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Fluticasone propionate attenuate induced nitric oxide synthase through dephosphorylation of p38 and Akt

Introduction: The upregulation of the inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production have been implicated in inflammatory pathologies. Although research has revealed that non selective glucocorticoids (GCs) such as dexamethasone and hydrocortisone inhibit iNOS expression and NO production, the selective GCs , fluticasone propionate, action on iNOS expression and function remain to be investigated. In addition, investigations were performed to distinguish the GC and non-GC actions using receptor antagonists. Since the effects of GCs on upstream signalling pathways remain vague, further studies were conducted to investigate whether fluticasone regulates the p38 mitogen-activated protein kinases or protein kinase B (Akt) pathways, both of which have been reported to be critical for the induction of iNOS.

Methodology: All experiments were conducted using primary cultures of rat aortic smooth muscle cells (RASMCs). The cells were activated with bacterial LPS (100 μg/mL) and interferon-gamma (IFN-γ, 100 U/mL) to induce iNOS and NO. Nitrite levels in cellular supernatants were quantified by the Griess assay, and expressions of iNOS, phospho-p38 (P-p38) and phospho-Akt (P-Akt) were investigated by western blotting.

Results: Fluticasone (0.1 nM–3.0 μM) inhibited NO production and iNOS expression partially (~50%), and the effects were significant at 1 nM–3 μM. RU-486 (10 μM), a GC receptor (GCR) blocker, was able to reverse the inhibitions caused by fluticasone, though eplerenone (0.1–10.0 μM), the mineralocortocoid receptor blocker, had no effect. More importantly, fluticasone inhibited the phosphorylation of p38 and Akt in activated RASMCs. The inhibitions were reversed upon incubation with RU-486 (10 μM) for 1 h prior to the addition of fluticasone.

Conclusion: Fluticasone only partially inhibited iNOS expression and function. The inhibitions were reversed by RU-486, but not eplerenone, which strongly suggests a GC-mediated response to fluticasone and other receptors or pathways might be involved in regulation of iNOS expression and function. Mechanistic studies revealed that the GC can regulate key signalling pathways associated with the induction of iNOS. More specifically, fluticasone reduced the phosphorylation of p38, thereby suggesting that its actions can be mediated by suppressing these kinase pathways, which are widely reported to critically regulate iNOS expression and function.

Biography

Mahdi Alsugoor obtained a BSc (Hons) in pharmaceutical science from King Saud University in Saudi Arabia and MSc in pharmacology from University of Hertfordshire and PhD in molecular and cardiovascular Pharmacology from the University of Hertfordshire in the United Kingdom. He is currently work at Umm Al-Qura university as the Vice Dean for Development and Entrepreneurship and the head of public health department in the Health Sciences college. He worked as a visiting lecturer in the University of Hertfordshire and has served on the reviewer Board of the several international journals. His research interest and expertise is in cell signalling, focusing on induced nitric oxide synthase and stem cell differentiation. He is also interested in antimicrobial resistance and stewardship.