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Review

Targeting inflammation: New therapeutic approaches in chronic kidney disease (CKD)

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N-acetyl-L-cysteine (NAC) (PubChem CID: 12035)
Trolox (PubChem CID: 40634)
AST-120 (activated charcoal) (PubChem CID: 297)
CDDO-imidazolide (PubChem CID: 9958995)
RTA 405 (Bardoxolone methyl analogue) (PubChem CID: 400769)
Dihydro-CDDO-trifluoroethyl amide (dh404) (Bardoxolone methyl analogue) (PubChem CID: 400769)
Fenofibrate (PubChem CID: 3339)
WY 14643 (PubChem CID: 5694)
Ciprofibrate (PubChem CID: 2763)
Rosiglitazone (PubChem CID: 77999)
Pioglitazone (PIO) (PubChem CID: 4829)

ABSTRACT

Chronic inflammation and oxidative stress, features that are closely associated with nuclear factor (NF-κB) activation, play a key role in the development and progression of chronic kidney disease (CKD). Several animal models and clinical trials have clearly demonstrated the effectiveness of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy to improve glomerular/tubulointerstitial damage, reduce proteinuria, and decrease CKD progression, but CKD treatment still represents a clinical challenge. Bardoxolone methyl, a first-in-class oral Nrf-2 (nuclear factor erythroid 2-related factor 2) agonist that until recently showed considerable potential for the management of a range of chronic diseases, had been shown to improve kidney function in patients with advanced diabetic nephropathy (DN) with few adverse events in a phase 2 trial, but a large phase 3 study in patients with diabetes and CKD was halted due to emerging toxicity and death in a number of patients. Instead, palmitoylethanolamide (PEA) a member of the fatty acid ethanolamine family, is a novel non-steroidal, kidney friendly anti-inflammatory and anti-fibrotic agent with a well-documented safety profile, that may represent a potential candidate in treating CKD probably by a combination of pharmacological properties, including some activity at the peroxisome proliferator activated receptor alpha (PPAR-α). The aim of this review is to discuss new therapeutic approaches for the treatment of CKD, with particular reference to the outcome of two therapies, bardoxolone methyl and PEA, to improve our understanding of which pharmacological properties are responsible for the anti-inflammatory effects necessary for the effective treatment of renal disease.

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DN, diabetic nephropathy; ESRD, end stage renal disease; PEA, palmitoylethanolamide; PPARα, proliferator activated receptor alpha; TNF-α, tumor necrosis factor-α; RAAS, renin-angiotensin- aldosterone system; GFR, glomerular filtration rate; AngII, angiotensin II; NF-κB, nuclear factor; TGF-β, transforming growth factor-β; MCP-1, monocyte chemotactic protein-1; iNOS, inducible nitric oxide synthase; Nrf2-Keap1, nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1; MC, mast cell.

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Contents

1. Introduction

Oxidative stress is at the heart of the complex pathogenesis of both acute and chronic kidney diseases [1,2]. Acute kidney injury (AKI) affects millions of people and has been associated with increased mortality and hospital length of stay as well as putting the patient at risk for future chronic kidney disease (CKD) [3]. Oxidative stress is known to play an important role in the development of renal diseases such as glomerulonephritis, drug-induced nephrotoxicity, and CKD [4]. CKD is associated with mitochondrial dysfunction that leads to an imbalance between reactive oxygen species (ROS) and the natural anti-oxidants that normally quench these pathological free radicals. Treatment of CKD can slow its progression but the therapies remain limited. Blood pressure control using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) has the greatest weight of evidence, but still are often inactive. Thus, the need for new approaches to manage the exponentially increasing number of patients with CKD is urgent. One such approach that has been considered is to augment the natural cytoprotective responses of the body using small molecule activators such as bardoxolone methyl. The synthetic triterpenoid bardoxolone methyl (CDDO-methyl ester) and its analogs are the most potent inducers of the Nrf2/Keap1 pathway [5,6]. The structure and activity profile of bardoxolone methyl resembles those of the cyclopentenone prostaglandins, the endogenous activators of Nrf2, which favor the resolution of inflammation [7]. Similarly to cyclopentenone prostaglandins, bardoxolone methyl has anti-inflammatory activity by inhibiting the IKKβ/NF-κB signaling pathway [8]. Moreover, because the clinical development of bardoxolone methyl was halted due to unforeseen toxicity in phase 3, there is a need to determine if this toxicity is related to the mechanism of its beneficial effect in CKD or to an off-target effect. On the other hand, mast cell infiltration and activation have been well documented in several experimental models of inflammation and are gaining increasing interest as key factors in the onset and progression of renal disease [9]. Palmitoylethanolamide (PEA) is an endogenous fatty acid amide belonging to the family of the N-acylethanolamines. Recently, several studies have demonstrated that PEA is an important analgesic, anti-inflammatory, and neuroprotective mediator, acting at several molecular targets in both central and sensory nervous systems as well as immune cells (i.e. mast cells) [9]. A recent study also demonstrated that ultramicronized PEA attenuated the renal dysfunction and injury associated with ischemia reperfusion (IR) of the mouse kidney [9]. Another study in a compression model of spinal cord injury [10] showed that ultramicronized PEA treatment effectively reduces mast cell infiltration and activation, which occurs not only in inflammation, but also in inflammatory hyperalgesia and neuropathic hyperalgesia. Thus, because of its important pharmacological properties and a good safety profile, PEA could represent an alternative approach to delay renal disease progression. In this review, we discuss the possible therapeutic approaches in renal diseases and in particular the effects of bardoxolone methyl and PEA in the pathophysiology of CKD (Fig. 1).

2. Chronic kidney disease

2.1. Inflammation as a cause of CKD progression

CKD is characterized by a progressive loss of renal function, chronic inflammation, oxidative stress, vascular remodeling, and glomerular and tubulointerstitial scarring. Diabetic nephropathy (DN) is the leading cause of CKD and end-stage renal disease (ESRD) [11]. The incidence of CKD is increasing in both developed and developing nations. Increased circulating levels of inflammatory markers, such as C-reactive protein (CRP) and the pro-inflammatory cytokines interleukin (IL)-6, and tumor necrosis factor-α (TNF-α), have been described in CKD patients [12]. The prevalence of inflammation varies from 30 to 75% depending on multiple factors, such as residual renal function, geographic and genetic differences and dialysis therapy [12]. Moreover, dialytic therapy or kidney transplantation may even induce neurological complications. Dialysis can directly or indirectly be associated with dialysis dementia, disequilibrium syndrome, aggravation of atherosclerosis, cerebrovascular accidents due to ultrafiltration-related arterial hypotension, hypertensive encephalopathy, Wernicke's encephalopathy, hemorrhagic stroke, subdural hematoma, osmotic myelinolysis, opportunistic infections, intracranial hypertension and mononeuropathy [13]. Among these factors, oxidative stress has attracted a great deal of interest from researchers. Oxidative stress appears to increase in the serum of CKD patients because of increased oxidant activity as well as a reduced anti-oxidant defense system, which is accompanied by kidney dysfunction and/or severe cardiorenal syndrome [14].