FRUCTOKINASE INHIBITORS–IN DIABETIC NEPHROPATHY

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ABSTRACT
Recently Fructokinase has been studied in pathogenesis of DN, inhibiting Fructokinase suggest it could provide protection against diabetic nephropathy.

KEYWORDS:- Fructokinase (KETOHEXOKINASE-KHK), DN, uric acid.

INTRODUCTION
Fructokinase is the chief enzyme for metabolizing fructose and produces fructose-1-phosphate. Different than other sugar-metabolizing enzymes, the metabolism of fructose results in ATP reduction due to phosphate sequestration as fructose-1-phosphate with further generation of uric acid, oxidants, and inflammatory proteins.[1]

The two main places of fructokinase appearance are in the liver and the proximal tubule. Stimulation of liver fructokinase facilitates fatty liver through a process driven by oxidative stress and uric acid generation.[2] Hyperglycaemia itself produces oxidative stress.[3]

While most of the effects of the hepatic metabolism of fructose are expected to act within the liver, hepatic fructose metabolism can augment levels of serum lipids and serum uric acid, which could be accountable for some of the effects in the kidney.[4]

Nevertheless, it is possible that rises in serum uric acid induced by hepatic fructose metabolism might have certain effects on renal disease. Raising uric acid in rats can induce systemic and glomerular hypertension and induce micro-vascular, glomerular and tubulointerstitial disease.[5,6] Uric acid lowering agent with allopurinol (xanthine oxidase inhibitor)in diabetic mice has also been associated with a reduction in renal injury.[7]
FRUCTOKINASE INDUCES RENAL INJURY

Proximal tubule, sorbitol can be changed to fructose, which is then metabolized mainly by fructokinase, also recognized as ketohexokinase (KHK), leading to ATP reduction, proinflammatory cytokine expression, and oxidative stress.[4]

1. Fructose can induce proximal tubular injury in vitro through its metabolism by fructokinase to generate oxidants and uric acid.[8]
2. Proximal tubular fructokinase in vivo, as shown by the presence of increased cortical fructose, increased KHK expression, decreased ATP levels, and increased cortical uric acid. Mice deficient fructokinase presented less cortical uric acid deposition, signifying that the cortical uric acid reflected fructokinase activity.[4]
3. Glomerular injury was also prevented in diabetic khk−/− mice, as noted by decreased mesangial expansion and decrease glomerular macrophage infiltration, the mechanism for the glomerular protection is unknown.[4]
4. Repeated proximal tubular damage has been proposed as a pathogenic mechanism in the progression of diabetic nephropathy.[9]

PROBABLE MECHANISM OF DN:- URICACID INDUCED BY FRUCTOKINASE[4]

1. Uric acid is released into the circulation following fructose metabolism, where it could act to induce glomerular hypertension and injury.[10]
2. Uric acid is known to stimulate MCP-1/CCL2 and oxidative stress in vascular smooth muscle cells.[10,11]
3. Uric acid induces endothelial dysfunction.[12,13]
4. Uric acid has been shown to activate the renin angiotensin system, induce microvascular disease, alter renal auto-regulation, and increase glomerular hydrostatic pressure.[6,14]
5. Fructose can also increase the expression of intercellular adhesion molecule-1 in vascular endothelial cells throughout the kidney.[15]
6. Selective injury to the proximal tubule can result in glomerular damage, possibly because of connecting tubule glomerular feedback in which reflex arteriolar vasodilation from tubular damage causes increases in glomerular pressure.[16,17]

ANIMAL STUDY WITH FRUCTOKINASE INHIBITOR[18]

Luteolin – recently exposed as fructokinase inhibitor ameliorates renal injury.[18]

Acute kidney injury is linked with high mortality, particularly in intensive care unit patients. The polyol pathway is a metabolic path which convert glucose into fructose. Fructokinase
play vital role in the pathogenesis of ischaemic acute kidney injury (iAKI). Consistent with elevated urinary fructose in AKI patients, mice undergoing iAKI show significant polyol pathway activation in the kidney cortex expressed by high levels of aldose reductase, sorbitol and endogenous fructose. Wild type except fructokinase knockout animals demonstrate severe kidney injury associated with ATP depletion, elevated uric acid, oxidative stress and inflammation. Remarkably, both the renal injury and dysfunction in wild-type mice undergoing iAKI is significantly ameliorated when exposed to luteolin, a recently discovered fructokinase inhibitor.\textsuperscript{[18]}

Role of fructokinase in pathogenesis of DN\textsuperscript{[4]} is well clear and fructokinase inhibitors can ameliorate kidney injury/damage.\textsuperscript{[18]}

**Probable benefits of Fructokinase Inhibitors**

1. Decrease generation of oxidant and uric acid
2. Decrease oxidative stress
3. Inhibit endothelial dysfunction
4. Inhibit ischemia induce renal damage
5. Prevent glomerular hypertension and hyper-filtration.

Fructokinase is novel target for DN\textsuperscript{[4]} and needs further evaluation.\textsuperscript{[4,18]}

Unfortunately only one fructokinase inhibitor Luteolin is studied till date in kidney injury and diabetic nephropathy. Newer fructokinase inhibitor molecules should be tested in preclinical study.

**CONFLICT OF INTEREST**
The Author declares there is no conflict of interest regarding publication of this paper.

**DECLARATION**
The author has not conducted any animal study or Human Trial, the matter in the article is which comprises animal or human trial are the study done by researcher /scientist listed in the Reference section and cited appropriately and are taken up in the article to support the Hypothesis.
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REFERENCES:-


