Research Center for Medical Sciences
Division of Medical Engineering

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General Summary

The Medical Engineering Laboratory provides new and essential techniques for developments of medical treatment. We have developed a new concept for an acute ischemic stroke treatment. For this project we have collaborated closely with clinical departments and basic science laboratories, both in our university and hospitals and others. There is a key technology in our laboratory: polymeric micelle carrier systems. Polymeric micelle carrier systems are nano-sized drug carriers for both therapeutic drugs and diagnostic drugs. We have applied a polymeric micelle system to a magnetic resonance imaging (MRI) contrast agent for diagnosis in acute ischemic stroke. Owing to a risk of hemorrhage related to recombinant tissue plasminogen activator (rt-PA) in acute ischemic stroke, we have examined the permeability of the blood-brain barrier (BBB) to increase the safety of treatment with rt-PA. We found that the polymeric micelle MRI contrast agent exhibits an area with a hyperpermeable BBB in a rat transient middle artery occlusion model, and this polymeric micelle MRI contrast agent-based diagnostic system can improve the efficiency of rt-PA therapy. We will perform further experiments to show a relationship between the diagnosis with polymeric micelle MRI contrast agent's and the efficiency of rt-PA therapy. The polymeric micelle carrier systems have great potential for therapy when combined with the diagnosis for cancer and acute ischemic stroke.

Research Activities

Polymeric micelle drug carrier systems in ischemic stroke

Self-assembly block copolymers have been actively studied for drug targeting. Professor Yokoyama, the director of this laboratory, is an international pioneer in the development of self-assemblies of synthetic block copolymers, polymeric micelles, for anticancer drug targeting systems. We are attempting to develop the next generation of novel technology based on the polymeric micelle carrier systems.

We have shown that the polymeric micelle MRI contrast agent possesses the abilities to accumulate in target tissues where the tissues exhibit hyperpermeable vasculature and to provide high-contrast images in the tissues. We have been studying a novel concept of the polymeric micelle MRI contrast agent for the diagnosis of acute ischemic stroke. In cases of acute ischemic stroke, rt-PA is the only drug for treatment. However, rt-PA is known to increase the risk of hemorrhage. For safe use of rt-PA, a novel diagnostic concept is highly desired. In a rat model of transient middle cerebral artery occlusion (MCAO) reperfusion, it is well established that BBB exhibits hyperpermeability of macromolecules, such as serum albumin and other proteins. We focused on the hyperpermeable BBB area where macromolecules exhibit extravasation. We applied the polymeric micelle MRI

contrast agent to detect the hyperpermeable BBB area. In a 3-hour MCAO-reperfusion model, the polymeric micelle MRI contrast agent showed high-contrast foci within a part of the core of the ischemic hemisphere. The high-contrast foci did not completely overlap with the area of edema where both diffusion-weighted imaging and T_2-weighted imaging were provided. A conventional low-molecular-weight MRI contrast agent did not show such images as the polymeric micelle MRI contrast agent did. The results indicate that the polymeric micelle MRI contrast agent exhibits hyperpermeable BBB foci in ischemic hemisphere, and such foci have never been obtained clearly. Therefore, the polymeric micelle MRI contrast agent has great potential to assess a condition of acute ischemic stroke, namely the condition of hemorrhage risk after rt-PA treatment. We studied the time dependence of the permeability of BBB after MCAO-reperfusion by using the polymeric micelle MRI contrast agent and have found that BBB exhibits hyperpermeability in a time-dependent manner. Furthermore, we must optimize the MRI contrast agent system to assess the risk of BBB. We have started to synthesize new polymer-based MRI contrast agents to optimize the hyperpermeable BBB. We proved that the polymeric micelle carrier system will be useful for the diagnosis of acute ischemic stroke, and a the diagnostic and therapeutic approaches will be combined. This is our new and valuable challenge for next year.

Polymeric micelle drug carrier systems in immune system

We have been studying poly(ethylene glycol) (PEG)–related immune responses. The phenomenon exhibits a specific immune response for PEG, which is used for hydrophilic coverage of typical drug carriers. Previous reports have shown that PEG-liposomes induce a PEG-specific IgM antibody (anti-PEG IgM). We have confirmed that anti-PEG IgM is generated when PEG-poly(β-benzyl l-aspartate) (PBLA) block copolymer micelles (PEG-PBLA micelles) are intravenously injected. However, we have obtained 2 interesting results regarding the behavior of anti-PEG IgM. First, no results prove anti-PEG IgM binding to the PEG main chain, whereas the antibody is called anti-PEG IgM. To examine anti-PEG IgM binding behavior, we synthesized new PEG-triblock copolymers. We found that anti-PEG IgM exhibits bindings to PEG-coated plates where PEG chains were directly attached to the plates. However, anti-PEG IgM could not strongly bind to PEG-coated plates where PEG chains were indirectly coated. The results indicate that anti-PEG IgM exhibits specificity for a PEG chain; however, anti-PEG IgM does not strongly bind to a PEG chain itself. We found that only anti-PEG IgM can bind to a PEG chain possessing the proximity of hydrophobic blocks. Second, we have found that PEG-PBLA micelles exhibited different behaviors in the presence of anti-PEG IgM, as compared with PEGylated-liposomes' behaviors, although both nanoparticle systems possess PEG. The PEG-PBLA micelles exhibited no change in pharmacokinetics in the presence of anti-PEG IgM, whereas PEG-liposomes exhibited drastic changes in pharmacokinetics.

We attempted to solve this issue with our experiments. The maximum number of generated anti-PEG IgM antibodies was limited. In the presence of the limited number of anti-PEG IgM antibodies, we found that the number of PEG-PBLA micelles was nearly the same as the number of anti-PEG IgM antibodies. In contrast, we found that the number of

PEG-liposome particles was one tenth the number of anti-PEG IgM antibodies. Therefore, 10 anti-PEG IgM antibodies bind to each PEG-liposome particle, and anti-PEG IgM-bound PEG-liposomes exhibit a rapid blood clearance. We performed further experiments to show PEG-related immune responses. We have found that the first injection of PEG-PBLA micelle induces anti-PEG IgG and anti-PEG IgM in a dose-dependent manner. We will investigate the PEG-related antibody generation to prove PEG-related immune responses.