Metformin treatment affects ACTH receptor activation and downstream signaling: a potential treatment for ACTH Excess disorders and management of hyperandrogenic states

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Introduction

The peptide hormone adrenocorticotropin (ACTH or Corticotropin) is a major component of the stress response system in the Hypothalamus-Pituitary-Adrenal (HPA) axis. Under stress, it is secreted from the anterior pituitary and stimulates cortisol production from the adrenal cortex. Changes in ACTH production or action are associated with multiple disease conditions. In clinical situations like Cushing’s disease, ectopic ACTH syndrome and congenital adrenal hyperplasia, there is excess ACTH production and blocking the interaction of ACTH at its site of action would be a therapeutic option. Currently, effective therapy to block the action of ACTH is unavailable. Insulin-sensitizing treatment, such as metformin, has been used to ameliorate a few reported cases of adrenal disorders. However, the exact mechanism of how these insulin-sensitizing drugs affect the HPA axis is not known. To test whether insulin-sensitizing drugs such as metformin have a direct effect on the activity of ACTH.

Methods

In-vitro assays were performed to test the effect of metformin on ACTH receptor activation and signaling. The OS3 cells transfected with ACTH receptor (MC2R) and luciferase reporter plasmids were used, and cyclic AMP (cAMP) was measured by luciferase assay. The potential to shift the ACTH concentration-response curve (CRC) was evaluated to characterize the antagonist activity of metformin.

Results

In Fig 5: Dose response curve of metformin on MC2R transiently transfected OS3 cells in the presence of EC50 concentration of ACTH. The EC50 for metformin was 4.2 mM.

Conclusions

Metformin was found to inhibit the activation of the ACTH receptor and downstream signaling associated with ACTH response. Significant inhibition of ACTH induced receptor activation upon treatment with 10 mM metformin was observed. Metformin shifted the ACTH CRC towards the right by half log, indicating antagonism. This study could be useful in developing new strategies for management of hyperandrogenic states.


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