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Tight junction modulation and its relationship to drug delivery ☆

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Abstract

In order for therapeutic agents to exert their pharmacological effects, they have to cross the biological membranes into the systemic circulation and reach the site of action. Drugs cross the membranes by one of two pathways; paracellular or transcellular. Most drugs are transported transcellularly depending on their physiocochemical properties, however the paracellular route is usually the main route of absorption for hydrophilic drugs (proteins, peptides, etc.). The paracellular pathway is governed by the tight junctions (TJs). The modulation of the TJs by absorption enhancers for paracellular drug transport enhancement and hence drug delivery improvement has been hampered for so many years by lack of comprehensive understanding of the structure and function of the TJs. The TJs are a multiple unit structure composed of multiprotein complex that affiliates with the underlying apical actomyosin ring. TJ proteins identified include transmembrane proteins; occludin and claudin, and cytoplasmic plaque proteins; ZO-1, ZO-2, ZO-3, cingulin, and 7H6. Among the new absorption enhancers that evolved in the past few years is Zonula Occludens toxin, Zot. In vivo and in vitro studies have shown that Zot and its biologically active fragment ΔG could be effectively used to increase the transport/absorption of paracellular markers and low bioavailable drugs across the intestinal epithelium. Above all, the transient opening of the TJs by Zot suggests that it could be used as a novel approach for the safe drug delivery of therapeutic agents.

Keywords: Zonula Occludens toxin; Paracellular permeability; Blood borne barrier; Oral delivery; Zonulin

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1. Introduction

Alternatives to the parenteral route of drug delivery present a series of attractive advantages for the administration of therapeutic compounds via oral delivery. These advantages are particularly relevant for the treatment of pediatric patients and include the avoidance of pain and discomfort associated with injections and the elimination of possible infections caused by inappropriate use or reuse of needles. Moreover, oral formulations are less expensive to produce, because they do not need to be manufactured under sterile conditions.

In the past few years we have witnessed an explosion in research aimed at creating new drug delivery systems. This research has been fuelled by unprecedented challenges, such as the need to deliver new, more complex drugs (e.g., proteins, hormones, etc.) that are becoming available through recombinant DNA technology. Thus, considerable attention has been directed at finding ways to increase the oral bioavailability of these compounds. However, the intestinal absorption of these molecules is profoundly limited by their physicochemical characteristics.

The identification of therapeutic agents has been sometimes compromised by their biological behavior following administration. For drugs to be therapeutically effective, they have to possess favorable characteristics to cross the biological membranes into the systemic circulation and reach the site of action. Drugs cross the membranes via the transcellular or the paracellular routes (Fig. 1). The transcellular pathway involves the passage of the drug across the cells, while the paracellular pathway refers to the passage of drugs in between the adjacent cells. The major pathway for absorption or transport of a drug depends on its physicochemical characteristics as well as the membrane features. In general, lipophilic drugs cross the biological membrane transcellularly while hydrophilic drugs cross the membrane paracellularly. In order to ameliorate drug absorption via the transcellular pathway, the physicochemical features of the drug have to be manipulated (lipophilicity, pKa, conformation, H-bond characteristics, etc.) or the membrane characteristics have to be altered.

Agents used to increase the penetration or absorption of drugs are called absorption/penetration enhancers. In most cases, those that act via alteration of the characteristics of the membrane to be more permeable, tend to compromise cell viability. On the other hand, manipulation of the paracellular pathway could be used to increase the transport of hydrophilic drugs and modify the absorption route of the fraction absorbed paracellularly for other drugs. The manipulation of the paracellular route has only been explored recently because the structural features of the TJs governing the permeation via this route have been partially unraveled in the past few years. In this report, we will focus on the use of the paracellular pathway to increase the bioavailability of therapeutic agents. Novel absorption enhancers will be discussed with emphasis on Zonula Occludens toxin.

2. The paracellular route

Paracellular transport is the transport of drugs through the intercellular spaces. The paracellular