Research Center for Medical Sciences
Division of Medical Engineering

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General Summary

The division of Medical Engineering provides new and essential techniques for developments of medical treatment. We have developed a new concept for an acute ischemic stroke treatment by the use of polymeric micelle drug carrier systems. For this project, we have collaborated closely with clinical departments and basic science laboratories, both in our university and hospitals and others. In acute phase of ischemic stroke, recombinant human tissue-type plasminogen activator (rt-PA) is an only therapeutic drug for the thrombolysis therapy. However, there are a number of reports that rt-PA accelerates a risk of hemorrhage. For safety treatment of rt-PA therapy, a novel diagnostic concept to reduce the hemorrhage risk is highly desired. We have developed a novel approach for diagnosis of acute ischemic stroke and have assessed the risk of hemorrhage in rt-PA therapy. We have applied a polymeric micelle magnetic resonance imaging (MRI) contrast agent to assess the risk of hemorrhage. We have examined fundamental study of poly(ethylene glycol) (PEG)-related immunogenicity. PEG is the most popular polymer for pharmaceutics, cosmetics, and foods. PEGs are known to exhibit very weak immunogenicity, however, immunogenicity of PEGylated drugs has become a serious concern for PEGylated therapeutic drugs. We revealed the reason of PEG-related immunogenicity and found that PEG-related immunogenicity is controllable. We further examined fundamental study of PEG-related immunogenicity to reveal responses of T-cell independent antigens.

Research Activities

Assessment of hyper-permeable blood-brain barriers (BBBs) in ischemic stroke

In acute ischemic stroke, rt-PA is an only drug for the thrombolytic treatment. However, there are a number of reports that rt-PA accelerates a risk of hemorrhage. For safety use of rt-PA, a novel diagnostic concept is highly desired. We have developed polymeric micelle carrier systems, and the polymeric micelle carrier systems are nano-sized drug carriers which capable of carrying therapeutic drugs and diagnostic drugs. We are trying to develop the next generation of novel treatment based on the drug carrier systems. We have applied the polymeric micelle MRI contrast agent system to hyper-permeable BBB in a rat acute ischemic stroke model and had obtained high contrast images in the tissues. We started to examine molecular weight (MW)-dependent hyper-permeability in BBB. To assess the hyper-permeable BBB, we prepared two different MW of poly(glutamic acid) (P(Glu))-based MRI contrast agents. To examine BBB's MW-dependent hyper-permeability, we used a rat transient middle cerebral artery occlusion (MCAO)-reperfusion model. In a 3-hour MCAO-reperfusion model, we injected P(Glu)-based MRI contrast

agents at immediately after reperfusion. The injected dose was 0.033 mmol Gd/kg which is one third dose of the clinical dose. Firstly, we examined 30k MW P(Glu)-based MRI contrast agent. However, we obtained very faint contrast in the tissues, whereas we succeeded in the MCAO model. This was probably owing to short plasma half-life of the 30k MW P(Glu)-based MRI contrast agent, as well as a rapid clearance rate of the 30k MW P(Glu)-based MRI contrast agent from the tissues. Next, we examined 100k MW P(Glu)-based MRI contrast agent. This P(Glu)-based MRI contrast agent exhibited high contrast in the tissues in a short time period. In contrast, we found that the obtained contrast became low at 3 h after reperfusion.

One serious concern for a development of MRI contrast agent is toxicity of gadolinium ion. Free gadolinium ions released from gadolinium-chelate complexes are deposited on tissues, as a result, insoluble gadolinium precipitate caused nephrogenic systemic fibrosis (NSF). To avoid such release of free gadolinium ions, we must use a very stable gadolinium-chelate complex as a MRI contrast agent. We have been studying polymer MRI contrast agents, however, one carboxylic group of a chelate group was used for a conjugation to polymer backbone. Therefore, gadolinium-chelate complexes, which was conjugated to polymers, were not extremely stable. For preparation of the stable gadolinium-chelate complex, we started to use a novel chelate for gadolinium ions for P(Glu)-based MRI contrast agent. We are trying to evaluate stability of a P(Glu)-based novel gadolinium-chelate complex, as compared with previously prepared P(Glu)-based MRI contrast agents.

Polymeric micelle drug carrier systems in immune system

We have been studying immunogenicity of poly(ethylene glycol) (PEG). PEG has been widely used for drug carriers, as well as protein drugs. However, generation of antibodies against PEG (anti-PEG antibodies) have become serious issues in the PEGylated proteins-treated patients. Repeatedly injected PEGylated proteins induced anti-PEG antibodies, and efficacy of therapy was lost. These PEGylated protein-treated patients exhibited anti-PEG IgG and anti-PEG IgM. Furthermore, there are reports that PEG-liposomes induced specific IgM antibody against PEG (anti-PEG IgM). We confirmed that PEG-poly(β-benzyl L-aspartate) block copolymer (PEG-PBLA) induced anti-PEG IgM. Although PEG has been known to show no or very weak immunogenicity, the phenomenon exhibits a specific immune response against PEG. We revealed that PEG is an essential part to exhibit PEG-specific antibody responses, however, PEG itself does not exhibit the PEG-specific antibody response. We concluded that this was owing to PEG possessing no strong binding affinity. Very unique characteristics of PEG motivate us to examine further study of PEG-related immunogenicity, and we found fundamental insights in immune response system. We repeatedly injected PEG-PBLA, as an antigen, to induce antibody against PEG and found that PEG-PBLA induced anti-PEG IgG, as well as anti-PEG IgM. We only found anti-PEG IgG responses at very low dose PEG-PBLA as the first dose, and the anti-PEG IgG response was not observed when high dose PEG-PBLA was injected at the first dose. We performed further experiments to examine anti-PEG IgG responses. We found that switch Ig class to IgG occurred when the anti-PEG IgM response exhibited low responses, while switch Ig class did not occur when the anti-PEG

IgM response exhibited high responses. We concluded that PEG-related antibody responses are a dose dependent response, and high affinity antigens need low doses to induce antibody responses. Therefore, in general, we observe IgM responses by high affinity T-cell independent antigens, but this response does not exclude IgG responses.

Publications

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