Effects of antidiabetic drugs on NLRP3 inflammasome activity, with a focus on diabetic kidneys

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Inflammatory responses have a pivotal role in the development of diabetic nephropathy (DN). The nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome is a newly recognized and potent inflammatory mediator that induces inflammatory responses in several disorders, including DN. The suppression of procytokine release and inflammatory response is integral to the prevention of complications arising from the inflammatory process. In this review, we discuss the role of the NLRP3 inflammasome in the pathogenesis of DN, focusing on its effects on interleukin (IL)-1β and IL-18. Furthermore, we review the potential anti-inflammatory effects of antidiabetic drugs used in routine clinical practice, such as insulin, biguanides, Sodium-glucose co-transporter-2 (SGLT2) inhibitors, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors. In addition, we discuss whether these drugs can also modulate NLRP3 inflammasome activity in renal tissues.

Introduction

Globally, DN is the most common cause of end-stage renal disease (ESRD) leading to dialysis [1]. Together with the rising incidence of diabetes in recent decades, the incidence of DN has also increased, imposing a huge cost burden on individuals and healthcare systems [1]. DN is a debilitating disorder with a complicated pathophysiology, involving oxidative stress, inflammation, protein kinase C (PKC), the renin-angiotensin system (RAS), adenosine, transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), the JAK/STAT pathway, and a variety of adhesion molecules [2]. However, inflammation can be considered as a central facet of the disease process that is linked to several of the molecular pathways involved in DN development and progression [1].

Inflammatory responses have a pivotal role in the pathophysiology of DN [1]. In fact, a background of chronic low-grade inflammation contributes significantly to renal dysfunction because it acts as a potent upstream event for the further pathological mechanisms involved in DN [1]. The inflammatory response exerts various pathological effects, such as increasing free radical generation; inducing both oxidative and nitrosative stress; inducing insulin resistance in peripheral tissues with consequent metabolic changes; increasing the generation and/or release of prostaglandins and phospholipase A2; enhancing renin-angiotensin system activity; inducing hemodynamic variations;, increasing the permeability of vascular endothelial cells in renal tissues; disturbing the normal metabolism of lipids leading to more toxic by-products; and suppressing thrombomodulin expression [1,3]. Moreover, procytokines can effectively induce transcription factor activity and so upregulate adhesion molecules as well as other proinflammatory mediators, such as TNF-α [1]. Strong evidence

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also suggests that inhibition of inflammatory responses by therapeutic strategies can effectively prevent DN development and improve renal function in patients with diabetes [4].

Inflammasomes are a class of cytosolic complexes of proteins, first identified by Martinon and coworkers in 2002. They have an important role in innate immune responses against invading pathogens, and recent evidence suggests that inflammasomes are able to promote the expression, maturation, and release of a multitude of inflammatory cytokines, triggering a cascade of inflammatory responses that are well documented in pathophysiological conditions, such as chronic hyperglycemia [5].

An inflammasome generally has a cytosolic nucleotide-binding oligomerization domain-like receptor (NLR) that recognizes diverse pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to create an activated inflammatory complex, which includes adaptor protein apoptosis-associated speck-like protein containing CARD (ASC; an adapter protein) and a procaspase [5]. Several isoforms of the nod-like receptor family (NLRs) have been identified: NLRP1, NLRP2, NLRP3, NLRC4, NLRP6, NLRP7, and NLRP12. Among these, the NLRP3 isoform appears to be largely responsible for promoting inflammatory responses [5].

The assemblage of the NLRP3 inflammasome complex creates a potent inflammatory multiprotein that can upregulate several inflammatory cytokines, such as IL-1 and IL-18 [6]. Moreover, it can induce pyroptosis, a form of cellular death distinct from apoptosis, and so enhance inflammation-dependent tissue damage [6]. NLRP3 inflammasome activation is directly related to an excessive inflammatory response and, therefore, is directly linked to the pathophysiology of chronic inflammatory disorders, such as diabetes and its complications [6].

In this review, we discuss the role of the NLRP3 inflammasome in DN pathogenesis, focusing on its effects on IL-1β and IL-18. Furthermore, we review the potential anti-inflammatory properties of both oral and injectable antidiabetic drugs and comment on data relating to the impact of antidiabetic drugs on NLRP3 inflammasome activity in renal tissues.

The NLRP3 inflammasome and diabetic nephropathy

DN is an inflammatory disorder involving excessive activation of inflammatory mediators [2]. Different cell types, such as renal, epithelial, endothelial, and mesangial cells, and podocytes, are negatively affected by inflammation [7]. Recent evidence supports the relationship between DN and NLRP3 inflammasome activation [7]. In this context, NLRP3 inflammasome expression has been demonstrated in a variety of renal cell types, such as podocytes, and intercalated and mesangial cells [7].

Shahzad *et al.* described NLRP3 inflammasome activation in glomerular endothelial cells and podocytes of diabetic mice, whereas NLRP3-deficient mice were protected against DN [7]. Kim and colleagues found that uric acid-induced NLRP3 inflammasome activation increased chemokine signaling in the proximal tubules of renal cells, thereby promoting DN progression [8], while Wang and coworkers demonstrated that inhibition of inflammasome activity by IL-22 effectively alleviates renal injuries via the NLRP3/caspase-1/IL-1β-dependent pathway, improving renal function of patients with diabetes [9]. Moreover, Yi *et al.* reported that suppression of the nuclear factor (NF)-κB/NLRP3 inflammasome signaling pathway by long intergenic noncoding RNA (lincRNA) of Gm4419 inhibited inflammatory responses in renal tissues and prevented DN [10]. Further evidence was provided by Wang and coworkers, who showed that NLRP3 inflammasome downregulation by pioglitazone had potent renoprotective effects and ameliorated renal damage in patients with diabetes [11].

The NLRP3 inflammasome converts the procytokines of IL-1β and IL-18 to their active forms, inducing a downstream inflammatory response in renal cells [12]. In this context, ASC-knockout mice are protected against proteinuria and DN development [12]. The exact mechanism of NLRP3-ASC assembly in renal cells has not yet been elucidated, but renal cells were shown to have all the necessary cellular components to accomplish this assembly [12]. In support of this, renal tubular cells are known to secrete IL-1β and IL-18 in response to metabolic stressors [1].

The role of IL-1β and IL-18 in the pathogenesis of inflammation in renal cells

IL-1β and IL-18 secreted from inflammasomes have essential roles in the pathogenesis of inflammatory responses in renal cells involved in the onset of DN [1]. IL-1β itself induces other inflammatory mediators, such as IL-6, TNF-α, prostaglandins, interferon γ (IFN-γ), TGF-β, and nitric oxide (NO), and increases the consequent inflammatory responses [3]. Hasegawa *et al.* showed that IL-1 is associated with inflammation-induced DN [13]. IL-1β activates inflammatory responses in all lines of renal cells [1], and Sassy-Prigent *et al.* demonstrated that IL-1β was upregulated in renal tissues in animal models of DN, which suggests a role of this cytokine in the inflammatory responses of diabetic kidneys [14]. IL-1β is also implicated in hemodynamic abnormalities in glomeruli because it induces prostaglandins and phospholipase A2 secretion [15]. Moreover, IL-1β recruits circulating monocytes and macrophages, further enhancing local inflammation in kidney tissues [1].

IL-18 is also a potent cytokine that triggers a cascade of inflammatory responses in renal cells [4]. Fujita *et al.* showed that IL-18 closely correlated with renal injuries in patients with type 2 diabetes mellitus (T2DM) [16]. Yaribeygi *et al.* reported that inhibition of IL-18 expression by crocin attenuated renal injuries and improved renal function in the diabetic milieu [3]. Moriwaki and coworkers demonstrated that elevated levels of IL-18 were positively correlated with renal dysfunction during hyperglycemia [17]. Infiltrating monocytes, macrophages, and T cells, along with renal proximal tubular cells, are potential sources of IL-18 [4]. Furthermore, IL-18 induces the release of other inflammatory mediators, such as IL-1, IL-6, and TNF-α, the expression of adhesion molecules [e.g., intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion protein-1 (VCAM-1)] as well as endothelial cell apoptosis in renal tissues [1]. Therefore, it is likely that IL-18 is a key biomarker in DN development, with its serum and urinary levels closely related to DN progression [3]. A summary of the role of the NLRP3 inflammasome on the pathogenesis of DN is provide in Fig. 1.

The role of antidiabetic drugs on the NLRP3 inflammasome: possible effects in the kidneys

Antidiabetic drugs are used primarily to achieve glycemic control, but can have additional beneficial effects on NLRP3 inflammasome expression and/or activity, as discussed below.

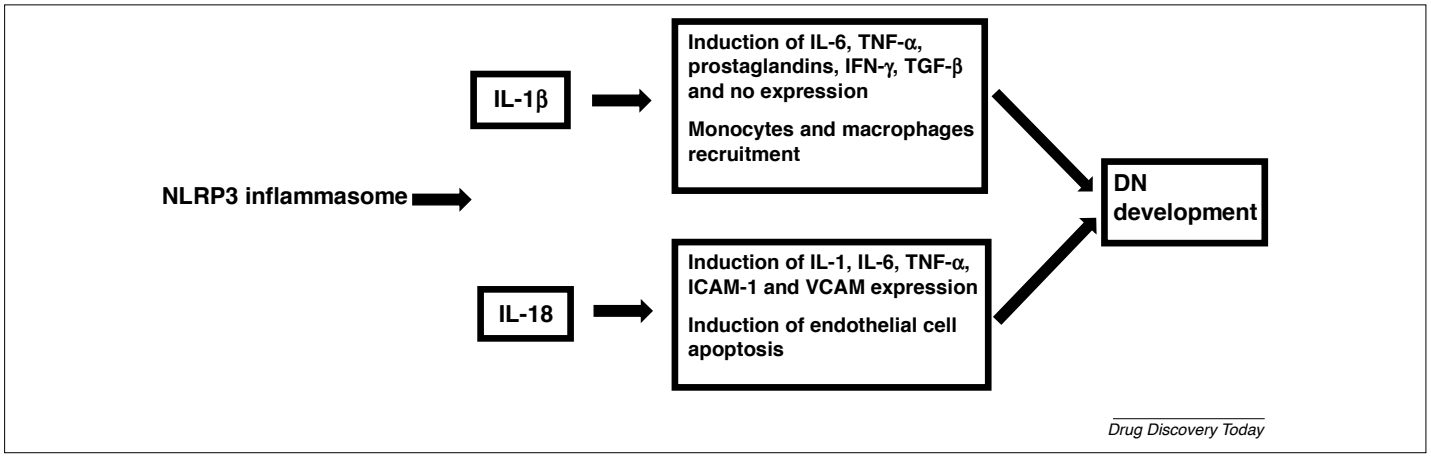

FIGURE 1

The role of the nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome in the pathogenesis of diabetic nephropathy (DN). Abbreviations: ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL, interleukin; NO, nitric oxide; TGF-β, tumor growth factor-β; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion protein-1.

Insulin

Insulin is the primary metabolic hormone produced by pancreatic β cells; its deficiency, either relative or absolute, leads to the development of T2DM or type 1 diabetes mellitus (T1DM), respectively. Insulin is also the required treatment for T1DM and is often used in T2DM when first-line oral therapies fail to adequately maintain blood glucose at target levels [18]. Insulin facilitates glucose uptake into the liver, fat, and skeletal muscle cells, thus lowering plasma glucose levels [18].

Apart from its role in maintaining glucose homeostasis, insulin might also exert anti-inflammatory properties [19]. Insulin can affect the inflammatory responses by at least four molecular mechanisms as described below.

Normoglycemia

Glucose is a potent inducer of the inflammatory response *per se* because recruitment and expression of inflammatory mediators is activated in the presence of hyperglycemia [19]. For example, Brix-Christensen *et al*. reported that insulin suppressed IL-6 and TNF-α expression by reducing blood glucose levels [20]. Therefore, insulin-induced normalization of hyperglycemia shows the potent anti-inflammatory effects of insulin by reducing blood glucose levels [20].

Insulin-dependent NO release

Early observations indicated that insulin might exert effects on inflammatory mediators, as documented by Steinberg *et al*. [21]. These authors reported that insulin suppressed inflammatory responses indirectly via stimulating NO release, thus promoting further anti-inflammatory effects induced by NO [21]. In an *in vitro* model of ischemia-reperfusion (I/R), Li and colleagues found that insulin prevented TNF-α expression and suppressed related downstream inflammatory responses through the protein kinase B (Akt)-endothelial NO synthase (eNOS)-NO-dependent signaling pathway [22]. Insulin is a potent inducer of NO release, which is an inhibitor of leukocyte recruitment, leucocyte and platelet adhesion to endothelial cells, and ICAM-1, P-selectin, and TNF-α expression, these being the main anti-inflammatory effects of insulin therapy [22].

NF-κB suppression

Further evidence concerning the anti-inflammatory effects of insulin were provided by Aljada *et al.*, who reported that insulin suppressed NF-κB and subsequently monocyte chemoattractant protein 1 (MCP-1) expression in the endothelial cells of human aorta [23]. NF-κB is the main transcription factor involved in the procytokine expression of, for example, ICAM-1, TNF-α, IL-1, IL-6 and IL-18; therefore, suppressing NF-κB is an important mechanism whereby insulin modulates inflammatory responses [23].

Suppression of Toll-like receptors

Toll-like receptors (TLRs) are a group of receptors involved in the innate immune response and tissue inflammation; thus, their suppression provides an opportunity to modulate inflammatory responses [24]. Some evidence has shown that insulin suppresses TLR expression at the level of transcription and so diminishes the inflammatory response [25]. Thus, inhibition of TLRs is another molecular mechanism by which insulin suppresses the inflammatory response.

However, no data exist in relation to the effects of insulin on NLRP3 inflammasome activity. Further research is needed to elucidate the presence of such effects.

SGLT-2 inhibitors

SGLT-2 inhibitors (SGLT-2i) are a newly introduced class of antidiabetic drugs that increase renal glucose excretion by inhibiting glucose reabsorption in the S_2 and S_3 segments of the renal proximal tubules, thus reducing plasma glucose levels in an insulin-independent manner [26]. SGLT-2i might also exert anti-inflammatory properties [26].

Tahara *et al*. reported that ipragliflozin administration in diabetic animals suppressed IL-6, TNF-α, MCP-1, and C-reactive protein (CRP) expression [26], while Chen and coworkers showed that a selective SGLT-2i (BI-38335) decreased inflammatory markers and suppressed the TLR pathway in pancreatic islets [27]. Recently, Xu and coworkers suggested that empagliflozin can attenuate obesity-induced inflammatory responses by inhibiting macrophage activity and reducing TNF-α expression [28].

Recent observations suggested that SGLT-2i modulates NLRP3 inflammasome expression and activity, thus beneficially affecting renal activity in mice with T2DM [29]. Birnbaum *et al.* reported that dapagliflozin attenuated inflammation-induced DN by suppressing NLRP3 inflammasome activity and decreasing the mRNA levels of ASC, IL-6, IL-1β, TNF-α, and caspase-1, independent of its glucose-reducing activity [29]. Ye *et al.* also found that dapagliflozin prevented the development of diabetic cardiomyopathy by attenuation of NLRP3 and/or ASC inflammasome activity, independently of glucose lowering [30]. Similarly, Benetti *et al.* showed that empagliflozin markedly decreased NLRP3 inflammasome activity and attenuated the downstream inflammatory responses in diabetic kidneys [31]. Although more research is needed, SGLT-2i appear to exert anti-inflammatory effects via the suppression of NLRP3 inflammasome activity, thus beneficially affecting diabetic kidneys.

SGLT-2i have been reported to exert several cardiovascular and renal benefits in terms of improving not only glucose, but also weight, blood pressure, uric acid, arterial stiffness, albuminuria, lipids, sympathetic nerve activity, myocardial oxygen consumption, and cardiac workload [32].

SGLT-2i might be an attractive therapeutic option for DN based on their renoprotective properties via attenuation of inflammation, glomerular hyperfiltration, and oxidative stress [32]. The above-mentioned protective cardiorenal effects of SGLT-2i might account for the significant reductions in cardiovascular and renal morbidity, hospitalization for heart failure, and cardiovascular mortality observed in the randomized controlled cardiovascular outcome trials with these hypoglycemic agents [i.e. the Canagliflozin cardiovascular Assessment Study (CANVAS)] [33]. Only empagliflozin was shown to significantly decrease all-cause death [34], whereas canagliflozin significantly increased the risk of bone fractures and doubled the risk for amputations, especially in patients with peripheral artery disease or pre-existing amputation [33]. Whether the effects of different SGLT-2i on inflammation affected these results, both in terms of efficacy and safety, remains to be established.

Biguanides

Biguanides are chemical compounds derived from guanidine (guanylguanidine), a naturally occurring substance found in some vegetables, that pharmacologically constitute a class of oral drugs with glucose-lowering effects [35]. Several forms of biguanide have been used for decades in the treatment of T2DM, but because of adverse effects, only metformin is currently in use [35]. Metformin is the first-line recommended antidiabetic drug that reduces glucose via several intracellular pathways: suppression of hepatic glycogenesis; increase in glucose consumption because of enhanced peripheral insulin sensitivity; improvement of insulin signaling via AMP-activated protein kinase (AMPK) activation; and induction of glucose transporter type 4 (GLUT-4) localization [35].

There are also data showing that metformin exerts anti-inflammatory effects [36]. For example, Bulcão and coworkers found that metformin reduced IL-6 and CRP levels in patients with impaired glucose tolerance [36]. Furthermore, Woo *et al.* reported that metformin attenuated the inflammatory responses in cultured hepatocytes via AMPK pathway activation [37]. In this context, the impact of metformin on inflammasome activity has also been investigated. Lee and coworkers found that metformin treatment markedly reduced NLRP3 inflammasome expression in patients with T2DM [38]. Similarly, Li and colleagues reported that metformin inhibited the NLRP3 inflammasome expression by suppressing oxidative stress via upregulation of Drp1 phosphorylation in an AMPK-dependent pathway [39].

Little direct evidence is available regarding the effect of metformin on the NLRP3 inflammasome activity in the kidneys. Although Lee and coworkers demonstrated that metformin attenuated NLRP inflammasome activity in renal tissues of patients with T2DM [38], further research is needed in this field.

Thiazolidinediones

Thiazolidinediones (TZDs) are a class of chemical compounds that are selective ligands for peroxisome proliferator-activated receptors (PPARs), thus enhancing the expression of several proteins involved in glucose homeostasis [40]. TZDs exert their antidiabetic effects by the reduction in insulin resistance and increase in glucose uptake in peripheral tissues [40]. Both pioglitazone and rosiglitazone have been reported to have anti-inflammatory properties [40]. Furthermore, newly introduced TZDs, such as LPSF/GQ-2 and 2,4-thiazolidinedione, have also demonstrated anti-inflammatory effects in different *in vivo* and *in vitro* models [40]. Also, Ohga *et al.* reported that pioglitazone attenuated inflammation by inhibition of NF-κB and ICAM-1 expression in cultured renal glomerular endothelial cells, thus preventing DN development [41].

A few studies recently suggested that TZDs inhibit NLRP3 inflammasome activity as well as other inflammatory mediators [11]. Wang and colleagues reported that pioglitazone ameliorated inflammasome-dependent renal damage in diabetic animals [11]. Similarly, Zhang and coworkers showed that pioglitazone suppressed NLRP3 inflammasome activity in an I/R animal model [42]. However, further studies are necessary to establish the possible role of TZDs in NLRP3 inflammasome activity.

Sulfonylureas

Sulfonylureas are widely used antidiabetic drugs that induce insulin secretion from pancreatic β cells by targeting ATP-sensitive K+ (K_{ATP}) channels, depolarizing the cells and, thus, opening the voltage-gated Ca^{2+} channels, which markedly stimulates proinsulin release [43]. K_{ATP} channels are upregulated in monocytes and macrophages, a process with a significant role in the onset of inflammatory responses via the MAPKs/NF-κB pathways [43]. Therefore, blocking K_{ATP} channels with sulfonylureas can suppress the inflammatory responses [43].

There is evidence suggesting that sulfonylureas inhibit procytokine release and inflammatory responses [44]. In this context, David *et al.* demonstrated that two types of sulfonylurea, CP-424,174 and CP-412,245, both inhibited IL-1β formation in human monocytes [44]. Ling *et al.* reported that glibenclamide reduced inflammation in arterial plaques by closing K_{ATP} channels [45]. Moreover, it was shown that glibenclamide reduced IL-1β production in polymorphonuclear neutrophils (PMNs) of patients with T2DM [46].

In recent studies, sulfonylureas were reported to inhibit the activity of inflammasome [6]. The initial evidence was provided by

Lamkanfi *et al.*, who reported that glyburide suppressed the NLRP3 inflammasome and inhibited macrophage-dependent IL-1β release [47]. Coll and coworkers suggested that MCC950 (a newly identified sulfonylurea) selectively inhibited NLRP3 inflammasome activity, thereby preventing inflammatory responses [6]. Moreover, Robertson *et al.* showed that many isoforms of sulfonylureas were capable of inhibiting NLRP3 inflammasome activity and suppressing related inflammatory pathways [48].

In the presence of DN, we lack sufficient evidence to support the suppression of inflammation by sulfonylureas. However, taken into consideration that these drugs showed significant anti-inflammatory effects in other tissues, it is probable that they might exert the same effects in the kidneys, thereby preventing the development and progression of DN. Nevertheless, more studies are needed in this field.

DPP-4 inhibitors

Inhibitors of DPP-4 are a class of antidiabetic drugs that exert hypoglycemic effects by inhibition of DPP-4 and glucagon release, leading to enhanced insulin secretion and increased circulating insulin levels [49]. DPP-4 inhibitors also prevent the inactivation of glucagon-like peptide 1 (GLP-1), thus increasing the levels of active GLP-1, which itself enhances insulin secretion and suppresses glucagon release [49]. Sitagliptin, alogliptin, linagliptin, saxagliptin, and vildagliptin are DDP-4 inhibitors that can be used alone or in combination with other antidiabetic drugs [49].

In addition to hypoglycemic effects, some evidence suggests anti-inflammatory properties for these drugs [55]. In this context, Shirakawa and colleagues reported that DPP-4 inhibition by des-fluoro-sitagliptin protected against diet-induced inflammation via the downregulation of sterol regulatory element-binding protein-1c, fatty acid synthase, and stearoyl-CoA desaturase-1, as well as upregulation of PPAR-α in the liver [50]. Satoh-Asahara *et al.* found that sitagliptin decreased inflammatory mediators, such as serum amyloid A-LDL (SAA-LDL), CRP, and TNF-α in T2DM [51]. Linagliptin was also reported to significantly decrease IL-6 levels in patients with T2DM undergoing hemodialysis [2].

More recently, studies demonstrated that inhibition of DPP-4 might also affect NLRP3 inflammasome expression and/or activity [52]. Dai *et al.* showed that DPP-4 inhibition by either sitagliptin or NVPDPP728 attenuated NLRP3 and IL-1β expression through PKC inhibition in macrophages [52]. Similarly, Ye *et al.* reported that saxagliptin reduced the NLRP3 and/or ASC inflammasome, as well as IL-1β, IL-6, caspase-1, and TNF-α expression, in the myocardium of diabetic animals [30].

DPP-4 inhibitors were also shown to exert protective effects against DN [29]. Birnbaum and coworkers found that saxagliptin reduced renal injury and prevented DN progression through NLRP3 suppression in diabetic mice [53]. Similar results were reported by the same authors with a dapagliflozin-saxagliptin combination [29]. However, more clinical trials are needed to establish the protective effects of DPP-4 inhibitors in DN.

GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1 RAs) are a class of injectable hypoglycemic drugs that increase circulating GLP-1 levels [49]. GLP-1 is a hormone belonging to the incretin class, and is mainly released from intestinal L cells in response to feeding [49]. These agents exert antidiabetic effects by mimicking the incretin hormone function, thereby increasing postprandial insulin secretion, inhibiting glucagon release, and slowing stomach emptying after feeding, thus delaying glucose absorption into the blood stream [49].

TABLE 1

Effects of different antidiabetic drugs on the NLRP3 inflammasome

Antidiabetic agents	Effects on inflammatory responses/ Cytokines	Effects on NLRP3 inflammasome	Effects on Renal Tissues in relation to NLRP3 inflammasome	Refs
Insulin	Improvements in inflammation either directly (via suppressing inflammatory mediators) or indirectly (by normalizing hyperglycemia)	No verified effects	No verified effects	[22,61]
SGLT2i	Suppression of IL-6, TNF-α, MCP-1, CRP, and TLR expression and/or release	Suppression of NLRP3 activity and ASC expression	Decreases in NLRP3 inflammasome activity	[26–31]
Biguanides	Reduction in IL-6 and CRP levels, attenuation of inflammatory responses by AMPK activation pathway	Attenuation of NLRP3 inflammasome by AMPK pathway and suppression of oxidative stress	Attenuation of NLRP3 inflammasome	[36,37,39,62]
TZDs	Inhibition of inflammation by suppression of NF-κB, CRP, PAI-1, TNF-α, and ICAM-1 expression	Reduction in NLRP3 inflammasome activity, amelioration of NLRP3-dependent renal damage	Amelioration of NLRP3-dependent renal damages	[11,42,63]
Sulfonylureas	Inhibition of IL-1β formation and improvement in inflammation in arterial plaques by closing K_{ATP} channels	Suppression of NLRP3 inflammasome and inhibition of related inflammatory responses	No verified effects	[6,44,45,47]
DPP-4 inhibitors	Suppression of inflammatory mediators	Attenuation of NLRP3 inflammasome	Prevention of inflammatory-dependent renal injuries	[29,51–53]
GLP-1 receptor agonists	Amelioration of inflammatory cytokines expression	Inhibition of NLRP3 inflammasome expression	No verified effects	[52,55,56]

GLP-1 RAs, including liraglutide and exenatide, were shown to decrease serum CRP levels in a recent meta-analysis [54]. GLP-1 RAs might also exert anti-inflammatory effects in different tissues, including the kidneys; for example, they ameliorated inflammatory markers, such as TNF-α, IL-6, plasminogen activator inhibitor-1 (PAI-1), cyclooxygenase-2 (COX-2), and VCAM-1, in different tissues of diabetic animal models [55]. Furthermore, GLP-1 receptor stimulation was shown to attenuate NLRP3 inflammasome expression and activity [52]. Dai *et al.* confirmed that GLP-1 stimulation suppressed NLRP3 inflammasome and IL-1β in human macrophages [52]. Similarly, Peebles and coworkers demonstrated that GLP-1 signaling attenuated the NLRP3 inflammasome as well as IL-13 and IL-33 levels in the respiratory tract [56]. Liraglutide, a GLP-1 RA, was reported to decrease NLRP3 expression in cardiomyoblasts [57].

Although there is evidence for the potential anti-inflammatory effects of GLP-1 RAs against renal injuries in the diabetic milieu [55], no study has yet been performed to test the same effects on the NLRP3 inflammasome in diabetic kidneys. Of note, GLP-1 receptors are widely expressed in glomerular capillaries, glomeruli, and proximal convoluted tubules [58]. Given that GLP-1 RAs might exert anti-inflammatory effects in renal tissues as well as decreasing NLRP3 inflammasome activity in other tissues, it follows that these drugs might also affect NLRP3 inflammasome activity in the kidney (and, thus, DN progression), although this needs to be verified in future studies.

Other antidiabetic drugs

Other drugs showing antidiabetic effects include Lyn kinase activators and α-glucosidase inhibitors, which might also have anti-inflammatory properties [59,60]. Further studies are required to evaluate their possible effects on NLRP3 inflammasome activity (Table 1).

Concluding remarks

NLRP3 inflammasome activity has an important role in inflammatory responses, involving IL-1β and IL-18, in DN development. This inflammatory mediator can trigger a cascade of inflammatory responses, thus worsening renal dysfunction. Here, we presented data on the potential anti-inflammatory properties of both oral and injectable antidiabetic drugs. Some antidiabetic drugs also have potent anti-inflammatory capabilities and can modulate NLRP3 inflammasome activity, preventing the development of DN.

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