Dapagliflozin improves Lafora disease symptoms in a zebrafish model

Research simplification

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RESEARCH SIMPLIFIED BY

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CURRENT USES OF DAPAGLIFLOZIN IN HUMAN MEDICINE

Dapagliflozin and similar drugs, known as inhibitors for sodium glucose co-transporter 2 (SGLT2), are being studied as potential treatments for Lafora Disease. These medications are already approved to treat type 2 diabetes because they lower blood sugar levels without requiring insulin. They work by blocking SGLT2 transporters, which are proteins responsible for reabsorbing sugar in the kidneys. Notably, these same transporters are also found in the brain. By blocking SGLT2 in the brain, these drugs may reduce the amount of sugar and sodium entering brain cells. This could lower glycogen storage in those cells and help calm overactive brain activity, potentially reducing seizures.

In addition to these effects, studies suggest that SGLT2 inhibitors might protect brain cells by influencing important processes in the brain, like cell signaling, inflammation, and energy production.

AIMS AND METHODS

Studies on mouse models have shown that dapagliflozin and another drug, empagliflozin, can prevent glycogen buildup in the kidneys in glycogen storage diseases such as Fanconi-Bickel Syndrome and von Gierke disease. They have also been shown to reduce kidney damage, improve symptoms related to immune cell dysfunction, and enhance autophagy, which is the body's natural process of cleaning out damaged cells.

These findings suggest that these drugs may have broad potential in managing conditions involving glycogen buildup. As a result, researchers tested the effect of SGLT2 inhibitors such as Dapagliflozin (DAPA), canagliflozin (CANA), and empagliflozin (EMPA) in a zebrafish model of laforin deficiency (epm2a−/−).

DAPA was selected for further study because, of all the SGLT2 inhibitors approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for pediatric use, it showed the most promising improvement in the abnormal behavior of the LD zebrafish. This made it a strong candidate for understanding and potentially treating LD.

RESULTS

Overall, the SGLT2 inhibitor drugs were effective in reducing or even reversing overactive brain activity and movement problems in the zebrafish model. Specifically, dapagliflozin reduced seizure-like events in zebrafish larvae lacking the EPM2A gene. Data showed that treatment with dapagliflozin slightly decreased glycogen levels in the larvae, reduced inflammation and oxidative stress, which improved cell survival. It also enhanced the function of lysosomes, which are important for cellular waste disposal.

In summary, this preclinical study demonstrated that dapagliflozin improved some of the Lafora disease symptoms in the zebrafish model of laforin deficiency. These findings suggest that dapagliflozin and other SGLT2 inhibitor drugs could potentially be repurposed as a treatment for LD.

CONCLUSION & NEXT STEPS

Although the study has shown promise in reducing and alleviating Lafora disease symptoms in the laforin deficient zebrafish model, there were limitations to this study. For one, it was not possible to differentiate whether the decrease of glycogen came from the brain or the muscles in the zebrafish models. In addition, the zebrafish model does not develop Lafora bodies (LB) in the early stages of the disease, which limits the ability to assess whether dapagliflozin can prevent or reduce LB formation. Given these limitations, further research is needed to explore the therapeutic potential of dapagliflozin and if this drug should be prescribed to LD patients. A proposed next step would be to test the effect of dapagliflozin in laforin deficient mouse models.

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