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The off-target NHE1 inhibitory effect of SGLT2 inhibitors in cardiac remodeling

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Abstract
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, approved for the treatment of diabetes mellitus, have gained attention for their cardioprotective effect. The exact mechanism by which SGLT-2 inhibitors exert their cardioprotective effect remains unclear. Recent studies have suggested that empagliflozin (EMPA), an SGLT inhibitor, exerts its cardioprotective effect by inhibiting the Na^+/H^+ exchanger (NHE); a group of membrane proteins that regulate intracellular pH and cell volume. Increased activity and expression of NHE isoform 1 (NHE1), the predominant isoform expressed in the heart, leads to cardiac hypertrophy. Our research group investigates the indirect mechanisms by which SGLT inhibitors exert their cardioprotective effect and have demonstrated that angiotensin II (ANG)-induced hypertrophy of H9c2 cardiomyoblasts is accompanied with increased SGLT-1 and NHE1 protein expression; an effect which is reversed in the presence of EMPA. In addition, we demonstrated that dapagliflozin improved survival of transgenic mice expressing cardiac-specific NHE1.

KEYWORDS
cardiac remodeling, NHE1, SGLT1/2, cardiovascular disease

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1. INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, approved for the treatment of diabetes mellitus, have gained attention for their cardioprotective effect. The exact mechanism by which SGLT-2 inhibitors exert their cardioprotective effect remains unclear. Recent studies have suggested that empagliflozin (EMPA), an SGLT inhibitor, exerts its cardioprotective effect by inhibiting the Na^+/H^+ exchanger (NHE); a group of membrane proteins that regulate intracellular pH and cell volume. Increased activity and expression of NHE isoform 1 (NHE1), the predominant isoform expressed in the heart, leads to cardiac hypertrophy.

2. METHODS

In our study, H9c2 cardiomyoblasts were treated with angiotensin II (ANG) to activate NHE1 and gen-

erate a hypertrophic model. We aimed to understand whether EMPA reverses the ANG-induced hypertrophic response, and to elucidate the molecular pathway contributing to the cardioprotective effect of EMPA. *In vivo*, transgenic mice expressing cardiac specific NHE1were administered dapagliflozin, an SGLT inhibitor, and heart function was measured by echocardiography.

3. RESULTS

Our study demonstrated that ANG-induced hypertrophy of H9c2 cardiomyoblasts is accompanied with increased SGLT-1 and NHE1 protein expression; an effect which is prevented in the presence of EMPA. In addition, we demonstrated that dapagliflozin improved the survival and ejection fraction of transgenic mice expressing cardiac-specific NHE1.

4. CONCLUSION

EMPA reduces ANG-induced hypertrophy through the inhibition of SGLT-1 and NHE1 expression, while dapagliflozin improves the survival and ejection fraction of transgenic mice expressing cardiac-specific NHE1.

CONFLICT OF INTEREST STATEMENT
The author declares no conflicts of interest.