Chapter 9

Rectal and Vaginal Absorption of Peptides and Proteins

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1. INTRODUCTION

Peptide/protein drugs are increasingly becoming a very important class of therapeutic agents as a result of our gaining more understanding of their role in physiology and pathology as well as the rapid advances in the field of biotechnology/genetic engineering. These drugs are generally not suitable for oral administration, since they are poorly absorbed and easily degraded by proteolytic enzymes in the gastrointestinal tract (Lee and Yamamoto, 1990). For systemic delivery of peptide and protein drugs, parenteral administration is currently required in order to achieve their therapeutic activities. However, these administration routes are poorly accepted by patients and may cause an allergic reaction. Thus, alternative routes such as nasal (Hirai et al., 1981a), buccal (Ishida et al., 1981), rectal (Nishihata et al., 1983), vaginal (Okada et al., 1982), conjunctival (Yamamoto et al., 1989), and transdermal (Liu et al., 1988) are being investigated for peptide and protein delivery. Among these routes, rectal and vaginal are potentially important routes for peptide administration, although they are poorly accepted in several countries. In contrast to the oral route, the rectal delivery of peptide/protein drugs provides the advantage of greater
systemic bioavailability, especially with the coadministration of adjuvants. Additional advantage is the avoidance of first-pass elimination (de Boer et al., 1980). On the other hand, in the vaginal membrane, the predominant transport of lipophilic substances takes place by partition and diffusion through the transcellular lipoidal passage.

In this chapter, we introduce the anatomical and physiological aspects of the rectum and vagina, which are related to the characteristics of absorption of drugs and peptides from these routes. We also review the effect of absorption promoters on peptide absorption from the rectum and vagina and their mechanisms of enhancing action. Further, we describe the contribution of the transcellular and paracellular routes and lymphatic transport of drugs via a rectal route and the metabolic property of peptides in the rectal mucosa, which is another important barrier for systemic delivery of these drugs.

2. RECTAL BARRIER

2.1. Anatomy and Physiology of the Rectum

The rectal epithelium is columnar or cuboidal with numerous goblet cells. However, unlike the small intestine, the rectal epithelium does not contain villi. In addition, the mucus-containing goblet cells are interspersed in an organized fashion among absorptive cells in the small intestine, gradually increasing in number toward the large intestine. In the descending colon of humans, goblet cells are numerous, comprising one-eighth of the epithelial cell population (Forstner, 1978). The human rectum has a length of 5 inches and a surface area of only about 200 to 400 cm², compared with 2,000,000 cm² for the small intestine (Wilson, 1962). Consequently, from a surface area consideration, one would expect absorption to be much less from the rectum than from the upper gastrointestinal tract. Indeed, the rectal bioavailability of peptide drugs is generally very low; e.g., less than 1% for the nonapeptide leuprolide in women, 5–16% for the tetrapeptide tetragastrin in rats, and about 1% for the tripeptide thyrotropin-releasing hormone (TRH) in humans (Hoogdalem et al., 1989). For the polypeptide insulin, a pharmacological availability of 5.3% was observed, using suppositories in rabbits. Therefore, larger polypeptides and proteins require absorption promoters in order to improve the rectal absorption of these macromolecules.

On the other hand, in the vasculature of the rectum, the upper venous drainage system (superior hemorrhoidal vein) is connected to the portal system, whereas the lower venous drainage system (inferior and middle hemorrhoidal veins) is connected directly to the systemic circulation by the ileac vein and vena cava (Banga and Chien, 1988). Thus, an opportunity to reduce the extent of hepatic first-pass elimination exists in the rectum, especially when the drug is administered in the lower region