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EDITORIAL

Hepatic Handling of Radiopharmaceuticals: Is the In Vitro Model Useful?

Somatostatin is a hyothalamic polypeptide that inhibits the secretion of the pituitary growth hormone. It also inhibits the secretion of prolactin and thyroid-stimulating hormone and has a variety of other inhibitory effects. These divergent functions of hormones are generally related to the biodistribution of their corresponding receptors. The receptors for somatostatin are expressed in the brain, the anterior lobe of pituitary gland, acinar and islet cells of the pancreas, stomach mucosa, intestinal mucosa and the adrenal gland. In addition, these receptors are also expressed on tumor cells of neuroendocrine origin, including meningioma, gastrinoma, carcinoid and insulinoma. Naturally, somatostatin is considered as a reagent useful for in vivo scintigraphic imaging as well as for therapy of such tumors.

However, native forms of somatostatin that are 14 or 28 amino acid peptides (somatostatin-14 and somatostatin-28, respectively) have very short biological half-lives; therefore, their clinical usefulness is limited. They are metabolized very rapidly through the action of aminopeptidases and endopeptidases principally in the liver. Synthetic somatostatin analogs were synthesized to increase their stability in vivo (*1*). An octapeptide octreotide, SMS 201-995, is a somatostatin analog that possesses D-isomer of phenylalanine (D-Phe) and amino alcohol of threonine (Thr(ol)) at N-terminal and C-terminal end, respectively. This analog is resistant to proteolysis and has a long half-life. It has been used for the treatment of growth hormone-producing pituitary adenoma and gastrinoma (*2,3*). Furthermore, derivatives of this analog have been labeled with radionuclides to visualize somatostatin receptors expressed in tumors of neuroendocrine origin. Initially, a phenylalanine of octreotide has been replaced by tyrosine to allow iodination (^{125}I or ^{123}I-Tyr[3]-octreotide), and nuclear imaging of endocrine-related tumors was tested (*4*). However, high abdominal background was a major drawback. Radioiodinated Tyr[3]-octreotides were rapidly cleared from the circulation principally through the liver and secreted into the biliary system. This hepatobiliary clearance resulted in high hepatic and intestinal accumulation (*5*). Subsequently, a diethylenetriaminepentaacetic acid (DTPA) has been conjugated to phenylalanine of octreotide for ^{111}In labeling ([^{111}In-DTPA-D-Phe[1]]-octreotide). In contrast to radioiodinated Tyr[3]-octreotide, ^{111}In-DTPA-D-Phe[1]-octreotide was cleared predominantly by the kidneys and hepatic accumulation was not observed (*6*). The modification of the N-terminal D-Phe residue with the ^{111}In-DTPA group appears to have inhibited hepatic clearance. The difference in metabolism and biodistribution between [^{123}I-Tyr[3]]-octreotide and [^{111}In-DTPA-D-Phe[1]]-octreotide was confirmed by an in vivo system in man (*7*). Thus, the modifications of peptides with different radionuclides may change their metabolism and biodistribution in vivo.

The liver and the kidney are the two major organs for metabolism and clearance but more so the liver because it is located in the center of the abdominal cavity and by itself causes a high background. In addition, metabolized radionuclides may be secreted into the intestine through the biliary tract, thereby increasing abdominal background and interfering with nuclear imaging. As the modifications of the peptides with different radionuclides seem to change their metabolism in the liver, the availability of an in vitro system to examine hepatic handling of modified reagents will help us to understand the pharmacokinetics of bioactive reagents and may be useful in predicting their behaviors in vivo. Such a system also will provide information on the uptake and intracellular processing of reagents that are difficult to study in vivo.

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In this issue of the *Journal*, De Jong et al. have compared hepatic handling of [^{125}I-Tyr^3]- and [^{111}In-DTPA-D-Phe^1]-octreotide in the recirculating rat liver (*8*). A model was developed to investigate multiple parameters of biodistribution such as clearance, examination of degradation products and secretion into the biliary tract (*9*). This perfusion model consists of only two compartments; a medium compartment and one tissue compartment (liver). Therefore, calculation of the biodistribution components is easier than that of the in vivo model. Furthermore, sampling of specimens difficult to obtain in vivo, such as bile juice, is possible in this system. They confirmed that [^{125}I-Tyr^3]-octreotide was rapidly taken up and cleared by the liver, whereas [^{111}In-DTPA-D-Phe^1]-octreotide was not. In addition, it was found that 60% of the [^{125}I-Tyr^3]-octreotide was excreted intact into the bile after 60 min.

These results are in accordance with in vivo scintigraphic findings using [^{123}I-Tyr^3]- and [^{111}In-DTPA-D-Phe^1]-octreotide (*7*). Thus, this in vitro model seems to simulate in vivo metabolism of radiopharmaceuticals in the liver and may therefore be useful in predicting their behavior in vivo. In addition, the model may also be useful for studying hepatic clearance of other bioactive peptides, since the liver is an important organ for peptide clearance.

Hepatic clearance of immunoreactive somatostatin had been previously studied (*10*) using a perfused rat liver system similar to the method described in the present study. However, this system may not be suitable for a long-term biodistribution study, since the model relies on the assumption that physiological functions of the liver are maintained during experiments. Furthermore, carrier protein(s) may be required for the uptake or cellular transport of the molecule of interest.

It is important to know that serum factors may affect biodistribution. A composition of perfusion medium may need to be optimized at each experiment. On the other hand, this animal model will be useful for identifying and the characterizing carrier proteins that are required for the uptake or cellular transport of a molecule (*9*). It is also important to know that species specificity may exist in hepatic handling of bioactive peptides. When these potential limitations are well understood, the recirculating rat liver perfusion model will probably serve as an excellent tool for the study of hepatic handling of radiopharmaceuticals.

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