Cocaine use and kidney damage

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The high frequency of cocaine abuse has been well documented. In a university population in the US 6% of adolescents were cocaine users as documented by hair analysis [1], in Switzerland about 3% of adolescents had taken heroin or cocaine at least once in their life [2]. Apart from having mood elevating properties, cocaine is capable of causing myocardial infarction, arrhythmia, sudden death, stroke, seizures, bowel necrosis, and numerous other complications [3]. The acute and chronic effects of cocaine use on other vasculatures than the kidney have been reasonably well known, the full extent of the effects of cocaine on the kidney, however, has become apparent more recently.

In the following, I discuss renal pathology induced by or associated with cocaine use.

Cocaine and rhabdomyolysis

The first reports on the association between cocaine abuse and acute renal failure were on cases with rhabdomyolysis [4,5]. This is still the most common form of cocaine-induced renal pathology. Cocaine-related rhabdomyolysis has a high mortality. The mechanism of cocaine-associated rhabdomyolysis is unclear, but potentially includes ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure. Cocaine-associated rhabdomyolysis shares many features with excited delirium. Compared with victims of fatal acute cocaine toxicity, both victims of rhabdomyolysis and fatal delirium are more likely to be black, male and younger; to have administered cocaine by smoking or injection; and to have experienced excitement, delirium, and hyperthermia; they are also less likely to have had seizures [6]. It is thought that this
syndrome is caused by changes in dopamine processing induced by chronic and intense use of cocaine rather than by the acute toxic effects of the drug. Histology shows necrosis of skeletal muscle without specific lesions [7].

**Cocaine and end-stage renal disease without rhabdomyolysis**

Several patients with accelerated or malignant hypertension have been described in whom the habitual use of cocaine appears to have hastened the development of renal failure, often requiring dialysis [8,9]. The patients had smoked cocaine for several years, often continuously, and presented with severe hypertension and renal insufficiency. Blood pressure was extremely elevated, often quite out of proportion to the degree of end organ damage and frequently quite refractory to treatment. It has also been described that scleroderma renal crisis, characterized by accelerated hypertension, rapidly progressive renal failure and hyperreninaemia can be precipitated by heavy cocaine abuse [10]. Surprisingly, hypertension may be absent on presentation and severe renal arteriolosclerosis without hypertension has been reported after cocaine use [11,12]. Apart from rare cases with renal infarction [13], antiglomerular basement membrane antibody-mediated glomerulonephritis [14] or acute interstitial nephritis [15], the mechanisms leading to renal insufficiency after cocaine abuse are at present not clear.

Hypertension was thought to be a major factor [8], especially in black patients. It was speculated that the habitual use of cocaine might worsen hypertension, make it more difficult to control, thus precipitating hypertensive crises culminating in uraemia [8]. The association of acute hypertension with cocaine use has been well documented [8,16]. The acute effects are thought to be at least partially caused by vasoconstriction, such as has been described with ergotamine, epinephrine, and amphetamine derivatives [17]. Recently it was shown, however, that there are no differences of blood pressure in black cocaine users as compared to an appropriate age matched control group (NHANES III study) [17]. It was concluded that chronic cocaine use is associated with acute but not chronic hypertension in middle-aged black males. Cocaine did not cause microalbuminuria. Thus, the discussion about the relationship between cocaine abuse and chronic hypertension is not easy. In an autopsy study of cocaine-induced cerebral haemorrhage, 88.5% of cases had hypertensive cardiovascular disease as shown by increased heart weight, left ventricular hypertrophy, and nephrosclerosis [18]. Cardiac hypertrophy can be associated with cocaine in the absence of hypertension, however [19]. Since it is known that cocaine may accelerate atherosclerosis in the aorta and coronary arteries, it has been speculated that a similar phenomenon may occur in the renal vasculature [11]. Few papers have systemically addressed the question whether chronic cocaine use directly leads to nephropathy. Barroso-Moguel et al. [20] treated male Wistar rats with an aqueous solution of cocaine hydrochloride by daily intraperitoneal injection. Renal histology showed early changes on day 15, with damage to glomerular capillary walls and swelling of tubular epithelium. After 90 days lesions had progressed to glomerular atrophy and sclerosis. The tubular epithelial cells were necrotic and sloughed, and the lumen of papillary ducts contained destroyed red blood cell casts. The interstitium had numerous foci of necrosis and haemorrhage. Most unfortunately, data on the acute and chronic effects of cocaine on blood pressure, renal function or proteinuria were not given in the paper. DiPaolo et al. [21] investigated kidneys at autopsy obtained from 40 cocaine users and made a histological comparison with kidneys from victims of automobile accidents, that were not known to have used cocaine and were race and age matched. Semi-quantitative analysis showed that the ratio of hyaline glomeruli to normal glomeruli was increased in the users as compared to the non-users (0.09, SD 0.13 and 0.005, SD 0.001 respectively). The difference was highly significant ($P<0.00005$). The increases in the dimensions of the arterial vessels such as lumen perimeter, intima perimeter, media perimeter, media and intima area as well as media thickness were also highly significant. A comparison of the histology from human autopsy material to the histology of the animal model shows little similarity.

**Cocaine exposure in utero**

The acute effects of maternal cocaine abuse on blood flow of the fetal kidney and the fetal hourly urine output were studied by Mitra et al. [22] using colour-flow mapping, pulse-wave Doppler studies and ultrasonographic biometry. The resistance index of the fetal renal artery of normal pregnancies had a negative association with gestational age ($P<0.05$). Cocaine-exposed fetuses had a significantly higher resistance index of the renal artery ($P<0.01$) than did normal fetuses of corresponding gestational ages. A decrease in the hourly urine output of cocaine-exposed fetuses was observed, compared with control fetuses of corresponding gestational ages ($P<0.01$). A retrospective study has suggested that cocaine exposure in utero leads to an increased incidence of hypospadia and an increased incidence of renal tract abnormalities [23]. Abnormalities included horseshoe kidney, unilateral abnormal small kidney, duplex kidney and renal tract dilatation. Prospective studies confirming these findings are lacking, but earlier studies in mice [24] have shown that intraperitoneal injection of cocaine may result in dilated or cystic ureters, hydronephrosis, grossly distended bladders, cryptorchidism and renal artery ablation in addition to limb reduction abnormalities, gastrointestinal atresia and cardiac abnormalities.
Conclusion

Renal abnormalities are part of the spectrum of acute and chronic cocaine toxicity. Chronic cocaine abuse may damage the kidney not only in utero, but also later in life. Rhabdomyolysis and hypertension are important pathogenetic factors, but may not be the only mediators of renal disease; accelerated renal arteriosclerosis in cocaine users may occur in the absence of hypertension. Studies in experimental animals or prospective studies in patients are surprisingly rare, so that knowledge of the relevant mechanisms and the extent of the problem is limited.

References