

Development of New Strategies for Enzyme Replacement Therapy for Lysosomal Storage Disorders

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Enzyme replacement therapy (ERT) is a well-established means of treating lysosomal storage disease (LSD). However, classical IV infusion based ERT method produces less than ideal results, especially, CNS defects and quality of life in patients. To improve these main problems of parental IV formulation for LSDs, we investigate modified ERT method and evaluated the efficacy in animal model.

Keywords: MPS II, Intraventricular (ICV), Subcutaneous (SC), Enzyme replacement therapy

Introduction

Enzyme replacement therapy (ERT) is a well-established means of treating lysosomal storage disease (LSD). This method of treatment is dependent on the delivery of intravenously delivered enzyme to cell-surface receptors of the affected tissues. In the past, many LSDs have been successfully treated by this method. In many cases, however, infusion of enzyme produces less than ideal results. In some cases, rapid clearance of infused enzyme from the circulation by insulin like-growth factor II/cation-independent mannose 6-phosphate receptor (IFG-II/MPR) in the liver or spleen lead to the lack of delivery of enzyme across the blood-brain barrier (BBB)¹⁾. Some of LSDs like MPS II have neurodegenerative phenotype. Thus, IV infusion of enzyme has limitation for central nervous system (CNS) defect in MPS II. And most of recombinant enzymes for LSDs are often high volume formulations thus developed primarily as intravenous formulations. Such parenteral drugs need, however, outpatient clinic, or specialty pharmacy solely for drug therapy. Not only do these issues raise health care costs, but also decrease patient satisfaction and compliance.

In response to this challenge from parental IV formulation for LSDs, we have investigated modified ERT method and evaluated

the efficacy in animal model.

1. Intracerebroventricular (ICV) ERT

Usually, ERT by IV infusion has been successful in treating hepatosplenomegaly, cardiomegaly, and skin, etc. However the neuropathic forms of LSD are generally difficult to treat with ERT because of limited enzyme uptake across the BBB²⁾. A major challenge for the treatment of many CNS disorders is the lack of convenient and effective methods for delivering biological agents to the brain. In response to this challenge, we try to evaluate potential treatments for the neuropathic forms of LSDs. Nowadays we treat the MPS II mouse model with direct, repeated intraventricular (ICV) administrations of recombinant IDS enzyme. Then amount of total GAGs or heparan sulfate (HS) and histopathology are examined in the mouse tissues. Furthermore various behavior tests are performed during experiment to investigate the improvement of brain functions in MPS II mice. ICV ERT bypasses the BBB, allowing for direct uptake of the enzyme drug by neuronal cells. Therefore we expect this study will be strong evidence for the potential of ICV ERT as an effective treatment for neuropathic forms of LSD like MPS II.

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2. Subcutaneous (SC) administration of enzyme

Mentioned earlier, most of recombinant enzymes for LSDs were developed as IV formulations. ERT based on SC administration may significantly improve patients' quality of life (QOL). SC ERT avoids prolonged infusion, frequent visitation to clinics or hospitalization, typically required by IV administration. And SC ERT may also make it possible for patients to self-administer enzyme drug without the need for direct professional care during the administration.

Based on these unmet needs, we focus on the development of method for SC based ERT. First and second projects are MPS II and Fabry diseases. In PK study, we compared bioavailability after single administration of enzyme via subcutaneous or intravenous route in mice. Then, now we perform the efficacy study in disease mouse model. The therapeutic effect of SC based ERT will be demonstrated by reduction of GAG level in tissues or urine of MPS II mice or reduced level of Gb3 in plasma and tissues of Fabry mice. Until now, there is no successful commercial product of SC type of iduronate-2-sulfatase or alpha-galactosidase A formulation. However there are many trials of SC formulations in other researchers. It means improvement in QOL and compliance for patients is very important for drug development. Therefore, the present study provides a highly efficient, clinically

desirable and patient-friendly approach for LSDs treatment and represents a significant advancement in the field of ERT.

Conclusion

The most of recombinant enzymes for LSDs were developed as IV formulations. However the neuropathic forms of LSD are generally difficult to treat with IV based ERT because of limited enzyme uptake across the BBB. And IV ERT requires professional care and decreases QOL in patients. Based on these unmet needs, we try to develop modified methods; ICV ERT for CNS defects and SC ERT for patient-friendly treatment. The efficacy is evaluated in disease mouse model. The present study provides evidence for the potential of ICV or SC ERT as an effective treatment and represents a significant advancement in the field of ERT.

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