Modifying blood–brain barrier transport to bring hope for patients with lysosomal storage diseases

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Urayama et al. demonstrate that a variety of pharmacological agents can enhance the delivery of a lysosomal enzyme, phosphorylated β -glucuronidase (P-GUS) to brain.¹ Those results potentially have major clinical implications for the treatment of lysosomal storage diseases (LSDs).

The LSDs are a group of devastating disorders. They are mostly caused by genetic mutations in enzymes that degrade lipids, glycoproteins and mucopolysaccharides, resulting in an accumulation of material within lysosomes.² In some types of LSDs, enzyme replacement therapy (ERT) has proven beneficial.² An alternate potential approach, to inhibit production of the substrate for the mutated enzyme, is also now approved by the Federal Drug Administration for Gaucher disease type I. However, while considerable progress has been made, particular difficulties arise in the approximately two-thirds of LSDs which have neurological symptoms and progressive neurodegeneration,² as the presence of the blood–brain barrier (BBB) greatly limits the entry of plasma proteins and many other potential therapeutics.

While the BBB limits the penetration of proteins into brain, there are low levels of receptor-mediated and adsorptive transcytosis.³ In a groundbreaking work, Urayama et al. showed that the lysosomal enzyme P-GUS underwent receptor-mediated transport across the BBB in neonatal but not adult mice⁴ and that such transport could be induced in adults with epinephrine.⁵ That work suggested it might be possible to use systemic ERT to treat the neurological consequences of LSDs, a concept supported by studies by Koeberl et al. who showed that co-administration of β 2-adrenergic agonists with systemic ERT had some beneficial effects in brain and muscle in a murine model of Pompe disease.⁶

The acid test for such a combination therapy is whether it can safely deliver enough lysosomal enzymes to reverse the course of an LSD or prevent disease progression. The results in the paper by Urayama et al. in this issue¹ advance the field by indicating that multiple agents can enhance the delivery of P-GUS into brain

(and heart). Retinoic acid and insulin, as well as epinephrine, increased P-GUS uptake into brain in mice of different ages. Thus, there are multiple opportunities to enhance P-GUS transport across the BBB by mechanisms which may differ in their effectiveness in delivering lysosomal enzymes to the brain and safety.

There are issues that need to be addressed. These include maximizing enzyme delivery to the brain. Even after treatment with epinephrine, insulin or retinoic acid, the BBB permeability of P-GUS is still relatively low.¹ This suggests that high plasma levels of the lysosomal enzyme will have to be maintained for effective therapy, and one limitation of current ERT is that patients can have an immune response to the recombinant enzymes.²

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