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Gemfibrozil Halts the Nicotine Mediated Acute Kidney Injury in Rats: Role of Hyperlipidemia and Oxidative Stress

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ABSTRACT

Background: Genfibrozil capable to attenuate the nephrotoxicity by controlling oxidative stress and proinflammatory molecules in rats.

Objective: The present study investigated the possible effect of gemfibrozil (peroxisome proliferator-activated receptors-α agonist) in nicotine-induced acute kidney injury (AKI) in rats.

Methods: Nicotine (2 mg/kg/day, intraperitoneally) was administered for 4 weeks to induce AKI in rats. Lipid profile and renal oxidative stress were measured and along with serum and renal tissue nitrite levels. Serum creatinine, blood urea nitrogen and microproteinuria were estimated along with the kidney histology, as markers of kidney function. Treatment with Gemfibrozil (30 mg/kg per oral, 4 weeks) was initiated 3 days before the administration of nicotine and continued for 4 weeks from the day of administration of nicotine.

Results: Nicotine administered rats developed apparent AKI confirmed by elevated markers of kidney function and noticeable glomerulosclerosis and tubular cell degeneration. Nicotine altered lipid profile, decrease oxidative stress, assessed in terms of increase in serum thiobarbituric acid reactive substance and a marked decrease in tissue reduced glutathione. However, gemfibrozil significantly prevented the development of nicotine-AKI by reducing serum creatinine, BUN, and urinary protein, normalizing the lipid profile, reducing renal oxidative stress, and concentration of serum and renal nitrate levels.

Conclusion: Gemfibrozil offers superior therapeutic options against nicotine-induced AKI, suggesting a possibility of the nephroprotective action mainly mediated through its antihyperlipidemic, antioxidant, and maybe potential to submaximal eNOS expression activation.

Key Words: Nicotine, Gemfibrozil, Acute kidney injury, Nephroprotective

INTRODUCTION

In the society cigarette smoking mediated nicotine exposure is considered to be a hallmark and considerable risk factor involved in the development of and progression reno-cardiovascular complications. Importantly, smoking has been repeatedly noted confirmed possible determinant for the development and progression of kidney disease in patients.[1] The two major determinates are hyperlipidemia and oxidative stress involved in the induction and progression of the nicotine mediated kidney functional and structural changes abnormalities.[2,3] The major step in this process is the involvement of vascular endothelial dysfunction (VED), results in reduced of activation of endothelial nitric oxide synthase (eNOS), reduced generation and bioavailability of nitric oxide (NO).[4,5] VED which is one of the important among the earliest stages has been associated in the pathogenesis of hypertension, coronary artery diseases and nephropathy.[6,7] A correlation between VED and kidney injury by the role of hyperlipidemia and oxidative stress has been demonstrated previously.[8,9] The subsequence events include nodular glomerulosclerosis followed by glomerular basement membrane thickness and mesangial expansion by the VED and shown to be involved in the induction and progress of nephropathy.[9,10]

Frequently it has been proven that exposure of nicotine plays a key role in inducing VED by increasing hyperlipidemic.[4,7,8] This contention is supported by another study that the nicotine-induced hyperlipidaemia and increased oxidative

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stress noted in rats.[11,12] The steps involved in the nicotine in the development of acute kidney injury (AKI) by accelerate glomerulosclerosis and provokes reno-vascular pathogenesis [13,14]. Together, nicotine is forcefully inducing VED fallowed by the hyperlipidemia and oxidative stress. However, no promising therapeutic option is available yet to attenuate nicotine mediated acute kidney injury and other vascular pathogenesis. Considerable studies markedly focus on the interesting fact that numerous vascular and reno-protective pleiotropic effects of gemfibrozil.

Gemfibrozil is well known to produce antihyperlipidemic action by activation of peroxisome proliferator-activated receptor-α (PPAR-α) 15. In addition to this, Genfibrozil capable to attenuate the nephrotoxicity by controlling oxidative stress and proinflammatory molecules in rats.[16] Incessantly, it was noted that the PPAR-α agonist upregulates the expression of eNOS thus has been reported to ameliorate nicotine-induced endothelial dysfunction by reducing hyperlipidemia and oxidative stress.[12] In addition, in our laboratory, we have shown that treatment with fenofibrate and concurrent administration of benfotiamine, prevented the development of diabetic nephropathy indicating PPAR-α agonist-mediated renoprotection.[10]

These studies certainly suggest avascular and reno-protective potential of gemfibrozil. However, the effect of gemfibrozil in nicotine-induced AKI is not yet known. Thus, the growing evidence says that the use of gemfibrozil attenuates nicotine-mediated hyperlipidemia and oxidative stress. Therefore, the present study was aimed to explore the effect of gemfibrozil as a possible therapeutic strategy to prevent nicotine-induced AKI.

MATERIALS AND METHODS

Drugs and Chemicals

Nicotine was obtained from Nicosulf India Pvt. Ltd., Dakor, Gujarat, India. All other chemicals and kits used in the present study were of analytical grade. The Gemfibrozil was obtained from Ranbaxy Laboratory Ltd., Gurgaon, India. 1,1,3,3 tetra methoxypropane and carboxymethyl cellulose were purchased from V. K. Chemicals and Instruments, Ambala, India.

Experimental animals

Age-matched young Wistar rats weighing about 200-250 g were housed in a room maintained at approximately 24±1°C temperature and humidity of 55±5% with 12-hour light/dark cycle. Free access to food (standard chow from Ashirwad Industries, India) and water was allowed. The animals were acclimatized for at least 3-4 days before the initiation of the experiment and were observed for any sign of disease. The animals were maintained under proper conditions till the termination of the experiment. Approval for all experiments was obtained from the institutional animal ethical committee (IAEC) NO: 1117/POBC07CPCSEA and Committee for Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Animal model and drug treatment

Nicotine (2 mg/kg/day, intraperitoneally [i.p.]) was administered for 4 weeks to induce acute kidney injury in rats. At the end of the study (4 weeks), the rats were sacrificed by cervical dislocation. Gemfibrozil was administered 3 days before the administration of nicotine, and it was continued for 4 weeks from the day of administration of nicotine. All the parameters were assessed at the end of 4 weeks in normal and rats administered nicotine with or without drug treatments (Figure 1).

Experimental protocol

Three groups were employed in the present study and each group comprised of 8 animals. The Gemfibrozil was dissolved in 1% w/v of carboxy methylcellulose (CMC). Group I (normal control) rats were maintained on standard food and water and no treatment was given, group II (nicotine control) rats were administered nicotine (2 mg/kg/day, i.p., 4 weeks), and group III (Gemfibrozil-treated nicotine group) rats were treated with gemfibrozil (30 mg/kg/day, peroral [p.o.]), the treatment was initiated 3 days before the administration of nicotine, and continued for 4 weeks from the day of administration of nicotine.

Estimation of renal tissue nitrite levels

Nitrite levels in tissue were estimated as described earlier. The total nitrite content was expressed as nmoles per mg of protein.[17]

Assessment of lipid profile

At the end of the experimental protocol, the blood samples were collected and serum was separated after allowing to clot followed by centrifugation. The serum samples were frozen until analyzing the biochemical parameters. The total cholesterol, triglyceride and HDL-cholesterol concentration estimated by commercially available kit (Bio Lab Diagnostics India Private Limited) using a spectrophotometer.

The serum total cholesterol and HDL cholesterol were estimated by cholesterol oxidase peroxidase (CHOD-POD) method[17], using the commercially available kit (Bio Lab Diagnostics India Private Limited). The serum triglyceride was estimated by glycerophosphate oxidase peroxidase (GPO-POD) method using the commercially available kit (Kamineni Life Sciences Pvt. Ltd., Hyderabad, India).

Assessment of oxidative stress

Estimation of serum thiobarbituric acid reactive substances (TBARS)

The serum concentration of TBARS was estimated spectrophotometrically to assess oxidative stress. A standard graph using 1, 1, 3, 3 tetramethoxypropane (1–50 µM) was plotted to calculate the concentration of TBARS.[4,7]

Estimation of renal glutathione (GSH)

Preparation of renal homogenate

The renal homogenate was mixed with 10 % w/v trichloroacetic acid in 1:1 ratio and centrifuged at 4 C for 10 min at 5000 rpm. The supernatant (0.5 mL) was mixed with 2 mL of 0.3 M disodium hydrogen phosphate buffer (pH 8.4) and 0.4 mL of distilled water. Then, 0.25 mL of 0.001 M freshly prepared DTNB 5, 50–dithiobis (2-nitrobenzoic acid) dissolved in 1 % w/v sodium citrate was added to the reaction mixture, and incubated for 10 min. The absorbance of the yellow-coloured complex was noted spectrophotometrically at 412 nm. A standard curve using the reduced form of glutathione was plotted to calculate the concentration of renal GSH. The renal GSH concentration was expressed as lM/g wet weight of renal tissue.[18]

Assessment of nicotine-induced acute kidney injury

The development of AKI in rats was confirmed 4 weeks after the administration of nicotine, was assessed by measuring serum creatinine and blood urea nitrogen concentration using commercially available kits. Besides, histopathological studies were performed to assess nicotine-induced renal structural abnormalities. Markers of renal injury including serum level of creatinine estimated by alkaline picrate kinetic method, blood urea nitrogen were estimated by Berthelot method and urinary protein concentration was estimated by pyrogallol red method using the commercially available kit (Span Diagnostics Ltd., India).[10]

Histopathological study

Nicotine-induced renal structural changes in glomeruli and tubules were assessed histologically. The changes in glomeruli were assessed using histopathology. Briefly, the kidneys were excised and immediately immersed in 10% formalin. The kidney was dehydrated in graded concentrations of alcohol, immersed in xylene and then embedded in paraffin. From the paraffin blocks, sections of 5-µm thickness were made and stained with hematoxylin and eosin to assess pathological changes in glomeruli using light microscopy (200 X).[10]

Statistical analysis

All values were expressed as mean ± S.E.M. The data for nitrite level, serum TBARS, renal GSH, lipid profile, serum and tissue nitrates and creatinine, blood urea, urinary protein were statistically analyzed using one-way ANOVA followed by Dunnett test. The p-value <0.05 was considered to be statistically significant.

RESULTS

No mortality was observed in the animals within the 4 weeks of nicotine administration.

Effect of pharmacological interventions on serum lipid concentration

The significant increase in serum concentration of total cholesterol and triglycerides and decrease in HDL were noted in rats with nicotine mediated AKI when compared with normal rats. However, treatment with gemfibrozil markedly reduced the nicotine-induced alterations in serum lipids (Table 1).

Effect of pharmacological interventions on serum TBARS and renal glutathione

The marked increase in serum TBARS and decrease in renal glutathione was noted in nicotine administered rats. However, treatment with gemfibrozil significantly attenuated the nicotine-induced increase in serum TBARS concentration and decrease in renal glutathione (Table 1)

Effect of pharmacological interventions on serum and renal tissue nitrate level

The serum and renal nitrate level were noted to be reduced in nicotine administered rats when compared with normal rats. However, treatment with gemfibrozil significantly attenuated nicotine-induced decrease in serum and renal level of nitrate. Gemfibrozil produced marked restoration of decreased serum and renal nitrite level in rats administered nicotine (Table 2).

Effect of pharmacological interventions on serum creatinine, blood urea, and proteinuria

The serum creatinine, blood urea nitrogen and proteinuria levels were noted to be markedly increased in nicotine-administered rats as compared to normal rats. However, treatment with gemfibrozil markedly reduced the nicotine-induced high serum concentrations of creatinine, blood urea, and elevated urinary protein (Table 3).

Effect of pharmacological interventions on the histopathological study on kidney

The significant renal structural pathological abnormalities in the glomerulus and tubules were observed in nicotine-

administered rats. The pathological changes in the glomeruli such as reduced capillary size and extracellular mesangial expansion in nicotine administered rats after 4 weeks when compared with normal rats. Treatment with gemfibrozil markedly reduced the pathological changes in glomeruli by improving the glomerular capillary size and reducing the mesangial expansion. (Figure 2)

DISCUSSION

The increasing prevalence in developed and developing countries of kidney disease calls for stronger measures to halt the progression of kidney injury. The promising approach is smoking cessation and this may be a valuable tool in this direction. The smoking significantly contributes to renal disease growth by eliciting microvascular injury and speed up global glomerulosclerosis.[13] Also, it is has been noted that smoking reportedly exerts deleterious effects on renal function and structure.[14,19] Nicotine exposure via chronic cigarette smoking is an emerging cause that accelerates the microvascular complications. The study noted evidently and suggests that nicotine forcefully induces the kidney injury in rats.[19,20] Sometime it is difficult to predict and understand the smoking-mediated microvascular issues because nicotine has intricate mechanisms. In addition, nicotine is responsible for eNOS downregulation and induces VED in rats, which is a first step in the pathogenesis of acute kidney injury.[9,12,21] Moreover, nicotine also noted to worsen the nephropathy by activation of hyperlipidemia and high-grade oxidative stress.[21,22]

Gemfibrozil, an activator of PPAR-α, is a well-known therapeutic regimen for lipid management[15] PPAR-α activation results in the activation of lipoprotein lipase and increases lipolysis and reduced triglyceride levels.[23] It is interesting to note that nicotine alters the lipid profile by increasing the level of low-density lipoproteins (LDL) and total cholesterol and consequently decreasing the level of high-density lipoprotein (HDL) to induce the formation of hyperlipidaemia.[24] Nicotine causes impairment of lipoprotein lipase, an enzyme involved in the hydrolysis and clearance of triglycerides from the circulation.[25,26] Thus, nicotine-induced kidney damage is often associated with hypercholesterolemia and hypertriglyceridemia. This contention is supported by the results obtained in the present study that the total cholesterol and triglycerides levels were noted to be markedly reduced and HDL level gets increased after gemfibrozil treatment in nicotine administered rats.

In the last few decades has seen several significant studies, both on animal models, as well as human subjects, to support strongly suggest the role of cigarette smoking in the progression of renal failure. Nicotine-administered kidneys are more susceptible to oxidative damage because of the induction of deficiency in antioxidant defence enzymes. Similar kind of reduction of antioxidant level and increase in oxidative stress has been observed in previous studies where nicotine in renal tubular cells produced oxidative stress and reduced the level of SOD (superoxide dismutase) along with a reduction in renal cell viability.[27,28] Further, the same line the nicotine demonstrated to increase the oxidative stress and pays risk factor for micro and macrovascular complications.[12,14] Moreover, nicotine induces oxidative stress by generating ROS via activation of NADPH oxidase, assessed in terms of increase in serum TBARS and superoxide anion generation and increase in expression of mRNA for p22phox in other studies has been proven.[12,22] For instance, nicotine has a potent effect on accelerating the up-gradation of oxidative stress-mediated renal tissue damage. This is further supported by the fact that in the present study the nicotine administered rats showed high-grade oxidative stress by increasing serum and tissue TBARS. Additionally, a marked decrease in renal GSH was noted in nicotinic rats as compared to normal rats indicate nicotine-induced oxidative stress, which is reversed by the treatment with gemfibrozil.

In the recent and previous observations, vascular endothelium plays an important role in the pathogenesis of kidney injury.[9,10] Few clinically and preclinical studies have documented the nicotine plays a key role in mediating endothelial dysfunctions by decreasing the generation and bioavailability of NO and downregulating the expression of eNOS, which is the first step in the pathogenesis of acute kidney injury.[12,29,30] Gemfibrozil has been noted to improve the function of endothelium mediated renal damage by reducing the oxidative stress.[16,23] The vascular protecting potential of fenofibrate in preventing the development of vascular endothelial dysfunction and kidney injury may be attributed to its antihyperlipidemic property and/or its pleiotropic actions such as activation activity and function of soluble guanylyl cyclase and generation of NO and consequent reduction in oxidative stress to improve the integrity and function of the endothelium and renal functions in nicotine administered rats.[24]

Acute kidney injury (know as an acute renal failure) is defined as a multifactorial syndrome, characterized by an abrupt loss of renal function which results in the accumulation of metabolic waste and toxins, such as serum creatinine and blood urea nitrogen, and/or decreased urine output.[33,34] The increase in serum creatinine, blood urea and proteinuria and pathological changes in glomeruli have been documented to be an index of AKI.[10,33.] Creatinine, a non-protein waste product is freely filtered by the kidney and as the serum creatinine level depends on the glomerular filtration rate (GFR), thereby is considered to be an index of renal dysfunction.[22,34] We observed in the present study that nicotine-administered rats exhibited a marked elevation in serum creatinine. These results suggest the induction of kidney injury with renal functional abnormalities in nicotine-administered rats. Another waste

product of protein metabolism namely urea is cleared from the bloodstream by the kidney and it has been considered as an important biomarker for the dysfunction of the kidney.[22] Accordingly, we reported that the blood urea and proteinuria were noted to be increased in nicotine-administered rats as compared to normal rats. The morphological changes in the kidney are considered as direct evidence for the confirmation of AKI. In the present study, histopathological analysis revealed renal structural abnormalities that occurred in glomerulus and tubules, with degeneration in the glomerular wall and mild hypertrophy in glomerulus were noted in nicotine-administered rats. These results suggest the development of nicotine-induced acute kidney injury. The treatment with gemfibrozil markedly prevented the aforementioned renal functional and structural abnormalities in nicotine administered rats. Consequently, gemfibrozil might be a potential therapeutic approach in the prevention of nicotine-induced AKI. It is noteworthy that gemfibrozil plays pleiotropic actions in the prevention of kidney injury. In support of this proposal, the gemfibrozil mediated multifactorial potential is explored. Our study has demonstrated for the first time that pleiotropic actions of gemfibrozil in the nicotine-induced AKI by reducing hyperlipidemia, oxidative stress and may be submaximal and subsequently upregulated the expression of eNOS and have played a key role in the protection of renal function.

CONCLUSION

The gemfibrozil and its strong antihyperlipidemic and antioxidant activity facilitate to prevent the kindly damage induced by the nicotine. This affordable action may be further supported by the submaximal activation of NO pathway.

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Table 1: Effect of gemfibrozil on serum lipid profile

Assessment	Normal Control	Nicotine Control	Gemfibrozil treated nicotine control
Serum cholesterol (mg/dl)	71.11±7.5	171.52±8.1[a]	99.4±4.01[b]
Triglycerides (mg/dl)	81.2±5.6	142±9.1[a]	92.8±6.3[b]
High density lipoprotein (mg/dl)	37.6±03	31.1±0.7[a]	37±0.6[b]

All values are represented as mean±SD. [a]P<0.05 vs normal control. [b]P<0.05 vs nicotine control

Table 2: Effect of gemfibrozil on serum TBAR, renal GSH, serum nitrite/nitrate (μM) and renal tissue nitrite levels.

Assessment	Normal Control	Nicotine Control	Gemfibrozil treated nicotine control
Serum TBAR (μM)	3.6±0.3	8.4±0.26[a]	6.35±0.66[b]
Renal GSH (μM/g wet weight of renal tissue)	0.73±0.02	0.23±0.01[a]	0.53±0.02[b]
Serum nitrite/nitrate (μM)	11.5±0.34	6.2±0.4[a]	10.21±0.5[b]
Renal tissue nitrite (nmoles/mg protein)	0.85±0.30	0.45±0.21[a]	0.60±0.11[b]

All values are represented as mean±SD. [a]P<0.05 vs normal control. [b]P<0.05 vs nicotine control.

Table 3: Effect of gemfibrozil on serum creatinine, blood urea, and proteinuria levels.

Assessment	Normal Control	Nicotine Control	Gemfibrozil treated nicotine control
Serum creatinine (mg/dl)	3.4±0.3	8.4±0.26[a]	6.76±0.56[b]
Serum blood urea	0.75±0.07	0.25±0.02[a]	0.51±0.02[b]
Urinary protein concentration	11.8±0.44	6.1±0.4[a]	11.01±0.4[b]

All values are represented as mean±SD. [a]P<0.05 vs normal control. [b]P<0.05 vs nicotine control.

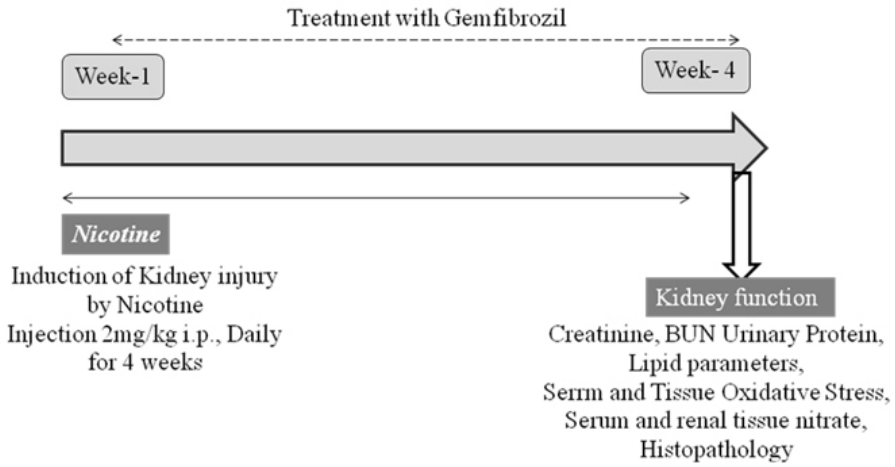

Figure 1: Graphical Abstract.

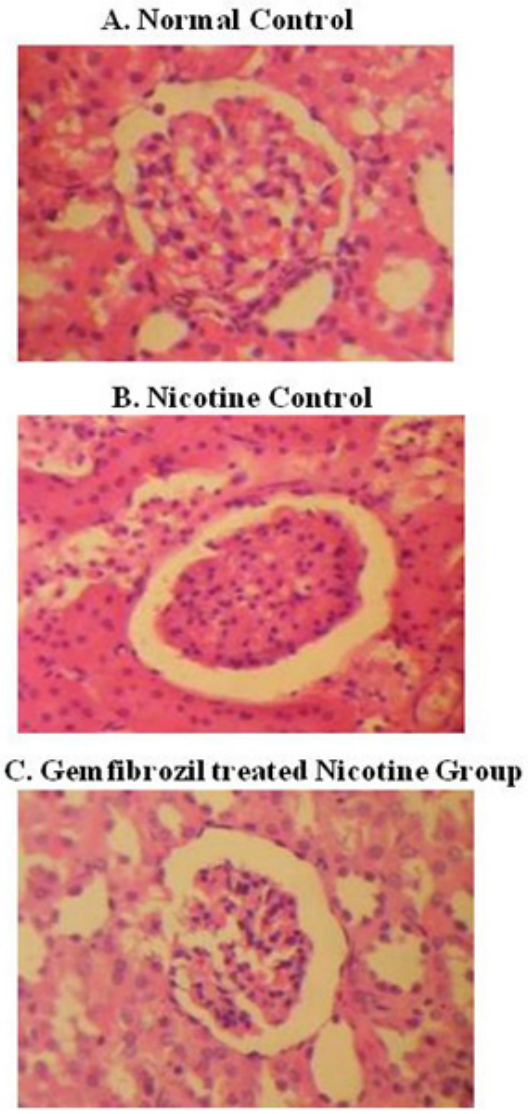

Figure 2: Histopathological changes associated with nicotine and treatment groups (A: Normal Control, B: Nicotine Control, C: Gemfibrozil treated nicotine group).