Vildagliptin and Linagliptin Inhibit NLRP3 Pyroptosis in Diabetic Lungs

Ahmed A. Sedika[1], Nesma Esmata[1], Wagdy K. B. Khalilb[2], Aliaa EL-mosallamya[1]*

1) *Pharmacology Department, Medical Research and Clinical Studies Institute, National Research Centre, Cairo, Egypt*

2) *Department of Cell Biology, Biotechnology Research Institute, National Research Centre, El-Buhouth*

Background

Diabetes mellitus (DM) is a multifactorial metabolic disorder characterized by hyperglycemia that induces damage across multiple organs, including the lungs. Recent evidence suggests that Nod-like receptor protein-3 (NLRP3)-mediated pyroptosis contributes significantly to diabetic complications.

Di-peptidyl peptidase-4 (DPP-4) inhibitors, such as linagliptin and vildagliptin, are established antihyperglycemic agents with additional pleiotropic effects, including anti-inflammatory and antioxidant properties. However, their potential protective effects on diabetic lung injury remain underexplored.

Aim and Objectives

This study aimed to investigate the effects of linagliptin and vildagliptin on pulmonary function, oxidative stress, and NLRP3-induced pyroptosis in streptozotocin (STZ)-induced diabetic rats. The objectives were to:

1. Evaluate the ability of both agents to restore glucose and insulin homeostasis.
2. Assess their impact on oxidative and inflammatory markers.
3. Examine histopathological and immunohistochemical changes in lung tissue.

Methods

Thirty-two male Sprague Dawley rats were acclimatized for seven days before the experimental procedures. Type 1 DM was induced by a single intraperitoneal injection of STZ (60 mg/kg).

To prevent hypoglycemia, all animals received 5% glucose solution overnight. After 72 hours, fasting blood glucose levels ≥250 mg/dL confirmed diabetes. Rats were then randomly assigned into groups and treated daily with either vildagliptin (5 mg/kg, p.o.) or linagliptin (5 mg/kg, p.o.) for 30 days. A control group received a vehicle only. Pulmonary function parameters, oxidative stress indices, inflammatory markers, histopathology, and NLRP3pyroptosis-related proteins (IL-1β, Caspase 3) were assessed.

Results

STZ-induced diabetes caused significant pulmonary dysfunction, oxidative imbalance, and upregulation of inflammatory and pyroptotic markers in lung tissue. Treatment with vildagliptin markedly improved pulmonary function and restored glucose, insulin, and redox balance compared with untreated diabetic rats. Vildagliptin also significantly suppressed IL-1β expression, attenuated NLRP3 inflammasome activation, and reduced Caspase 3 immunohistochemical expression, thereby alleviating structural lung damage. Linagliptin showed protective effects as

well, but these were less pronounced compared with vildagliptin.

Conclusions

Pyroptosis mediated by the NLRP3 inflammasome contributes to diabetic pulmonary injury in rats. Vildagliptin exerts superior protective effects compared to linagliptin by ameliorating oxidative stress, inflammation, and pyroptosis, thereby mitigating diabetes-induced lung injury. These findings highlight the therapeutic potential of vildagliptin in targeting pulmonary complications of diabetes.

Keywords

Diabetes mellitus; DPP-4 inhibitors; vildagliptin; linagliptin; NLRP3 inflammasome; pyroptosis; pulmonary dysfunction.