

# Potential Efficacy and Proposed Mechanisms of Action of Empagliflozin for the Management of Experimentally-Induced Migraine Headache

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## INTRODUCTION

Migraine is a primary headache disorder that is listed as the sixth most disabling disorder globally. The particular migraine pathophysiology is not completely understood. Recently, epigenetics provided new insight into migraine pathogenesis and therapeutic response elucidation. Despite advances in therapeutic progress, migraine treatment is still unsatisfying. Triptans (e.g., zolmitriptan (ZOL)), a chief option for acute migraine treatments, have many central and cardiovascular adverse effects as well as poor membrane penetrability which may negatively influence their efficacy. Sodium-glucose co-transporter-2 inhibitors (e.g., empagliflozin (EMPA)), are a class of antihyperglycemic agents that can efficiently cross the blood-brain barrier to maintain glucose homeostasis. EMPA has myriad pharmacological actions with potential beneficial effects for migraine management.

## AIM OF THE WORK

The current study aimed at exploring potential EMPA efficacy and mechanisms for treating migraine headaches, emphasizing epigenetic mechanisms.

## METHODS

Using an animal model of migraine headache, the effect of oral/intranasal EMPA relative to ZOL on migraine headache serum pain marker; Substance-P and migraine symptoms; pain, and photophobia were assessed biochemically and behaviorally, respectively. Further, the influence on the expression of HDAC6/CGRP/CREB pathway components, Mir155-5P, 5HT1D, and c-fos in brain tissue was determined by qRT-PCR. Additionally, serum and brain serotonin levels as well as blood sugar/amylin levels were all assessed using ELISA technique.



## RESULTS

Results showed that both oral and intranasal EMPA significantly reduced migraine headaches as evidenced by the decreased serum level of substance P and pain symptoms. The intranasal route showed more powerful EMPA-induced pain reduction than the oral route. EMPA significantly increased brain serotonin levels and modulated the HDAC6/CGRP/CREB pathway, while ZOL acts by increasing brain serotonin levels and CGRP/CREB pathway without affecting the HDAC6 epigenetic pathway. Unlike intranasal EMPA, ZOL and oral EMPA demonstrated significant hypoglycemic effects

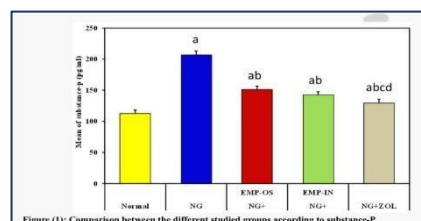


Figure (1): Comparison between the different studied groups according to substance-P

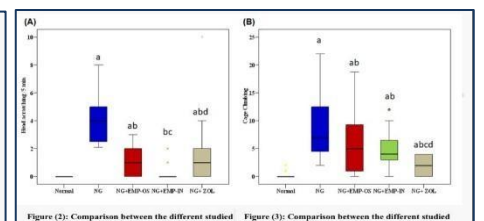


Figure (2): Comparison between the different studied groups according to head scratching

Figure (3): Comparison between the different studied groups according to cage climbing

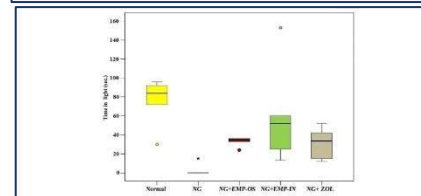


Figure (4): Comparison between the different studied groups according to time in light

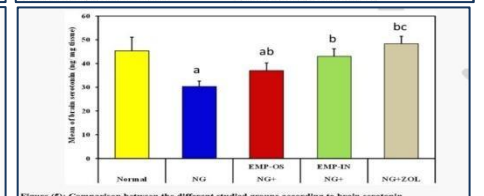


Figure (5): Comparison between the different studied groups according to brain serotonin

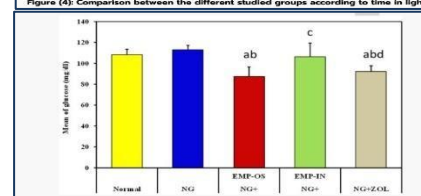


Figure (6): Comparison between the different studied groups according to serum glucose

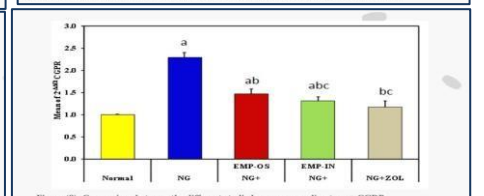


Figure (8): Comparison between the different studied groups according to 2-hCGRP

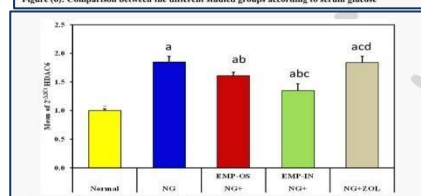


Figure (9): Comparison between the different studied groups according to HDAC6

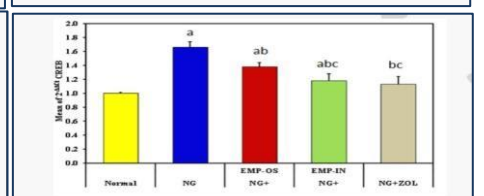


Figure (10): Comparison between the different studied groups according to CREB

a: Statistically significant difference between Normal and each other groups; b: between NG and each other groups; c: between NG+EMPA-OS and each other groups; d: between NG+EMPA-IN and NG+ZOL; Statistical significance is at  $p \leq 0.05$  (OS: orally, IN: intranasally, NG: Nitroglycerin)

## CONCLUSION

In conclusion, intranasal EMPA is a safe promising option to manage migraine headaches that can modify altered migraine epigenetics.

## REFERENCES

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