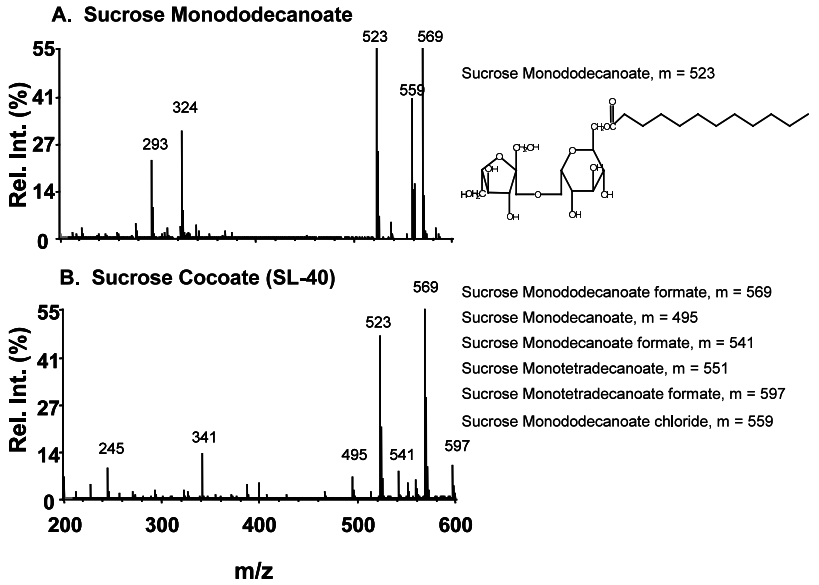

Fig. 1. MS in the negative ion mode of (A) authentic sucrose monododecanoate, and (B) sucrose cocoate (SL-40).

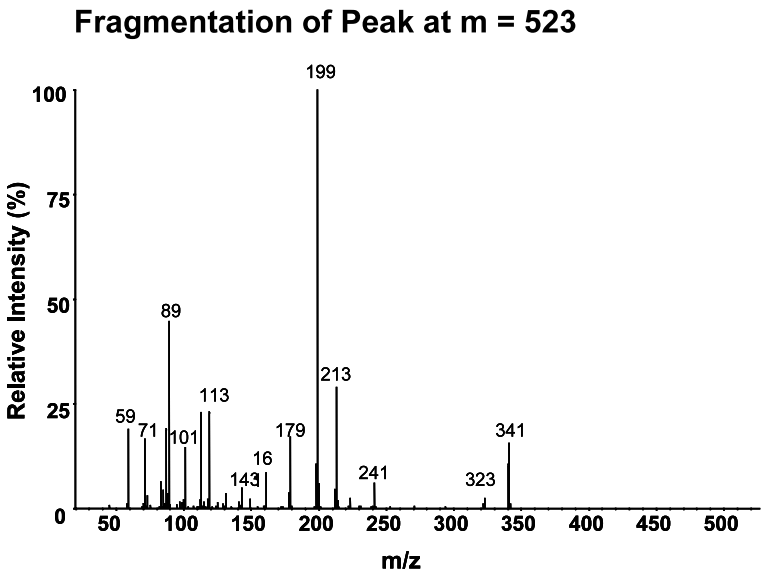

Fig. 2. Daughter ion profile produced by fragmentation of the predominant parent ion of SL-40 ($m = 523$) obtained by MSMS.

reflect a direct correlation between the concentration of sucrose cocoate in the formulation and the extent of insulin absorption ($r = 0.94$). Blood glucose concentrations were measured concomitantly in these experiments (Fig. 3B). Consistent with plasma insulin changes, nasal formulations containing 0.5 U insulin plus 0.125, 0.25 or 0.5% sucrose cocoate displayed a transient effect on blood glucose as measured via glucose AUC changes (Fig. 3B insert). The fact that the changes in blood glucose are not correlated with concentrations of sucrose cocoate in a linear manner can best be explained as a result of the fact that supraphysiological levels of insulin are achieved under these experimental conditions. Hence, even at low levels of sucrose cocoate (0.125%), significant plasma concentrations of insulin are achieved (80 ± 22 μU/ml, $P < 0.05$) and these produce a nearly maximal effect on blood glucose concentration. Addition of higher concentrations of sucrose cocoate to the nasal insulin formulation can produce still further increases in plasma insulin content, but the physiological response to insulin, i.e. the reduction in blood glucose content, can only be increased slightly before a maximum effect is reached.

When insulin was administered to the ocular surface with eye drops formulated in saline or with 0.5% sucrose cocoate, plasma insulin levels were increased from 5 μU/ml in rats that received insulin eye drops formulated in saline to 59 μU/ml in rats that received insulin eyedrops formulated with 0.5% sucrose cocoate (data not shown). The T_{max} for insulin was observed 20 min after the administration of eyedrops containing 0.5% sucrose cocoate. A modest, but significant decrease in blood glucose concentration was observed following ocular delivery of insulin formulated with 0.5% sucrose cocoate (data not shown).

Data from experiments utilizing insulin nosedrops and insulin eye drops were compared with data from experiments that utilized intravenously bolused insulin to establish the bioavailability of insulin achieved via each route of administration (Table 2). Nasal insulin delivery in the presence of 0.5% sucrose cocoate produced a larger increase in the plasma insulin AUC_{0-60} and caused a larger C_{max}, than ocular delivery of the same formulation. The T_{max} for nasally administered insulin was 10 min, while the T_{max} for ocularly delivered insulin was 20 min. Insulin bioavailability was increased in the presence of 0.5% sucrose cocoate

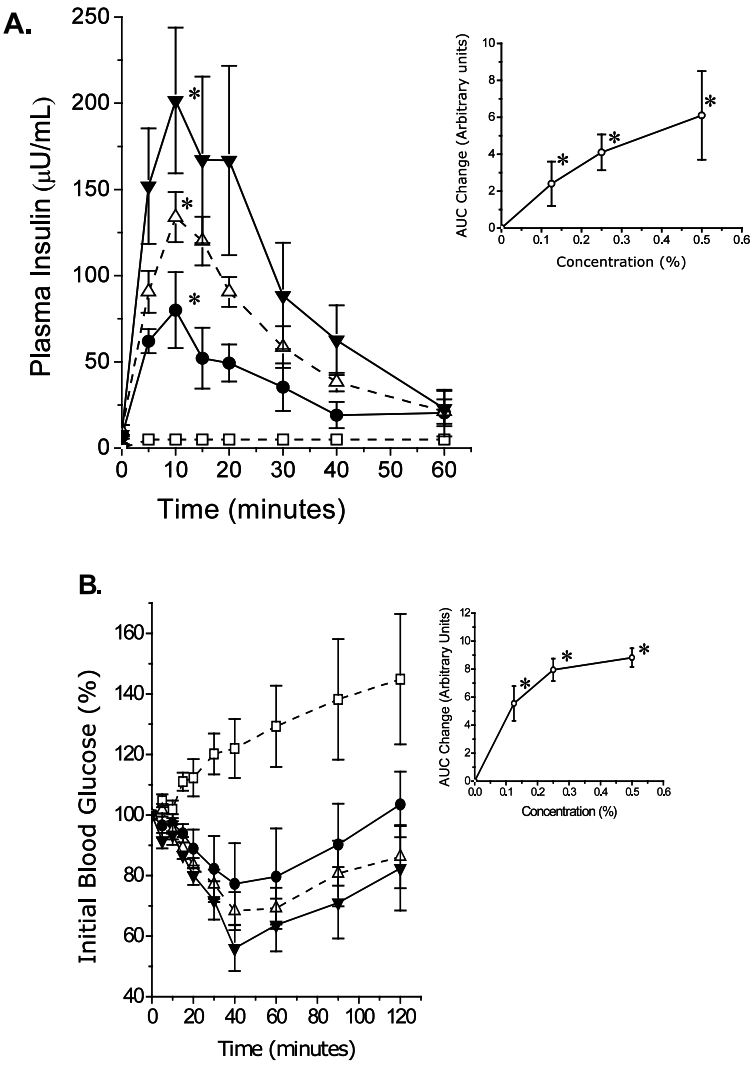

Fig. 3. Changes in (A) plasma insulin levels and (B) blood glucose levels after nasal administration of 0.5 U insulin formulated in saline (□) or 0.125% (●), 0.25% (△), and 0.5% (▼) sucrose cocoate. Blood glucose concentrations at time 0 (250–350 mg/dl) were normalized to a value of 100% in each animal. Data represent mean ± standard error of the mean, $n = 3$. Inserts represent changes in plasma insulin AUC_{0-60} (A) and changes in blood glucose AUC_{0-120} (B).

by ninefold following nasal insulin administration and by fourfold following ocular insulin administration (Table 2).

3.3. Nasal and ocular calcitonin absorption

Calcitonin absorption was measured after administration of nosedrops containing salmon calcitonin formulated in saline or in sucrose cocoate (Fig. 4). Administration of nose drops containing 2.2 U calcitonin formulated in saline caused no significant increase in plasma calcitonin levels, whereas administration of nosedrops containing calcitonin formulated in 0.5% sucrose cocoate caused a prompt and significant increase in plasma calcitonin levels (400 ± 60 pg/ml, $P < 0.05$) (Fig. 4A). Furthermore, rats receiving nosedrops containing 2.2 U calcitonin formulated with 0.5%

Table 2
Pharmacokinetic parameters of nasal, ocular, and intravenous insulin administration

	Sucrose cocoate (%)	Plasma insulin AUC_{0-60} (μU/ml × min)	Insulin bioavailability (%)	C_{max} (μU/ml)	T_{max} (min)
Nasal	0	< 675	< 1.4	< 5	N/A
	0.5	6200 ± 1800*	12.5	200 ± 44*	10
Ocular	0	< 675	< 1.4	< 5	N/A
	0.5	2560 ± 326*	5.2	59 ± 9*	20
Intravenous	0	48900 ± 6970	100	N/A	N/A

* $P < 0.05$ compared to sample with 0% sucrose cocoate.

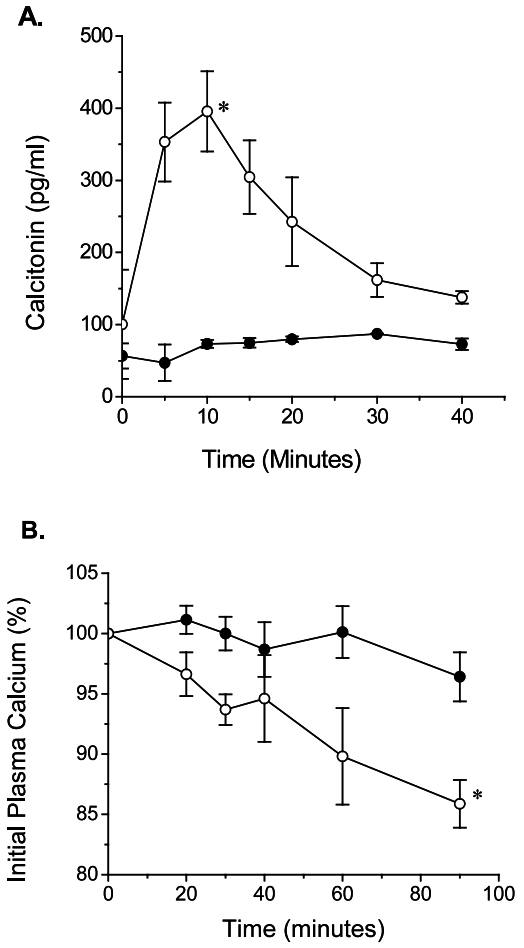

Fig. 4. Changes in (A) plasma calcitonin and (B) plasma calcium levels after nasal administration of calcitonin formulated in the absence (●) or presence (○) of 0.5% sucrose cocoate. Plasma calcium concentrations at time 0 (8–10 mg/dl) were normalized to a value of 100% in each animal. Data represent mean ± standard error of the mean, $n = 3$.

sucrose cocoate showed a significant decrease ($\sim 15\%$, $P < 0.05$) in plasma calcium levels, compared to the rats receiving calcitonin in nosedrops formulated with saline (Fig. 4B).

Ocular administration of 2.2 U calcitonin formulated with 0.5% sucrose cocoate produced smaller changes in plasma calcitonin and calcium values, that did not achieve statistical significance (data not shown). However, when the amount of calcitonin administered to the rats by eye drops was increased from 2.2 to 22 U, a significant increase in plasma calcitonin values was observed, along with a corresponding hypocalcemic response. The T_{max} for calcitonin absorption in the presence of sucrose cocoate, like the T_{max} for insulin absorption, was dependent on the route of administration. When 2.2 U of calcitonin was formulated with 0.5% sucrose cocoate and applied nasally, the maximal level of calcitonin was obtained 10 min after instillation of the nose drops (Fig. 4A). However, maximal levels of calcitonin were not observed until 20 min after ocular administration of a formulation containing 22 U calcitonin and 0.5% sucrose cocoate (data not shown).

3.4. Structure/in vivo activity characterization

Previous work in our laboratory has established a direct correlation between increasing alkyl chain length and the efficacy of alkyl sucrose esters as enhancers of nasal insulin absorption (Pillion et al., 2002). Nasal formulations containing insulin (2 U) plus individual synthetic fatty acid esters of sucrose containing alkyl chains of 10, 12, 13, and 14 carbons, at a concentration of 0.06%, have been

tested for their ability to cause a reduction in blood glucose concentration in hyperglycemic, anesthetized rats (Fig. 5). In order to cross-compare this previous data with that obtained with sucrose cocoate, which contains a mixture of alkyl sucrose esters, nasal formulations containing sucrose cocoate (0.06%) plus insulin (2 U) were administered and blood glucose reduction was measured.

The results of this comparison showed that nasal administration of insulin (2 U) in 0.06% SL-40 reduced blood glucose concentrations to a degree that fell midway between the effectiveness of insulin formulated in 0.06% sucrose monododecanoate and that formulated in 0.06% sucrose monotridecanoate (Fig. 5). These results are consistent with the mass spectrum which indicates sucrose monododecanoate to be the predominant component of sucrose cocoate.

4. Discussion

In composite, the experimental data indicate that sucrose cocoate can enhance the bioavailability of both insulin and calcitonin administered by the nasal or the ocular route. Such a finding is entirely consistent with other fatty acid esters studied previously for their ability to increase the absorption of peptide drugs across the nasal sinus epithelial layer (Kagatani et al., 1996; Lerk et al., 1996; Vermeire et al., 1996; Ganem-Quintanar et al., 1998; Aungst, 2000). The data also reflect the temporal and quantitative distinctions in peptide drug absorption following nasal versus ocular administration. The nasal route produces more rapid and robust delivery of peptide drugs than the ocular route when an absorption-enhancing agent is added to the formulation. Radiographic evidence supports the contention that ocular administration of peptide drugs leads to clearance from the surface of the eye via the nasolacrimal drainage and then results in absorption across the nasal sinus epithelium (Pillion et al., 1991). Little or no direct absorption of peptide drug into the systemic circulation occurs across the corneal surface (Chiou and Chuang, 1989).

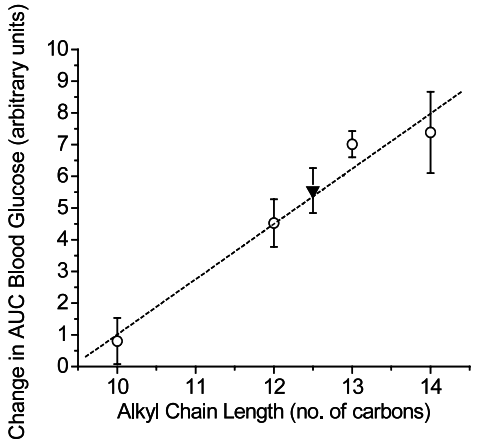

Fig. 5. Changes in blood glucose AUC_{0-120} after nasal administration of insulin (2 U) plus 0.06% sucrose monodecanoate, sucrose monododecanoate, sucrose monotridecanoate, or sucrose monotetradecanoate plotted as a function of alkyl chain length (○). The change in blood glucose AUC_{0-120} observed after nasal administration of insulin (2 U) plus 0.06% SL-40 (▼) is also included for cross-comparison. Data represent mean ± standard error of the mean.

Previous work in this laboratory has demonstrated that alkylglycosides containing maltose or sucrose linked to alkyl chains between 10 and 14 carbons in length, can increase the bioavailability of insulin (Ahsan et al., 2001b; Pillion et al., 1994a,b, 2002). More recently, we have demonstrated that tetradecylmaltoside increases the absorption of calcitonin applied to the eyes or nose of rodents (Ahsan et al., 2001b). Further studies have confirmed a structure–function relationship for a series of biochemically synthesized alkylglycosides, including two acyl esters of sucrose, sucrose monodecanoate (decylsucrose) and sucrose monododecanoate (dodecylsucrose) (Pillion et al., 1994b). Insulin permeation was enhanced minimally in the presence of purified alkylglycosides with shorter alkyl chains (C_6–C_9) linked to glucose, whereas alkylglycosides with longer side chains (C_{12}–C_{14}) linked to maltose caused maximal increases in insulin absorption. More recently, the structure–function relationship of alkylglycosides has been extended to include maltose glycosides with alkyl chains of C_{15}–C_{16} and to sucrose esters with C_{13} and C_{14} acyl chains (Pillion et al., 2002). The maximal stimulation of peptide

drug absorption was observed with C_{14} chains linked to either maltose or sucrose.

The current study is distinct from previous experiments that employed individual synthetic alkyl sucrose esters because sucrose cocoate (SL-40) represents an approved cosmetic formulation containing a mixture of acylsucrose esters. The most abundant sucrose ester in sucrose cocoate was sucrose monododecanoate, with smaller amounts of sucrose monotetradecanoate. In vivo experiments confirmed that sucrose esters with acyl chains of 12–14 carbons were the most effective enhancers of nasal peptide drug absorption.

Acknowledgements

This work was supported in part by an S.T.T.R. Award, ES08933, from the National Institute of Environmental Health Sciences, N.I.H., to CytRx Corporation and the University of Alabama at Birmingham School of Medicine. The purchase of the PE-Sciex API 3 mass spectrometer came from funds provided by NCRR grant 10 RR06487. Funds for the operation of the Mass Spectrometry Shared Facility are partly derived from the UAB Comprehensive Cancer Center Support Grant P30 CA-13148. We are indebted to Marion Kirk for performing the mass spectrometric analyses.

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