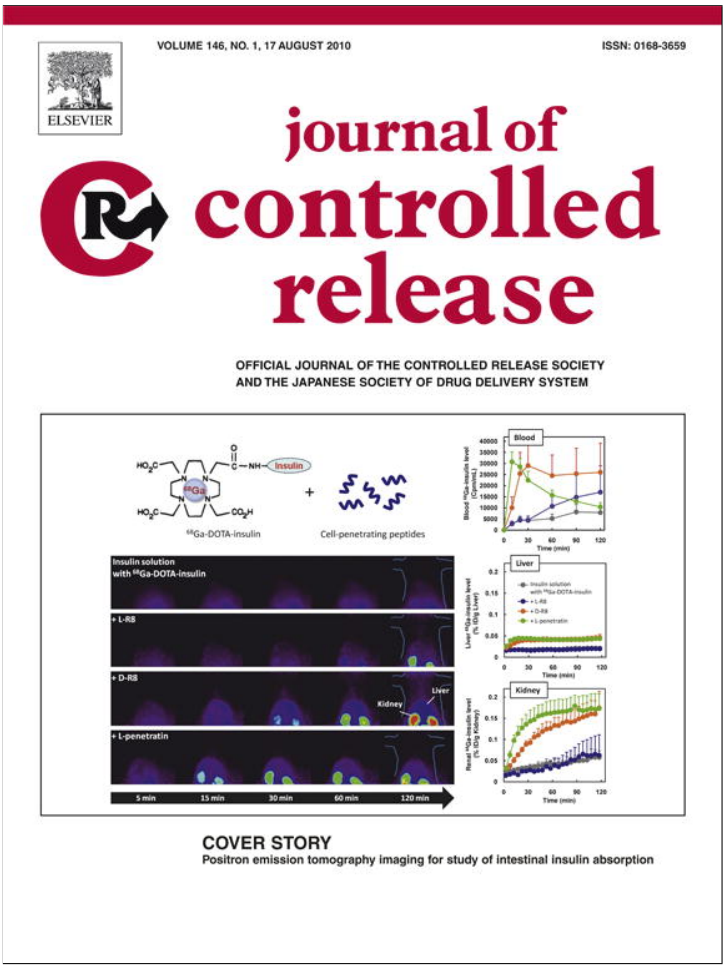

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Cover Story

Positron emission tomography imaging for study of intestinal insulin absorption

Molecular imaging technologies have recently progressed exponentially for clarifying the biological functions of endogenous molecules and the pharmacokinetics of drugs in vivo. Of the many imaging methodologies developed to date, the one using positron emission tomography (PET) is particularly attractive for diagnosis and treatment of many diseases, as it is noninvasive, highly quantitative, and able to trace the time-dependent accumulation of a drug in specific organs [1]. Such properties of PET imaging are also useful for investigating the efficacy of drug delivery systems.

Professor Morishita and her collaborators have been developing oral insulin formulations through the years. One of their recent findings is that the intestinal absorption of therapeutic peptides and proteins including insulin can be significantly improved by co-administration of cell-penetrating peptides (CPPs) in the animal studies [2–4]. The CPPs are known to be efficiently taken up by numerous cells and can bring other molecules ranging from small compounds to large proteins and particles into the intracellular compartment. In the past few decades, many types of CPPs have been identified, such as TAT peptide derived from human immunodeficiency virus (HIV)-1 transactivator of transcription, and penetratin derived from *Drosophila* Antennapedia homeodomain. At present, CPPs are regarded as one of the most attractive tools for intracellular delivery of therapeutic proteins and nucleic acids because of their ability of macropinocytosis [5]. Professor Morishita and her coworkers have employed the CPP's ability to accomplish the permeation of insulin from intestinal lumen to circulation. Although they have shown in the past that insulin absorption from the intestine could be enhanced significantly in the presence of CPPs, the effect of CPPs on the insulin pharmacokinetics has not been identified. It is important to clarify their pharmacokinetic dispositions in terms of the safety and effectiveness of CPPs.

In this issue, Professor Morishita and her colleagues describe the use of PET imaging method for studying the tissue distribution of insulin after absorption from intestine and the effect of CPPs on the distribution behavior of the absorbed insulin [6]. Their study using ^{68}Ga-DOTA-insulin has demonstrated that insulin absorbed from the intestine rapidly passes through the liver and accumulates significantly in the kidney. Their study also shows that such pharmacokinetic disposition of insulin after absorption is not affected by co-administration of CPPs, implying the safe use of CPPs to increase the intestinal insulin absorption. It is the first attempt to use PET imaging for visual and quantitative evaluation of the intestinal absorption and subsequent pharmacokinetics of insulin in animals.

The study by Professor Morishita and her collaborators in this issue is significant. It shows that PET imaging can be applied to the study of the roles of CPPs. Certainly, other absorption enhancing agents can be studied using the same approach, and this will make the development of oral insulin formulations more systematic. Understanding the detailed pharmacokinetic disposition of insulin after absorption from the intestine will be invaluable for identifying the roles that each excipient may play in oral insulin formulations. The road to the development of oral insulin dosage forms has been long and winding with many blocks, but the study presented in this issue will make the road shorter and wider.

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