Pharmacological Use of NLRP3 Inflammasome Inhibitors: Novel Intervention Strategies in Diabetes-Associated Vascular Complications

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NLRP3 inflammasome has emerged as a key regulator of glucose and insulin homeostasis. Several studies have shown that activation of the NLRP3 inflammasome contributes to obesity-induced inflammation, diabetes, cardiovascular disorders and neurodegenerative disease. NLRP3 inflammasome has been recently demonstrated to play a crucial role in the progression of diabetes and its complications. Collectively, these data establish that selective inhibition of NLRP3 inflammasome is a promising target to prevent diabetes and slow down the progression of its complications.

Highlights:
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Keywords: NLRP3 inflammasome, diabetes, vascular complications.


NLRP3 inflammasome has emerged as a key regulator of glucose and insulin homeostasis. Several studies have shown that activation of the NLRP3 inflammasome contributes to obesity-induced inflammation, diabetes, cardiovascular disorders and neurodegenerative disease. NLRP3 inflammasome has been recently demonstrated to play a crucial role in the progression of diabetes and its complications. Collectively, these data establish that selective inhibition of NLRP3 inflammasome is a promising target to prevent diabetes and slow down the progression of its complications.

Diabetic cardiomyopathy was considered to be associated with oxidative stress which is regarded as one of the main incentives to initiate ventricular remodeling. Hyperglycemia, hyperlipidemia, and insulin resistance are major inducers of the chronic low-grade inflammatory state that characterizes the diabetic heart [3]. Several recent studies have emphasized that NLRP3 inflammasomes might represent the link between inflammation and metabolic disorders such as the diabetic heart. NLRP3 inflammasome promoted myocardial inflammation and cardiac dysfunction through the production of proinflammatory IL-1β. Kawaguchi et al. [5] has demonstrated that the NLRP3 inflammasome plays an important role in the development of myocardial ischaemia–reperfusion injury in ASC- and caspase-1-deficient mice. Mezzaroma et al. [6] showed that in a murine model of myocardial infarction, inhibition of NLRP3 by small-interfering RNA prevented inflammasome activation and cardiac cell death, resulting in an amelioration of myocardial remodelling. Moreover, Satoh et al. [7] has suggested that activation of NLRP3 inflammasome may contribute to chronic inflammation via maturation of IL-1β and IL-18 in the progression of coronary atherosclerosis.

According to previous study, glyburide, the type 2 diabetes drug, prevented activation of the NLRP3 inflammasome [8]. Shim et al. [9] reported that cichorium intybus linn. extract inhibits IL-1β secretion through attenuation of NLRP3 inflammasome activation, leading to an antidiabetic effect by improving glucose metabolism and inhibiting metainflammation. Kim et al. [10] reported that γ-tocotrienol inhibits the inflammasome activation, caspase-1 cleavage, and interleukin (IL) 1β secretion thereby delaying the progression of type 2 diabetes. The small molecule 16673-34-0 [11], an intermediate substrate in the glyburide synthesis free of the cyclohexylurea moiety, inhibits the formation of the NLRP3 inflammasome in cardiomyocytes and limits the infarct size following myocardial ischemia/reperfusion in the...
Diabetic nephropathy is the leading cause of end-stage renal disease in adults. The NLRP3 inflammasome-mediated inflammation is recently recognized in the development of diabetic nephropathy. A previous study reported that high glucose-induced activation of the NLRP3 inflammasome, regulates IL-1 family cytokine secretion, and causes the development of tubulointerstitial inflammation in diabetic nephropathy [14]. NLRP3 knock-out mice are protected from renal tubule damage and renal interstitial inflammation in kidney unilateral ureteral occlusion [15]. Yang et al. [16] reported that thrombomodulin domain 1 ameliorates diabetic nephropathy in mice via suppressing the NF-kB/NLRP3 inflammasome-mediated inflammatory process. Recently, Zhang et al. [17] reported that FGF-21 can significantly prevent diabetes-induced early-stage renal apoptosis, hypertrophy, and dysfunction, and significant prevented inflammation, oxidative damage and fibrotic effect.

Hyperuricemia is a common characteristic of type 2 diabetes, and contributes to the progression of inflammation in diabetic nephropathy. Kim et al. [18] reported that hyperuricemia-induced NLRP3 inflammasome activation of macrophages contributes to the progression of diabetic nephropathy. Furthermore, quercetin and allopurinol were found to suppress renal NLRP3 inflammasome activation, at least partly, via their anti-hyperuricemic and anti-dyslipidemic effects, significantly reduce renal tissue inflammation and improve renal function in kidney tissue of streptozotocin-induced diabetic rats [19].

Therefore, these data support that selective inhibition of NLRP3 inflammasome is a promising target to prevent diabetes and slow down the progression of its complications. Further investigations to clarify the precise mechanisms of NLRP3 inflammasome activation dependent on etiology would open novel therapeutic strategies for diabetes and its complications.

Declarations of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

This work was supported by grants from the Graduate student research innovation project of Hunan province CX2013B397. The authors state that they abide by the statement of ethical publishing of the Journal of Advanced Therapies and Medical Innovation Sciences Q[20].

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