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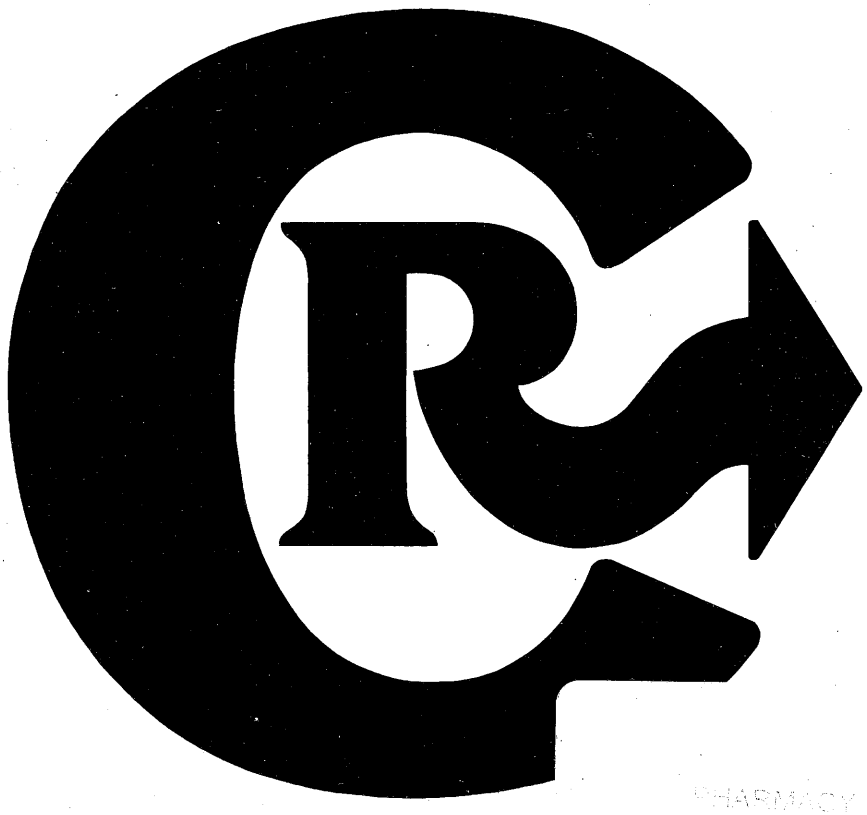

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Absorption of water-soluble compounds with different molecular weights and [Asu^{1,7}]-eel calcitonin from various mucosal administration sites

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Abstract

The absorption of water soluble compounds with different molecular weights, such as phenol red (MW 354), trypan blue (MW 960), fluorescein isothiocyanate dextrans, (MW 4400 and 9100) was studied in the lung, nasal cavity, buccal cavity, small and large intestine of rats. For all the compounds, maximal absorption was observed when administered to the lung. The rank order of absorption of each compound from various administration sites was lung>small intestine≧nasal cavity≧large intestine≧buccal cavity. In addition, the relationship between logarithm absorption % of the compounds from various administration sites and logarithm molecular weights of these compounds was examined. The absorption of compounds gradually decreased with increasing molecular weight for each site of administration. Moreover, the absorption of [Asu^{1,7}]-eel calcitonin (ECT) from these sites and the effect of 10 mM sodium glycocholate, an absorption enhancer, on its absorption were also investigated in rats. When ECT alone was administered into these sites, the lung had the best absorption site of ECT, followed by the nasal cavity, the large intestine, the small intestine and the buccal cavity. Therefore, the absorption of ECT was also dependent on the administration site, although the rank order of absorption % of ECT was different from the other compounds. Sodium glycocholate (NaGC) remarkably increased ECT absorption from the small intestine, while we found marginal increase in its absorption from the lung even in the presence of NaGC. These findings provided useful fundamental information that might aid in the selection of administration routes for drugs of differing molecular weights including peptide drugs as far as the degree of drug absorption is concerned.

Keywords: Drug absorption; Transmucosal drug delivery; Peptide drug delivery; Calcitonin; Absorption enhancer

1. Introduction

The oral administration of drugs is the most common and convenient route of drug administration. However, intestinal absorption of some drugs including water-soluble antibiotics, peptide and protein drugs (e.g. calcitonin and insulin) after oral

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administration is generally poor because they have low permeability due to their hydrophilic characteristics and large molecular size [1]. Moreover, as for peptide and protein drugs, they are extensively degraded by proteases in the intestinal mucosa [1], which is also related to their low absorption from the gastrointestinal tract. Therefore, parenteral injection must generally be used for their administration. However, injection can cause local side effects and allergic reactions by frequent administration. Consequently, alternative routes, including nasal [2], buccal [3], rectal [4], ocular [5], vaginal [6] and pulmonary [7–10], are being investigated for systemic delivery of drugs, especially protein and peptide drugs. These alternatives are also useful for the administration sites of drugs that are easily metabolized in the liver, since the drugs can avoid the hepatic first pass metabolism following their administration from these sites.

Previously, it was reported that rectal insulin was more efficacious than nasal, buccal and sublingual insulin, when administered without an absorption-promoting adjuvant [11], and absorption enhancers such as sodium glycocholate (NaGC) and laureth-9 significantly improved absorption from each studied site [12]. However, the extent and rate of absorption of drugs with different physicochemical characteristics from various administration sites have not been fully investigated in a single study. Furthermore, few studies have been carried out to compare the extent of absorption of peptide drugs from these administration sites in the presence or absence of absorption enhancers.

In this study, therefore, first of all, phenol red (MW 354), trypan blue (MW 960) and fluorescein isothiocyanate dextran with average molecular weights of 4400 (FD4) and 9100 (FD10), were chosen as water-soluble model compounds with different molecular sizes. The absorption of these compounds from the lung, nasal cavity, buccal cavity, small intestine and large intestine was examined in rats to compare their absorption from the administration sites. In addition, [Asu^{1,7}]-eel calcitonin (ECT), which is one of the most popular peptide drugs and should be administered parenterally as well as insulin, was chosen as a model peptide drug and the absorption of ECT from these administration sites was studied in rats. Furthermore, bile salts including NaGC are known to be typical absorption enhancers for improving the absorption of peptide and protein drugs from various administration sites [13]. In addition, our previous studies demonstrated that NaGC improved the intestinal absorption of phenol red without serious membrane toxicity [14,15]. Therefore, the effect of NaGC on its absorption from the administration sites was also examined to clarify whether the absorption enhancing effect of NaGC was site-dependent.

2. Materials and methods

2.1. Materials

Phenol red and trypan blue were purchased from Wako Pure Chemical Industries (Osaka, Japan). FD4 (average molecular weight; 4400), FD10 (average molecular weight; 9100) and NaGC were purchased from Sigma Chemical Co. Ltd. (St. Louis, MO, USA). ECT (MW 3364) was kindly supplied from Asahi Chemical Industry Co., Ltd (Shizuoka, Japan). All other chemicals and solvents were of reagent grade quality.

2.2. Preparation of drug solution

The adequate amounts of drugs were dissolved in isotonic phosphate buffer (lung, nasal cavity, buccal cavity, large intestine: pH 7.4, small intestine: pH 6.5). After surgical operation of each administration site as described below, phenol red, trypan blue, FD4, FD10 (each dose was 2 mg/rat) and ECT (1 μg/rat, 6 IU/μg) were administered to these mucosal sites. During the absorption studies, the solutions did not visibly leak from the site of administration. In certain experiments, 10 mM NaGC, an absorption enhancer, was added to the dosing solution of ECT. For intravenous administration, 0.4 mg of each compound or 0.1 μg (0.6 IU) of ECT was administered to the femoral vein of rats.

2.3. Animal experiments

Male Wistar rats (Shimizu Laboratory Supplies), weighing 200–250 g, were anesthetized with sodium pentobarbital (32 mg/kg body weight) injected

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