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Acute and delayed nephropathy due to methamphetamine abuse

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ABSTRACT

Methamphetamine is a highly addictive drug that acts as a stimulant for the central nervous system. It increases alertness and physical activity but can cause cardiac dysrhythmias, hypertension, hallucinations and violent behavior. The excretion rate of methamphetamine by the kidney can be seriously altered by urinary pH. Methamphetamine is a weak base, consequently, the proportion of the excreted amount of unchanged drug can vary from as little as 2% in alkaline (pH ≥8.0) to 76% in acidic urine (pH ≤5.0). Methamphetamine is metabolized by both hepatic metabolism and renal excretion via cytochrome P450 2D6 (CYP2D6). The effects of methamphetamine on the kidneys can be divided into the following sub-groups: vascular effects, non-traumatic rhabdomyolysis and direct nephrotoxicity. Additionally, methamphetamine directly stimulates the release of ET-1, a potent vasoconstrictor. ET-1 stimulates vasoconstriction, inflammation and fibrosis in kidney, thus promoting hypertension, atherosclerosis and chronic kidney disease.

Review

Implication for health policy/practice/research/medical education:
The effects of methamphetamine on kidneys could be divided into three sub-groups: vascular effects, non-traumatic rhabdomyolysis, and direct nephrotoxicity. Methamphetamine directly stimulates the release of endothelin 1 (ET-1) leading to vasoconstriction, inflammation and fibrosis, thus inducing hypertension, arterial sclerosis and chronic kidney disease. Acute kidney injury is also seen frequently with methamphetamine and is triggered indirectly via vascular (pre-renal) effects and rhabdomyolysis.

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Introduction

Methamphetamine, a methylated analogue of amphetamine that is more lipid soluble and more difficult to metabolize, has been applied to remedy attention deficit hyperactivity illness. Methamphetamine is a potent addictive psycho-stimulant causing insomnia and euphoria (1). Methamphetamine can be used by oral administration, intravenous injection and snorting, inhalation or smoking of the methamphetamine hydrochloride salt.

Materials and Methods

For this review, we used various sources including PubMed, directory of open access journals (DOAJ), Embase, Web of Science, Google Scholar and Scopus. The search was conducted with the following keywords or their equals; methamphetamine, rhabdomyolysis, endothelin, vasoconstrictor, acute kidney injury, chronic kidney disease, nephrotoxicity, inflammation, hypertension, hypernatremia, myoglobin, and glomerulonephritis.

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Methamphetamine in urine

The excretion rate of methamphetamine by the kidney can seriously alter according to urinary pH. Methamphetamine is a weak base and the proportion of unchanged methamphetamine excreted can alter from as little as 2% in alkaline (pH ≥8.0) to 76% in acidic urine (pH ≤5.0). Acidic urine enhances methamphetamine excretion and reduces its half-life in the body, while alkaline urine diminishes excretion and lengthens survival time in the body. Methamphetamine is distributed throughout the whole body. The absorption of methamphetamine in human is highest in the kidneys. The high accumulation of methamphetamine in kidneys could explain its high urine excretion rate (2,3).

Metabolism of methamphetamine

Methamphetamine is metabolized by both hepatic metabolism and renal excretion (Figure 1) via aromatic hydroxylation of methamphetamine by Cytochrome P450 2D6 (CYP2D6), producing primarily 4-hydroxymethamphetamine or *N*-demethylation of methamphetamine to produce amphetamine, catalyzed by CYP2D6; followed by beta-hydroxylation of amphetamine to create nor-ephedrine (4,5).

Methamphetamine and renal function and structure

The kidneys are responsible for filtering toxins from the body and excreting through the urine. In fact, the majority of illicit substances are excreted through the kidneys. Acute kidney injury is rare damage to the kidneys that causes them to not work correctly. It varies from minor loss of kidney function to complete kidney failure. The causes of acute kidney injury are commonly categorized into pre-renal, intrinsic and post-renal (7-9). Chronic kidney disease is usually caused by long-term diseases, such as hypertension or diabetes. Long-term use of illicit drugs could also cause gradual damage to kidneys and decrease their function over time.

Methamphetamine is one of the substances that is widely abused. This can disrupt the normal function of cellular and molecular systems. Several events such as oxidative stress, aging, apoptosis, necrosis and reactive oxygen species (ROS) are thought to play a role after administration of methamphetamine (7-10). Methamphetamine intoxication could be diagnosed using immunohistochemical changes in the kidney and renal function. The 70 kDa heat shock protein (HSP70), 8-hydroxy-20-deoxyguanosine (8-OHdG), 4-hydroxy-2-nonenal (4-HNE), and Cu/Zn superoxide dismutase (SOD) (8,9), malondialdehyde (MDA), catalase (CAT) activity, glutathione (GSH) and glutathione peroxidase (GPx) levels are oxidative injury related biomarkers in the kidney of methamphetamine abusers (10). The measurement of myoglobin is used to diagnose muscle injury. Additionally, tumor necrosis factor (TNF) is a pro-inflammatory cytokine and is released from the kidney in response to ischemia and reperfusion (7-10).

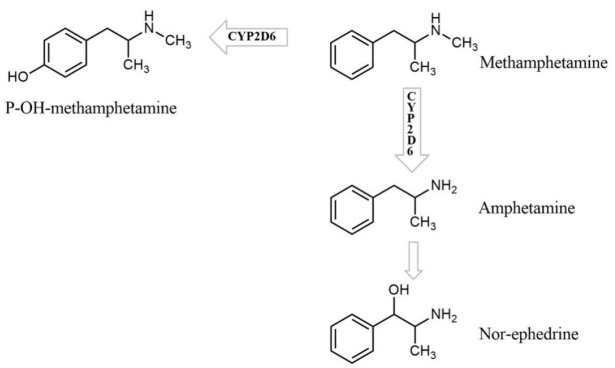

Figure 1. Main methamphetamine metabolite pathway by CYP2D6 (6).

Despite the fact that oxidative stress in kidneys is more severe than in brain and other organs (10), there are many reports about neurologic effects of methamphetamine, whereas the effects of methamphetamine on the kidney have not been paid enough attention.

The effects of 3,4-methylenedioxy-methamphetamine (MDMA) on the kidney cells are investigated by different research groups (11-13). In this review, the impact of chronic and acute methamphetamine abuse on kidney is the main objective. There are several reports regarding renal effects of this substance including renal function impairment and renal necrotizing vasculitis (14). Also there are reports suggesting serum creatinine level increase in renal transplant receivers, one year after transplantation from addicted donors (15). Additionally, effects of methamphetamine on histopathology parameters of kidney had been described (16). The effects of methamphetamine on kidneys can be classified into the following sub-groups: vascular effects, non-traumatic rhabdomyolysis and direct nephrotoxicity. These categories are discussed in further details below.

Vascular effects of methamphetamine

In a-5-year study of patient's medical history who administered methamphetamine, analysis of kidney biopsy samples revealed severe necrotizing vasculitis of arterioles and glomeruli (17). It is generally accepted that methamphetamine has potent vasoconstrictive effects, but its exact mechanism at the cellular level has not been known. Accordingly, an investigation found how methamphetamine directly stimulates the liberation of ET-1, as the most potent renal vasoconstrictor known (100-times more potent than noradrenaline), proposing an additional mechanism which methamphetamine induces vasoconstriction (18). ET-1production by

the kidney is much higher than any other organ (19). Increased production of endothelin1causes decreased renal blood flow and glomerular filtration rate (GFR) and consequently induces renal hypertension (20). In diabetic and hypertensive patients, plasma ET-1 concentrations can be increased several times compared to normal healthy individuals (21,22). The participation of ET-1 in renal function has been extensively studied (23). Two key renal actions have been recognized from these studies; (*i*) the adjustment of renal hemodynamics associated with its vascular activity and (*ii*) the variation of water and sodium secretion through its action on tubular cells. Hemodynamic changes induced by endothelin1causes a decrease in urine flow and sodium secretion. Regional production of endothelin1in tubular cells is adjusted by the osmolar condition and thus produces reverse effects leading to diuresis and natriuresis (hypernatremia). Many researchers have focused on the effects of ET-1 on the kidneys. But so far, there has been no study of the adverse effects of METH –induce renal insufficiency with ET-1. Vasoconstriction induced by methamphetamine results in major life-threatening complications as discussed below.

Hypertension as the side effect of methamphetamine

Methamphetamine indirectly increases blood pressure by constriction of blood vessels. It is important to identify that METH-induced hypertension is because of a hyper-adrenergic state (24,25). This hyper-adrenergic state triggers both α-adrenoceptors (mediating peripheral vasoconstriction) and β2-adrenoreceptors (mediating peripheral vasodilation). Additionally, ET-1 prompts the creation of angiotensin II (vasoconstrictor) through escalating the activity of angiotensin-converting enzyme (26,27), a main factor of hypertension.

Hypertension is a prevalent co-morbidity associated with chronic kidney disease. Hypertension is an important cause of chronic kidney disease too and plays a significant role in its progression. Also, hypertension is highly prevalent in chronic kidney disease patients, which, if uncontrolled, results in high risk of cardiovascular injury and death. Methamphetamine abuse can cause hypertension which is followed by chronic kidney disease.

Ischemia and hypoxia induced by methamphetamine

Vascular ischemia includes disruption of the arterial blood flow to tissue. Amphetamines have vasoconstrictive properties that force the kidneys to ischemia or hypoxia (28). ET-1is assumed to contribute to the pathogenesis of ischemia-reperfusion induced acute kidney injury (24). Intestinal ischemia or diminished blood flow to the small bowels can also be a result of methamphetamine administration. Amphetamine and methamphetamine can prompt progressive necrotizing vasculitis in different organs, including renal and gastrointestinal systems. There are few case reports of intestinal ischemia or infarction associated with methamphetamine abuse, which is suggested to be caused mainly by vasoconstriction and vasculitis (29,30). Hemodynamic instability may result in pre-renal acute kidney injury due to blood volume deficiency (hypovolemia) and, if continued and severe, can result in ischemic acute kidney injury (20,31).

Hyperthermia caused by methamphetamine

Hyperthermia by methamphetamine can produce indirect adverse effects on kidney due to damage to renal vasculature (32). Methamphetamine limits heat distribution to the external environment and potentiates body hyperthermia especially when injected intravenously. Hyperthermia enhances methamphetamine toxicity directly through disorder of protein function, ion channels and enhanced ROS production. Hyperthermia can lead to rhabdomyolysis, the breakdown of muscle tissue, hypotension, disseminated intravascular coagulation, and acute kidney injury.

Dysnatremia

A variety of factors contribute to the development of dysnatremia. Hypernatremia and hyponatremia both occur. The two main factors are dehydration and the syndrome of inappropriate antidiuretic hormone secretion SIADH, which is prompted by methamphetamine metabolites. Methamphetamine abusers usually do not drink sufficient amounts of fluids, causing dehydration. Methamphetamine metabolites are known to increase the synaptic concentration of serotonin and dopamine, both of which are involved in the release of arginine induced vasopressin (33).

Non-traumatic rhabdomyolysis

Amphetamines are myotoxic and lead to rhabdomyolysis causing impediment of the vasculature and tubular deterioration as a result of the deposition of myoglobin (9,34). Released myoglobin damages and reduces the function of filtration in kidneys resulting in acute kidney injury or renal failure. Methamphetamine was implicated as the most prevalent cause of rhabdomyolysis in several reports (35-37). During myocyte damage, the level of free myoglobin in the plasma increases and is filtered by the kidneys. Myoglobinemia and myoglobinuria have been linked to the progress of acute kidney injury. Rhabdomyolysis induced-acute kidney injury occurs in 13% to 50% of all cases. The pathophysiology of rhabdomyolysis-induced acute kidney injury is thought to be triggered by myoglobin as the toxin causing renal failure. The major mechanisms in which myoglobin causes renal failure are renal vasoconstriction and tubular

obstruction leading to lipid peroxidation and tubular damage. Recently, most reports state free iron-mediated formation of hydroxyl radicals (Fenton reactions) as the pathway starting lipid peroxidation. Alkaline conditions prevent myoglobin-induced lipid peroxidation by stabilizing the reactive ferryl myoglobin complex (38). In the acidic environment and hypovolemia, myoglobin reacts with Tamm-Horsfall protein and precipitates into tubules, which may then impede tubular flow (post-renal obstruction at tubular level).

Also, secretion of myoglobin causes increase concentrations of plasma ET-1. It is concluded that ET-1is at least partially, contributing to the significant tubular cell injury detected in myoglobinuric nephropathy (39).

Direct nephrotoxicity

While the effect of methamphetamine exposure on the transplanted kidney is not identified, there is rising confirmation in support of short and long-term renal dysfunction with acute or prolonged methamphetamine use. Clearly, it seems likely that donor kidneys from methamphetamine users are compromised and lead to reduced renal function in the transplant (18). In the situation of severe acute intoxication, methamphetamine exposure can provoke acute kidney injury with later improvement or cause chronic kidney disease needing dialysis. The effect of chronic methamphetamine exposure is, however, less established.

Intravenous amphetamine and methamphetamine use is known to cause acute kidney injury rarely due to acute interstitial nephritis (AIN) in the absence of any vascular or glomerular damage. In the studies by Foley et al (40) and Raju et al (41), direct effects of the amphetamine and methamphetamine are causes of AIN with negative test for myoglobin (the absence of muscle damage and any glomerular or vascular injury). Additionally, from renal biopsies performed in Cape Town patients who had been abusing with methamphetamine, almost 60% showed mesangiocapillary glomerulonephritis type 1. However, it is not known how methamphetamine causes lesions resembling mesangiocapillary glomerulonephritis (42). Conventional in-vivo evidence suggests that ET-1 functions as a mitogen in mesangiocapillary glomerulonephritis. The kidney is more sensitive to exogenous ET-1 as compared to all other organs. ET-1 stimulates vasoconstriction, inflammation and fibrosis, thereby promoting hypertension, atherosclerosis and chronic kidney disease. Increased urinary ET-1 secretion is related to a higher degree of renal failure and glomerular sclerosis (43,44). Furthermore, recent investigations show that administration of the ET-1antagonist reduced renal tissue damages and lead to improved kidney function (45,46). Similarly, N-acetylcysteine amide and caffeic acid are as recognized therapeutic drugs to protect tissue against METH-induced toxicity (12,13).

Conclusion

The effects of methamphetamine on the kidneys can be divided into three sub-groups: vascular effects, non-traumatic rhabdomyolysis and direct nephrotoxicity. Additionally, investigations have demonstrated that methamphetamine directly stimulates the release of ET-1. ET-1 stimulates vasoconstriction, inflammation and fibrosis, thus inducing hypertension, arterial sclerosis and chronic kidney disease. Frequently, effect of methamphetamine on kidney is indirect via vascular (pre-renal) effects and rhabdomyolysis. Direct effect of the methamphetamine on kidney (AIN) is rarely reported. Donor kidneys from methamphetamine abusers should be carefully assessed before transplanting.

Authors' contribution

xx and xxx searched the data and prepared the draft of the manuscript. FG edited and finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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