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Can Xanthine Oxidoreductase Inhibitor Protect Kidney against Progressive Injury?

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Hyperuricemia and Renal Disease

Hyperuricemia has been shown to associate with high incidence of cardiovascular or kidney disease [1,2] and the beneficial effect of the treatment with allopurinol has been shown in hyperuricemic chronic kidney disease (CKD) patients [3]. Moreover, recent investigations have demonstrated that monosodium urate crystals activate natural immune system through its binding to Toll-like receptors (TLRs) and nucleotide binding and oligomerization domain-like receptors (NLRs) [4]. These indicate that xanthine oxidoreductase (XOR) inhibitor is a good candidate for renoprotective agents. However, there is evidence that, in contrast to the pro-inflammatory action of monosodium urate crystals, soluble form of uric acid in plasma acts as a major anti-oxidant in body [5]. Furthermore, allopurinol has been speculated to have non-specific action on purine nucleotide metabolism pathway, because it is generated as purine nucleotide derivative. Thus, presently it is unclear whether treating non-symptomatic hyperuricemic subject with XOR inhibitor has beneficial effects on the progression of cardiovascular or kidney disease.

XOR Inhibition and Renoprotection

In our recent study [6], we have demonstrated that a novel XOR inhibitor, Febuxostat, moderates the inflammation and the progression of fibrosis in rat unilateral ureteral obstruction (UUO) model. Of interest was that the renoprotective effects of XOR inhibition was observed in rat UUO model, whose plasma uric acid level is maintained relatively lower (less than 3.0 mg/dL) than human due to the enzymatic activity of uricase in rat and the presence of intact contra-lateral kidney in this experimental model. These facts strongly suggest that the elevated plasma uric acid level itself in UUO model may have little role in tissue inflammation and fibrosis. Then, how can febuxostat generate anti-inflammatory and anti-fibrotic action in rat UUO model.

As demonstrated in Figure 1, a couple of idea arises to explain this phenomenon. Firstly, febuxostat may blunt oxidative stress which derives from xanthine oxidase (XO) activity [7]. Under physiological condition, XOR protein exists as a form of xanthine reductase (XR) which utilizes NAD^+ and generates NADH. In contrast, under stressed conditions, conformation of XR protein as well as its function changes. This form of protein is named XO, which start to use O_2 and generates oxidative stress, a key mediator of inflammation and fibrosis. Secondly, febuxostat may provide beneficial effect by reducing intracellular uric acid production. In contrast to the role of plasma uric acid as a strong anti-oxidant [5], intracellular uric acid induces oxidative stress by the activation of NADPH oxidase [8-10], and promotes inflammation and fibrosis. Although rats express uricase which can degradates uric acid, its expression has cell-specificity, since uricase activity was mainly observed in liver, kidney, and brain, but not detected in other organs [11]. Therefore, even in rats, intracellular uric acid may be elevated in particular cells. In addition to these two mechanisms, a part of the beneficial effects of febuxostat may originate from blunted XR activity that preserve NAD^+ concentration or from accumulated non-catalyzed hypoxanthine that activate salvage pathway, but presently no information are available for these hypothesis.

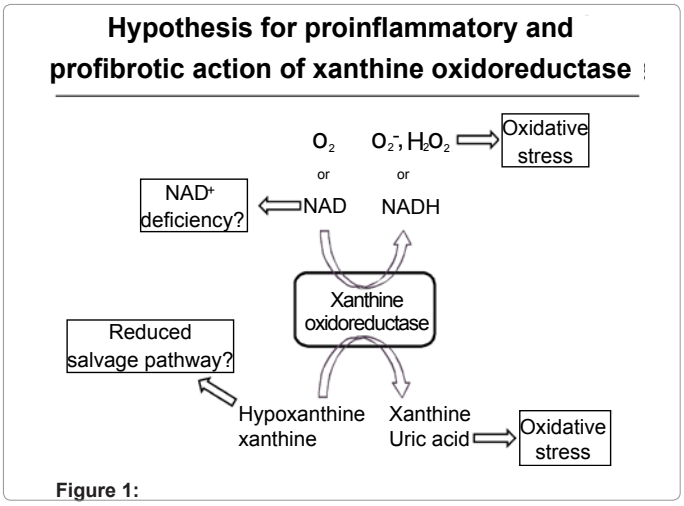

Figure 1:

Conclusions

In conclusion, with the novel XOR inhibitor; Febuxostat, we are now starting to reveal the significant role of XOR in the development of renal tissue inflammation and fibrosis, as well as the beneficial role of XOR inhibition as a therapeutic target for progressive kidney disease. The relationships between XOR activity and tissue inflammation or fibrosis may not be restricted to kidney, but also likely be applied to other important organs, including heart, brain and vessels.

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