A Review on Renal Toxicity Profile of Common Abusive Drugs

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Drug abuse has become a major social problem of the modern world and majority of these abusive drugs or their metabolites are excreted through the kidneys and, thus, the renal complications of these drugs are very common. Morphine, heroin, cocaine, nicotine and alcohol are the most commonly abused drugs, and their use is associated with various types of renal toxicity. The renal complications include a wide range of glomerular, interstitial and vascular diseases leading to acute or chronic renal failure. The present review discusses the renal toxicity profile and possible mechanisms of commonly abused drugs including morphine, heroin, cocaine, nicotine, caffeine and alcohol.

Key Words: Caffeine, Cocaine, Heroin, Morphine, Renal failure

INTRODUCTION

Drugs are the natural or synthetic substances that are used for medical purposes however, the repeated use of some of these leads to transient or chronic dependency [1]. Although human being has been using drugs for entertainment purposes since long time, yet the number of drugs dependents has increased over the last few years [2]. Drug abuse has become a major social problem of the modern world as it is very common and involves lifetime exposure of about 46% of the general population. In India, the National Household survey of Drug Use documented the nationwide prevalence of drug abuse and found that alcohol (21.4%) is the primary drug of abuse followed by opioids (0.7%). The prevalence of tobacco use is high at 55.8% in males between 41∼50 years of age. Cocaine abuse is epidemic in the United States with a total of 34.3 million Americans (14.6% of surveyed population) have used cocaine at some time. The majority of these substances or their metabolites are excreted through the kidneys and renal complications of drug abuse are very common. It includes a wide range of glomerular, interstitial and vascular diseases. The damage may be acute and reversible, or chronic and can leads to end stage renal failure. The involvement of the kidney due to drug abuse is either attributed to their elimination through the kidney, or a direct nephrotoxic effect [3].

Both endogenous and exogenous opioids have a strong influence on the renal functions. Endogenous opioids are known to play a pivotal role in controlling kidney function in normal and pathological states [4]. The endogenous opioid peptides are referred to as 'endorphins' and these bind to mu, delta and kappa receptors localized on the different parts of the kidney [5,6]. Kappa opioid receptors are mostly localized in the renal cortex [7]. Mu and kappa receptors are present on the mesangial cells of the kidney, while delta receptors are barely detectable in mesangial cells [6]. There is considerable variation regarding the presence and localization of these opioid receptors depending on the type of species. Mu and kappa opioid receptors are absent in guinea pig kidney, however, delta opioid receptors are identified in guinea pig kidney mainly in the region of corticomedullary junction, collecting ducts, renal tubule or vascular tissue [8]. Opioids produce physiological changes in kidney [6,9], and endorphins along with other opioid peptides participate in the development of uremic syndrome [10]. Opioids have been shown to enhance the renal interstitial scarring in HIV-associated nephropathy [11]. Studies have also suggested that chronic administration of clinically relevant doses of opioids causes structural abnormalities and renal dysfunction in a murine model of cancer [12]. Exogenous opioids like morphine and heroin produce

ABBREVIATIONS: ARF, acute renal failure; ESRD, end stage renal disease; UTI, urinary tract infection; AT1b, angiotensin II type 1b; NO, nitric oxide; GEC, glomerular epithelial cell; Hbs, sickle haemoglobin; FSGS, focal and segmental glomerulosclerosis; MPGN, membrano proliferative Glomerulo nephritis; ET-1, endothelin-1; AIN, acute interstitial nephritis; HPTEC, human proximal tubular epithelial cell; BE, benzoylecgonine; EME, ecgonine methyl ester; NCOC, norcocaine; ROS, reactive oxygen species; KTZ, ketoconazole; SHR, spontaneously hypertensive rats; TGF-β, transforming growth factor-β; α-SMA, α-smooth muscle actin; MCP-1, monocyte chemotactic protein; nAChR, nicotinic acetylcholine receptor; SHHF, spontaneously hypertensive heart failure; RVR, renal vascular resistance; ADPKD, autosomal dominant polycystic kidney disease; p1rIMCD, passage-1 rat renal inner medullary collecting duct cells; PAN, puromycin amino nucleoside; CrCl, creatinine clearance; ADH, antidiuretic hormone.

renal injuries. Morphine addiction can cause progressive chronic renal failure [13] and tubular epithelial cell degeneration [14]. Overdose of morphine increases the oxidative stress in the renal epithelial which leads to renal injury [15]. Heroin abuse is also responsible for the several renal complications [16]. Cocaine abuse may cause interstitial fibrosis [17], renal atherogenesis [18], glomerulosclerosis [19], renal infarction, electrolyte imbalance, acute renal failure and urinary tract infections (UTI's). The pathological role of smoking in the development of kidney injury has been recognized [20]. Chronic exposure to nicotine increases the severity of acute renal ischemia-reperfusion injury [21], which may be due to an increased oxidative stress in renal cells [22] or due to involvement of angiotensin II type 1b receptor (AT1b) found on kidneys [23]. Caffeine administration is associated with the rhabdomyolysis which leads to abnormality in kidney functions [24]. Both acute and chronic alcohol consumption can compromise the kidney function [25] and its consumption has been shown to reduce renal function [26]. Alcohol consumption is a probable risk factor for end stage renal disease (ESRD) [27]. In this review renal toxicities of commonly abused substances like opioids, cocaine, tobacco (nicotine), caffeine, and alcohol along with the possible mechanisms are discussed.

ENDOGENOUS OPIOIDS AND RENAL TOXICITY

Cholestasis-induced nephrotoxicity

Cholestatic liver disease is associated with major complications such as pulmonary and cardiovascular dysfunction, sepsis, pruritis and renal failure [28,29]. Renal failure is one of the most frequent complications of obstructive jaundice and renal failure is observed in $4 \sim 18\%$ of the patients [30]. The kidney undergoes non-specific changes and tubular necrosis in cholestasis, however, its exact mechanism is still unknown. There have been number of studies showing an increased opioidergic neuromodulation, increased total plasma opioid activity (upto 3 times), and elevated plasma enkephalin concentrations (upto 17 times) in cholestasis [31-33]. The studies have shown an important role of endogenous opioids, particularly methionine enkephalin, in several deleterious consequences of cholestasis including renal failure [34-37]. Recently, Deroee and co-workers described the critical role of endogenous opioids in an experimental model of cholestasis (bile duct ligation)-induced renal failure in rats. Naltrexone treatment was shown to significantly reverse bile duct ligation-induced increased biochemical parameters of liver injury (alanine aminotransferase and aspartate transaminase) and renal injury (N-acetyl-β-D-glucosaminidase activity) along with prevention of structural alterations in renal tubules [38].

The exact mechanisms for cholestasis-induced opioid overproduction and thereafter, renal failure is still unknown. Increased levels of opioids may produce detrimental effects by various mechanisms including oxidative stress, nitric oxide (NO) overproduction, apoptosis and vascular endothelial dysfunction [29,31]. In the liver, opioid receptor agonists have been shown to stimulate the production of superoxide anions in macrophages and neutrophils [39,40] and oxidative stress is very well documented to induce renal failure [39,41,42]. Free oxygen radicals cause lipid peroxidation in renal arterial endothelium, mesangial and re-

nal tubular cells and cause renal failure [43]. The opioid receptor agonists are also shown to induce apoptosis in different tissues by enhancing the expression of pro-apoptotic FasL, Fas, and Bad proteins, and reducing the expression of anti-apoptotic Bcl-2 oncoprotein [44-46].

EXOGENOUS OPIOIDS AND RENAL TOXICITY

Various studies have shown that administration of exogenous opioids also cause kidney diseases. The exogenous opioids that may produce kidney diseases are described:

Morphine

Clinical studies suggest that morphine addicts are at increased risk for progressive chronic renal failure [13,47,48]. Intravenous opiate addiction has also been considered a risk factor for the development of human immunodeficiency (HIV)-associated nephropathy [49,50]. Morphine is metabolized in the liver to morphine-3-glucuronide (55%), morphine-6-glucuronide (10%), and normorphine (4%), all of which are excreted through urine. However in renal failure, morphine and its metabolites accumulate in the plasma, serum, brain, cerebrospinal fluid and cause myoclonic spasm and respiratory depression [51,52]. The overdose of morphine (more than 0.1 gm, urine concentration 6384 ng/ml) produces rhabdomyolysis which in turn causes acute renal failure. In these patients, laboratory examination has revealed an elevated creatine kinase activity, increased urine myoglobin concentration and raised plasma creatinine signifying the development of acute muscle damage and renal failure [53]. Morphine administration is associated with reversible hydronephrosis and renal impairment in premature infants [54]. Within 24 h of morphine administration, infants have been shown to develop oliguria with very high level of the serum creatinine. The cessation of morphine results in rapid and complete resolution of the hydronephrosis and normalization of elevated creatinine [55]. Weber and his co-workers examined the effect of exogenous opioid treatment (chronic morphine) and reported an increase in kidney weight and glomerular volume in C57/BL6 WT mice.

Sumathi and Devaraj demonstrated that chronic administration of morphine causes an increased levels of urea, uric acid and creatinine in the serum and the increased levels of these end products of nitrogen metabolism might be due to the damage caused by long-term effect of morphine in the kidney. Morphine was shown to produce tubular epithelial cell degeneration with cellular casts within the lumen of the tubules in the kidney [14]. Morphine stimulates the production of superoxide by macrophages and mesangial cells [56,57]. Morphine inhibits the glutathione reductase which leads to increased oxidative stress in cells and renal injury [15]. Morphine is documented to enhance the proliferation of mesangial cells which is a precursor of glomerulosclerosis [58]. Morphine has a bimodal effect on glomerular epithelial cells (GEC). At lower concentrations, morphine promotes GEC growth, whereas at higher concentrations, morphine triggers apoptosis of these epithelial cells. Further, morphine also exerts a bimodal effect on heme oxygenase activity in GEC (stimulatory at lower and suppressive at higher concentrations) [59]. The chronic use of morphine leads to structural kidney abnormalities along

with upregulation of NOS, COX-2 and HO-1 in a murine model of cancer [12].

Very recently, Weber and co-workers suggested that clinically relevant doses (equivalent to approximately 50∼301 mg/70 kg human/day) of morphine increases the renal pathology in sickle mice. The authors employed three transgenic murine models expressing varying levels of sickle haemoglobin (Hbs), which included hBERK1 (∼26% Hbs), NY1DD (∼40% Hbs), and BERK (∼99% Hbs) to determine whether the effect of morphine on the kidney is strain-specific and/or influenced by variability of sickle haemoglobin expression. Morphine treatment was shown to induce glomerular expansion, tubular dilatation, and intraglomerular and peritubular congestion, increase in kidney mass in NY1DD mice by 23% (after 3 weeks) and by 40% in hBERK1 mice (after 6 weeks of treatment). Light microscopy showed increased number of juxtaglomerular cells and extremely high intraglomerular congestion in morphine treated mice [60].

Heroin

Heroin (diacetylmorphine, diamorphine) is the most commonly abused drug. It can be sniffed, eaten, smoked, injected subcutaneously or intravenously. It is often injected in combination of cocaine [61]. There are several renal complications from its abuse [16]. In heroin addicts, the renal disease complication is very common and is associated with membranous nephropathy, nephrotic syndrome, acute glomerulonephritis, focal and segmental glomerulosclerosis (FSGS) amyloidosis, interstitial nephritis, and rhabdomyolysis. Focal membranoproliferative glomerulonephritis with IgM and complement deposition is also found in heroin addicts with the nephrotic syndrome. There is a three-fold increased risk for renal dysfunction in heroin users versus non-drug users [62,63].

The patients with a history of a few months to 15 yr of heroin use are reported to develop hypertension and varying degrees of renal insufficiency, proteinuria, glomerulosclerosis and urinary abnormalities. Global, segmental, or mesangial sclerosis; glomerular basement membrane thickening; and epithelial cell foot process dropout has also been demonstrated in these patients [62]. Grishaman and co-workers reported the mesangial proliferation, membranoproliferative glomerulonephritis, dysproteinemias, and diabetic nephropathy in heroin users with renal disease. There are evidences that nephropathy is related to demographic, socioeconomic, or genetic factors of heroin users. FSGS is more predominant in black individuals and Memberano Proliferative Glomerulo Nephritis (MPGN) is more predominant in white individuals. Grishman and co-workers concluded that nephrotic syndrome of heroin addicts is mostly associated with focal segmental glomerular sclerosis and occasionally with minimal change disease or focal global sclerosis [64]. The heroin overdose is reported to induce rhabdomyolysis resulting in myoglobinaemia and renal failure. The pathophysiology of rhabdomyolysis in heroin addiction includes acidosis, systemic hypoxia, muscle compression and direct toxic and immunologic effects of drug [65,66]. The heroin addicts are shown to develop severe bilateral compartment syndrome complicated by rhabdomyolysis and renal failure [67]. A recent case report has suggested that a single exposure of heroin may also lead to development of rhabdomyolysis and acute kidney injury requiring dialysis. Heroin associated renal complications may be a consequence of immunologic/hypersensitivity reaction or direct myotoxic effect [68]. Renal amyloidosis is an important diagnosis in heroin addicts with proteinuria and nephrotic syndrome [69].

COCAINE

Cocaine is an alkaloid extracted from a shrub (*Erythroxylon coca*) which grows in the Andes mountains [70]. Cocaine abuse has been shown to result in both acute and chronic renal injury resulting in number of renal complications including ARF, renal infarction, and electrolyte imbalance and UTIs in infants exposed to cocaine in uterus. All routes of cocaine administration (i.v, insufflations, and intranasal and free-basing crack cocaine) have been associated with renal infarction. There is a dose relationship between maternal cocaine use and UTIs among infants born to cocaine abusing mothers [71]. Gottbrath and his co-workers observed a 14% incidence of UTI in cocaine exposed infants. This incidence was greater than that in the control group of premature infants (3%) who were expected to have a high incidence of UTI on the basis of prematurity alone. It is important to note that this high incidence of UTI in cocaine exposed infants is entirely not due to congenital abnormalities. These investigators described that ischemia and hypoxia after cocaine abuse may form renal scars in utero, leading to UTIs [18]. A case report has shown that cocaine use is associated with proteinuria, leukocytosis, elevated serum creatinine, renal artery dissection, thrombosis and renal infarction [72]. Other reports have also documented the development of cocaine induced renal infarction [73,74]. Renal infarction due to cocaine abuse is uncommon and is associated with fever, flank pain, urinary tract infection and nephrolithiasis. Renal infarction is characterised by severe persistent flank or abdominal pain associated with nausea or vomiting with or without elevated temperature. Cocaine-induced acute tubular necrosis may be due to acute rhabdomyolysis [75,76]. The pathophysiology of cocaine-induced rhabdomyolysis may involve ischemia, hyperthermia, direct toxicity of cocaine on muscle cells, and disseminated intravascular coagulation. In pregnancy, cocaine use may cause ARF due to abruptio placentae and preeclampsia [77]. Cocaine abuse may also cause ARF by precipitating/accelerating malignant hypertension [78] and acute interstitial nephritis (AIN) induced by cocaine intoxication [79]. The development of anti-glomerular basement membrane antibodies in cocaine addicts may be responsible for development of glomerular nephritis and acute renal failure [80,81]. Recently, Valente and co-workers employed the primary cultured human proximal tubular epithelial cells (HPTEC's) of the kidney to investigate the toxicity potential of cocaine and its metabolites such as benzoylecgonine (BE), ecgonine methyl ester (EME) and norcocaine. Cocaine is metabolized mainly by plasma and liver esterases, yielding the major metabolites BE, ecgonine and EME [82]. Anhydroecgonine methyl ester (AEME) and cocaethylene (CE) are two other metabolites known to potentiate cocaine-induced toxicity [83]. Only a minor part of cocaine is N-demethylated by the isoenzyme CYP3A, in humans, to norcocaine [84]. Norcocaine can be oxidized to N-hydroxynorcocaine and then to the free radical norcocaine nitroxide, and it has been proposed that this redox cycle may result in the production of reactive oxygen species which leads to oxidative stress [85,86]. Norcocaine is more potent than the parent compound, as it induces sig-

nificant cell death at 2.5 mm, while cocaine produces toxicity at 5 mm. The administration of ketoconazole (KTZ), CYP3A inhibitor, was shown to inhibit cocaine-induced nephrotoxicity and key role of NCOC in cocaine-induced nephrotoxicity was reported. Furthermore cocaine induced cytotoxicity was found to involve intracellular glutathione depletion at low concentrations and to induce mitochondrial damage at higher concentrations [87]. The pathophysiology in cocaine related renal injury involves changes in the glomerular matrix synthesis, changes in the renal hemodynamics and induction of renal atherogenesis [18]. The kidneys of cocaine abused patients have revealed mild mesangial expansion, interstitial fibrosis and intimal fibrosis affecting the interlobular and segmental arteries. Cocaine may enhance the renal cortical mRNA expression of tissue inhibitors of metalloproteinase-2 [17]. Accumulation of matrix along with mesangial proliferation may increase the development of the glomerulosclerosis [19,88,89]. Cocaine induced activation of the renin angiotensin system (RAS) may also be responsible for fibrosis in the mesangial tissue as angiotensin-II is well reported to stimulate the production of transforming growth factor-β, a potent fibrogenic agent [90]. Cocaine also enhances the epithelial-cell and mesangial-cell proliferation through interaction with macrophages with the key role of interleukin-6 and transforming growth factor-β [91].

The exact mechanisms of cocaine-induced renal infarction are not reported, but enhancement of platelet aggregation, thromboxane synthesis, and endothelial and vasospastic injury may contribute to renal infarction [18]. Experimental and autopsy findings confirm that cocaine is an accelerator of atherogenesis [92,93]. Cocaine increases the thromboxane production, platelet aggregation, and synthesis of collagen [94,95]. The studies have shown the arterial changes including medial thickening and luminal narrowing [96] along with severe renal arteriosclerosis in cocaine addicts [97,98]. Salcedo and Kim have shown the occurrence of renal vasoconstriction after *in utero* exposure to cocaine and noted a significantly thicker vessel wall in the renal arteries of infants and foetuses exposed to cocaine *in utero* compared with neonates and foetuses born to women who did not use cocaine during pregnancy [99]. The vasoconstrictive factors including endothelin may also be involved in the vascular changes caused by cocaine abuse [100]. Endothelin-1 (ET-1) is the major ET isoform involved in renal dysfunction, and the levels of this peptide are elevated in women with cocaine intoxication during pregnancy [101]. The increased ET-1 levels in pregnant cocaine abusers have been attributed to the ability of cocaine metabolities to stimulate ET-1 release [18]. Cocaine stimulated ET-1 release may also involve the RAS, and this response is inhibited by angiotensin converting enzyme (ACE) inhibitors [102]. Cocaine-induced vasoconstrictive changes are due to inhibition of synaptosomal uptake of catecholamines, blockade of reuptake of norepinephrine in sympathetically innervated tissues and increased release of norepinephrine and epinephrine from the adrenal medulla [18,103,104]. These vasoconstrictive and thrombotic effects of cocaine are responsible for cocaine-induced renal infarction [73]. Cocaine abuse has also been associated with an increase in oxidative stress in the kidney. The levels of intracellular glutathione, the most abundant cell thiol with antioxidant functions, are reduced in cultured kidney cells following exposure to cocaine [105].

NICOTINE

The pathological role of smoking in the development of kidney injury has been well recognized [20,106-108]. Smoking accelerates the rate of progression of renal failure to end-stage renal disease in the renal patients [107] and may elevate the risk of chronic renal injury even in the healthy population [20,108]. The harmful effects of smoking may be due to many different components of tobacco, one of them is the alkaloid nicotine which is an important component of smoking-induced renal injury [109]. The addiction potential of smoking has also been attributed to presence of nicotine and it also induces pathological changes in other organs including lung, heart and liver.

Nicotine is excreted by glomerular filtration and tubular secretion and has been found in high concentrations in the serum and the kidneys of the smokers [110]. Accordingly, the renal tubules are exposed to high levels of nicotine and its major metabolite, cotinine, which may cause direct tubular toxicity. Arany and co-workers selected a model in which cotinine concentrations stabilize at levels that are similar to those found in chronic smokers. The more salient finding of this study was that the chronic exposure to nicotine increases the severity of acute renal ischemia-reperfusion injury [21]. Tamaoki and co-workers studied the effects of nicotine on renal functions of normal and hypercholesterolemic rats and reported that nicotine reduces the inulin clearance in control rats, but not in hypercholesterolemic rats. Nicotine did not change the renal blood flow in control rats, but increased in hypercholesterolemic rats; whereas the renal vascular resistance was increased in control rats and unchanged in hypercholesterolemic rats. An impairment in renal autoregulation may explain why inulin clearance was unchanged in hypercholesterolemic rats [111]. Jaimes and co-workers reported that administration of nicotine augments glomerular injury in terms of an increase in the number of cells per glomerulus in a rat model of acute nephritis [112]. Hua and co-workers demonstrated that administration of nicotine worsens the severity of nephropathy in terms of increased urinary protein excretion (1-fold), glomerular hypertrophy, and mesangial area in diabetic mice [113]. Recently, Rezonzew and co-workers found that in rats with 5/6 nephrectomy the administration of nicotine significantly increases the urinary protein excretion, worsens the glomerular injury and increases the fibronectin, expression of NADPH oxidase 4 and transforming growth factor-β expression. Furthermore, the administration of nicotine to sham rats was reported to increase total proteinuria but not albuminuria suggesting its direct effects on tubular protein reabsorption [114]. The prenatal exposure to nicotine in rats [115] as well as its prenatal exposure to maternal cigarette smoking in humans [116] has been associated with impaired kidney growth and reduced kidney volume [117]. Prenatal exposure to nicotine leads to morphological and molecular changes in the kidneys which may contribute to foetal hypertension in genetically vulnerable individuals [23].

Smoking or chronic nicotine exposure might exacerbate acute renal injury by increasing oxidative stress [22]. Chronic exposure to nicotine increases oxidative stress in the kidney [118,119], cultured proximal tubule [120], and mesangial cells [109]. Furthermore, the *in vitro* studies have also demonstrated that H_2O_2-induced reactive oxygen species production is exacerbated upon chronic pretreatment with nicotine [21]. The critical role of oxygen free radicals

in mediating renal injury has been very well documented both in the preclinical as well as clinical studies. The possible source of nicotine-mediated ROS generation may be the NAPDPH oxidase system in cells [113].

Toledo-Rodriguez and co-workers demonstrated an increased expression of AT1b on the kidneys of offsprings of spontaneously hypertensive rats (SHR), exposed to nicotine during prenatal stage. The expression of the type AT1b subtype is mainly limited to the glomerulus where it may contribute to the regulation of renal blood flow and blood pressure [121]. DNA methylation plays an important role in regulating AT1b expression [122] and the studies suggest that nicotine may diminish DNA methylation by affecting DNA methyltransferases [123]. Accordingly, prenatal nicotine exposure induced development of foetal hypertension along with reduction in glomerular mass has been attributed to augmented AT1b expression in the kidneys in genetically vulnerable individuals. In turn, the upregulated AT1b receptors in glomerulus may induce vasoconstriction of uteroplacental vasculature followed by uteroplacental under perfusion, and consequently reduction in the flow of nutrients and oxygen to the foetus. Nicotine also suppresses maternal appetite, which may further decrease supply of nutrients to the foetus. The up-regulation of AT1b in response to prenatal exposure of nicotine in SHR has been possibly linked with up-regulation of genes in "glutamate receptor signaling" pathway involved in nervous system development and function [23].

The *in vitro* and *in vivo* treatment with nicotine-induced activation of inflammatory cascade may also be responsible for glomerular injury. The administration of nicotine significantly increases the fibronectin and COX-2 expression and mediates the mesangial cell proliferation in nephritic rats [112]. Arany and co-workers demonstrated the involvement of U-STAT3-dependent mechanism as inflammation in chronic nicotine-induced kidney injury. They reported the increased expression of U-STAT3 and levels of transforming growth factor β-1 (TGF-β1), α-smooth muscle actin (α-SMA), fibronectin, monocyte chemotactic protein-1 (MCP-1) in the ischemic kidneys of nicotine-exposed mice [124]. Rezonzew and co-workers demonstrated the role α 7-nAChR, one of the most important subunits of the nAChRs of nicotinic acetylcholine receptors (nAChRs), in nicotine-induced mesangial cell proliferation and hypertrophy by employing methyllicaconitine (α 7-nAChR blocker) [114]. An increased expression and phosphorylation of Akt in nicotine exposed diabetic mice and in human mesangial cells has also been reported suggesting that nicotine triggered Akt signalling may also be involved in renal damage [113].

CAFFEINE

Caffeine is the most important component in coffee and the concentration of this natural alkaloid is highest in coffee. Furthermore, it is also detected in tea leaves and other plants. In humans, it acts as a central nervous system stimulant and is the world's most widely consumed psychoactive drug [125]. It is known that caffeine mediates the renal natriuresis and diuresis in healthy and diseased liver through hepatorenal reflex. The hepatorenal reflex, activated by intrahepatic adenosine through A1 receptors, is involved in the regulation of urine production in healthy rats. Shirley and co-workers confirmed that a moderately high dose of caffeine causes a substantial acute increase in sodium excretion with diuresis. An increase in sodium excretion without any change in GFR indicates that the caffeine-induced natriuresis is due to the inhibition of fractional tubular reabsorption. Caffeine-induced decreased tubular reabsorption is due to its pressor effect [126,127] and increase in renal perfusion pressure leading to an increase in renal interstitial hydrostatic pressure [128]. Caffeine mediated blockade of A1-adenosine receptor [127] may also inhibit proximal tubular reabsorption [129,130]. Lee and his co-workers demonstrated the decreased expression of α-1 and β-1 subunits of Na$^+$/K$^+$-ATPase and type 3 Na$^+$/H$^+$ exchanger and increased expression of eNOS in the kidney following treatment with caffeine [131]. Nitric oxide has also been shown to inhibit both Na$^+$/H$^+$ exchange and Na$^+$/K$^+$-ATPase activity in the proximal tubules [132,133]. Caffeine mediated these changes may contribute to decreased proximal reabsorption.

Caffeine administration is associated with the rhabdomyolysis in coexisting severe hyponatremia. Kamijo and co-workers hypothesized that caffeine toxicity damages the muscle cells, which were fragile due to the potassium depletion induced by the coexisting hyponatremia to result in severe rhabdomyolysis [24]. The prolonged administration of caffeine to animals with high-renin hypertension causes progressive degradation of renal function. Tofovic and Jackson investigated the effects of long-term caffeine consumption on renal function in adult spontaneously hypertensive heart failure (SHHF/Mcc-facp) rats, (model of high-renin hypertension) and was reported that glomerular filtration rate, creatinine clearance and inulin clearance was decreased and proteinurea was increased in caffeine treated animals [134]. Caffeine consumption aggravates the renal failure in nephropathy associated with the metabolic syndrome. Tofovic and co-workers examined the renal effects of caffeine consumption and the effects of collateral antioxidant therapy in young obese, diabetic ZSF1 rats. Caffeine greatly augments the proteinuria and increases renal vascular resistance (RVR). Immunohistochemical analysis revealed significant glomerular and interstitial inflammation, proliferation, and fibrosis in control animals. Caffeine enhanced the influx of glomerular and interstitial macrophages influx, glomerular and tubular proliferative response, and glomerular collagen IV content in nephropathy associated with the metabolic syndrome. It was suggested that caffeine enhances the proteinuria and stimulates some of the key proliferative mechanisms involved in glomerular remodeling and sclerosis through the interaction with adenosine receptors and interference with anti-inflammatory and/or glomerular hemodynamic effects of adenosine [135].

Caffeine (inhibitor of phosphodiesterase) also has the potential to stimulate the progression of autosomal dominant polycystic kidney disease (ADPKD) [136-139]. ADPKD is the most common potentially lethal hereditary renal disorder in adults [140]. An increased production of cAMP in the kidney has an important role in the pathogenesis of the disease because it stimulates transepithelial secretion and accumulation of cyst fluid as well as cell proliferation [136,141]. Belibi and co-workers described that caffeine increases the production of cAMP in renal epithelial cells and contributes in the progression of ADPKD [142].

Cai and his co-workers described that caffeine, acetaminophen and salicylic acid toxic effects on the passage-1 Rat Renal Inner Medullary Collecting Duct Cells (p1rIMCD)

and effects of acetaminophen and caffeine are strongly additive. An increase in proliferation along with DNA damage and apoptosis has been observed in these cells. Caffeine alters the pathways involved in the cellular response to DNA damage. It reduces DNA damage-induced cell cycle arrest in G1, S, and G2/M, abolishes the G2/M checkpoint by inhibiting ATM kinase activity [143]. These kinases are activated by DNA damage and associated with DNA repair accompanied by cell cycle arrest [144]. Inhibition of ATM/ATR kinases by caffeine is a mechanism that might impair repair of the DNA damage. Caffeine also blocks p53 activation in response to DNA damage and blocks the repair of DNA damage caused by acetaminophen [145].

Tofovic and his co-workers investigated the chronic effects of caffeine on renal function and structure in puromycin aminonucleoside (PAN)-induced nephropathy. Caffeine consumption significantly augmented PAN-induced proteinuria after PAN injections. The injection of PAN is associated with decrease in urinary sodium excretion, development of ascites, and reduction in creatinine clearance [146]. In PAN-rats, caffeine treatment for 23 weeks significantly reduced inulin clearance, increased renal vascular resistance, potentiates the development of more severe tubulointerstitial damage and glomerulosclerosis [147].

ALCOHOL

Both acute and chronic alcohol consumption can compromise the kidney function [25] and its consumption has been shown to reduce renal function by promoting interstitial oedema and renal hypertrophy [26]. Chronic alcohol abuse increases the risk of acute renal failure (ARF) in unobstructed acute pyelonephritis [148] and also leads to development of renal papillary necrosis [149,150]. Alcohol consumption is a probable risk factor for end stage renal disease (ESRD) [27] and its chronic use has been associated with immunoglobulin A nephropathy [151], and renal papillary necrosis [150]. Alcohol consumption may potentiate the nephrotoxicity of lead [152] and antiinflammatory drugs [153]. The patients with postinfectious glomerulonephritis who consume alcohol may be at increased risk of progression to chronic renal failure [154]. Consumption of more than two alcoholic beverages per day has been associated with fourfold increase in the risk of ESRD [27]. Alcohol consumption may increase the risk of kidney failure by initiating and/or promoting atherogenic risk factors, such as high blood pressure [155,156], hyperuricemia [157], insulin resistance [158], and diabetes [159].

Alcohol inhibits the release of antidiuretic hormone (ADH), which promotes the formation of concentrated urine by inducing the kidneys to conserve fluids. In the absence of ADH, segments of the kidney's tubule system become impermeable to water, thus preventing it from being reabsorbed into the body. Under these conditions, the urine formed is dilute and electrolyte concentration in the blood simultaneously rises [25]. Gueye and his colleagues estimated the effect of alcohol dependency on renal graft and recipient survival and concluded that a history of alcohol dependency at the time of onset of ESRD is associated with shorter graft and patient survival [160]. The possible reason behind shorter graft survival is that alcohol modulates the immune system by increasing the circulating IgA levels which could be related to antibody production and dysregulation of cytokine production [161]. The prolonged use of alcohol activates the monocytes and macrophages to increase the generation of proinflammatory cytokines including TNF-α, interleukin (IL)-1, IL-6 and IL-8 [162]. In addition, chronic alcohol ingestion causes severe oxidative stress and depletion of the antioxidant glutathione [163]. The profibrotic cytokine transforming growth factor (TGF-β) has been associated with the development of chronic allograft nephropathy, which is characterized by renal graft fibrosis leading to early loss of function [164]. In the animal model, chronic alcohol ingestion has been demonstrated to increase the expression of TGF-β [165].

A study has reported that alcohol plays an important role in the onset of both acute pancreatitis and rhabdomyolysis [166]. Pezzilli and co-workers suggested that renal failure that follows acute pancreatitis is partly due to rhabdomyolysis and elevated serum concentrations of myoglobin [167]. Electrolyte abnormalities caused by alcohol intake are also important in muscle damage. Ethanol intoxication involves water-electrolyte and acid-base imbalance by excessive urinary excretion of calcium, magnesium, phosphate leading to development of metabolic acidosis, hypomagnesemia, hypocalcaemia and hypophosphatemia [168]. De Marchi and his co-workers evaluated the alcohol-induced abnormalities of renal function and assessed the relation between renal dysfunction and electrolyte imbalance. They found that the patients with chronic alcoholism have a variety of renal tubular abnormalities that occur in the presence of normal glomerular filtration and these abnormalities were reversible that disappear after four weeks of abstinence [169].

Various studies have indicated that ethanol interferes with the carrier functions of proximal tubular cells by decreasing the Na$^+$/K$^+$-ATPase activity [170-172]. The patients with chronic alcoholism have increased fractional excretion of β-2-microglobulin, urinary excretion of N-acetyl-d-glucosaminidase (a lysosomal enzyme from the proximal tubules) and alanine aminopeptidase suggesting the presence of proximal tubular defects [173,174]. Oxidation of ethanol by alcohol dehydrogenase generates acetaldehyde, and the oxidation of acetaldehyde by acetaldehyde dehydrogenase generates free radical oxygen species that are capable of damaging the cell membranes. The effect of ethanol in decreasing the Na$^+$/K$^+$-ATPase activity in the proximal tubular cells may decrease the tubular reabsorption of calcium [175]. De Marchi et al. reported the deleterious effects of prenatal exposure to ethanol on postnatal renal function [169]. The rats exposed to ethanol during foetal life had defects in potassium excretion, incomplete renal tubular acidosis, and impaired urine-concentrating ability [176,177]. Chronic alcoholism also causes acidosis due to the increased generation of keto acids [178,179] and the patients with metabolic acidosis have impaired renal acidification ability [169]. Alcohol directly affects the kidneys by altering its form and structure [25]. There is disorganisation of the proximal tubules with disorientation of microvilli and luminal casts. Some proximal tubule cells exhibit partial degeneration as evidenced by the reduced height of the cells and the presence of a prominent luminal area containing cellular debris while the other cells exhibit a large number of dense bodies in their cytoplasm. Some distal tubule cells even exhibit degeneration of their apical cytoplasm [180].

CONCLUSION

The drugs of abuse potential have been shown to induce the renal toxicity and various mechanisms have also been explored to understand the mechanisms involved in renal toxicity. However, there is a need to understand the molecular mechanisms involved in mediating renal injury, so as to establish the effective targets that may be modulated to attenuate renal toxicity.

ACKNOWLEDGEMENTS

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