Editorial

Kidney Res Clin Pract 36:109-110, 2017
pISSN: 2211-9132 • eISSN: 2211-9140
https://doi.org/10.23876/j.krcp.2017.36.2.109

KIDNEY RESEARCH AND CLINICAL PRACTICE

Anti-inflammatory and anti-apoptotic effects of paricalcitol in lipopolysaccharide-induced renal proximal tubular cell injury

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Vitamin D has long been regarded as an important regulator of calcium and bone metabolism. The classical actions of vitamin D are related to mineral metabolism and skeletal health. Recently, the nonclassical actions of vitamin D have also been shown to play an important role in the regulation of cellular proliferation, differentiation and inflammation [1]. In clinical practice, hypercalcemia is a common side effect of vitamin D administration. Paricalcitol (19-nor-1,25-hydroxy-vitamin D2), an active and nonhypercalcemic synthetic vitamin D analog, shows similiar biological activity as calcitriol, another commonly used synthetic vitamin D analog, but with fewer side effects [2]. Several recent studies have demonstrated the renoprotective effects of paricalcitol in various experimentally induced models of kidney diseases [3,4]. However, its underlying molecular mechanisms remain undetermined. Moreover, although we do know that vitamin D regulates gene expression associated with inflammation, apoptosis and fibrosis, via its specific control on the activation of vitamin D receptor, the action of paricalcitol on this pathway also remains unclear [5].

Sepsis is a severe derangement of the inflammatory response to infection and one of the major causes of acute kidney injury (AKI). Although recent advances in the understanding of the pathophysiology of septic AKI have been achieved, effective treatment options are still limited. Despite extensive research and progress in several other fields, the incidence rate and associated mortality rate of AKI remain unacceptably high. The pathophysiology of septic AKI is complex and multi-factorial in nature, including changes in intra-renal hemodynamic, endothelial dysfunction, infiltration of inflammatory cells in the renal parenchyma, tubular apoptosis around the inflamed lesion, and tubule lumen obstruction caused by necrotic cells and debris [6]. In this context, kidney tubular inflammation and apoptosis might be therapeutic targets for septic AKI.

Lipopolysaccharide (LPS) is a cellular wall component of gram-negative bacilli. Administration of LPS induces manifestations that mimic sepsis and, therefore, has been widely used to induce sepsis in animal models of septic AKI. In this issue of *Kidney Research and Clinical Practice*, Hong et al [7] investigated whether paricalcitol attenuates inflammation and apoptosis in LPS-induced renal proximal tubular cell injury through its action on the prostaglandin E_2 (PGE_2) receptor EP4. They found a significant increase in the expression of cyclooxygenase-2, PGE_2 and EP4 in LPS-exposed HK-2 cells treated with paricalcitol compared to cells exposed to LPS only. Paricalcitol prevented cell death induced by LPS exposure. Moreover, co-treatment with EP4 siRNA or EP4 specific antagonist, AH-23848, counteracted these cell-protective effects. EP4 specific antagonist or EP4 siRNA inhibited the suppressive effects of paricalcitol on p65 NF-κB nuclear translocation and the activation of Akt. The production of pro-inflammatory cytokines was also attenuated by paricalcitol in LPS treated HK-2 cells. Co-treatment with

Received March 8, 2017; **Revised** March 13, 2017;
Accepted March 14, 2017
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an EP4 antagonist attenuated these anti-inflammatory and anti-apoptotic effects of paricalcitol. The results reported by Hong et al [7] are in line with previous studies that have reported that paricalcitol exerts a protective effect against LPS-induced inflammation [8,9]. Paricalcitol prevents kidney injury by inhibiting renal inflammation, with the up-regulation of cyclooxygenase-2 and PGE_2, being one of the protective mechanisms of paricalcitol in LPS-induced renal tubule cell injury [7], as well as renal ischemia-reperfusion injury [9]. Furthermore, paricalcitol increased EP4 receptor expression in LPS-treated HK-2, which increased cell viability. This increase in EP4 receptor expression was counteracted by EP4 blockade using AH-23848 or EP4 siRNA. PGE_2 signaling, via the EP4 receptor, may provide a morphogenic signal to protect against kidney injury in AKI [10]. EP4 may, therefore, play an important role in the anti-inflammatory and anti-apoptotic effects of paricalcitol treatment in LPS-induced renal proximal tubule cell injury. Although there is lack of *in vivo* evidence, these observations provide good evidence that the paricalcitol-PGE_2-EP4 signaling pathway contributes anti-inflammatory and anti-apoptotic effects in LPS-induced tubule cell injury. A clinical study of the effects of paricalcitol in the treatment of septic AKI is warranted.

Conflicts of interest

The author has no conflicts of interest to declare.

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