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Review article

Vascular disease in cocaine addiction

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ABSTRACT

Cocaine, a powerful vasoconstrictor, induces immune responses including cytokine elevations. Chronic cocaine use is associated with functional brain impairments potentially mediated by vascular pathology. Although the Crack-Cocaine epidemic has declined, its vascular consequences are increasingly becoming evident among individuals with cocaine use disorder of that period, now aging. Paradoxically, during the period when prevention efforts could make a difference, this population receives psychosocial treatment at best.

We review major postmortem and *in vitro* studies documenting cocaine-induced vascular toxicity. PubMed and Academic Search Complete were used with relevant terms.

Findings consist of the major mechanisms of cocaine-induced vasoconstriction, endothelial dysfunction, and accelerated atherosclerosis, emphasizing acute, chronic, and secondary effects of cocaine. The etiology underlying cocaine's acute and chronic vascular effects is multifactorial, spanning hypertension, impaired homeostasis and platelet function, thrombosis, thromboembolism, and alterations in blood flow. Early detection of vascular disease in cocaine addiction by multimodality imaging is discussed. Treatment may be similar to indications in patients with traditional risk-factors, with few exceptions such as enhanced supportive care and use of benzodiazepines and phentolamine for sedation, and avoiding β-blockers.

Given the vascular toxicity cocaine induces, further compounded by smoking and alcohol comorbidity, and interacting with aging of the crack generation, there is a public health imperative to identify pre-symptomatic markers of vascular impairments in cocaine addiction and employ preventive treatment to reduce silent disease progression.

1. Phenomenology contributing to vascular damage

Cocaine, compared to other illicit drugs, poses a particular risk for vascular disease and is most involved in emergency room visits (40.3%), with highest rates for men aged 35–44 years, amounting to a vast social and economic burden [1]. Cocaine-induced damage to the cardiovascular and cerebrovascular systems is widely reported, and is linked with hypertension, tachycardia, ventricular arrhythmias [2], myocardial infarction [3,4], stroke [4,5], resulting in severe functional impairments or sudden mortality [6–10].

Vast efforts are geared toward psychosocial rehabilitation of cocaine use disorder (CUD). However, the accelerated development of vascular disease remains mostly undetected and asymptomatic presentation of vascular pathology in CUD results in silent disease progression.

"Crack-Cocaine" was introduced in the mid-1980s involving a new route of administration, smoking (as opposed to sniffing), which enhances vascular toxicity. Furthermore, the phenomenology of CUD consists of repeated drug use leading to tolerance, withdrawal, and compulsive drug-seeking behavior with inability to abstain, despite adverse effects to medical, social and occupational functioning. Underlying this addiction is CUD's association with abnormal brain morphology [11] and function involving inefficiencies in circuits that coordinate reward and self-control

Abbreviations: CUD, cocaine use disorder; MRI, magnetic resonance imaging; PET, positron emission tomography; CT, computed tomography; CBF, cerebral blood flow; 18F-FDG, 18F-fluorodeoxyglucose.

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processes [12].

Despite advances in characterization of addiction, knowledge about the contribution of vascular aging to brain impairments in human CUD is scarce. We review the mechanisms underlying the vascular damage associated with cocaine use and possible treatment directions.

2. Search strategy

We present the main mechanisms of acute and chronic cocaine-induced toxicity on vessels, brain and heart (Fig. 1) and the common vascular and systemic effects of cocaine use in humans (Fig. 2). Particular attention was given to the imaging studies that measured cocaine-induced changes to the human heart, brain, and arteries (Table 1), since these methods are gaining a central role as markers of inflammatory disease. Review methodology included search in two electronic databases (PubMed and Academic Search Complete) using relevant search terms (cocaine, inflammation, cardiovascular, cerebrovascular, carotid artery, MRI, magnetic resonance spectroscopy, PET, CT, and ultrasound) from 1978 to 2017; results are presented in Table 1 and Fig. 2. Major findings in circulating pathology are noted as well.

3. Pharmacodynamics of cocaine

Cocaine's main vasoactive metabolite benzoylmethylecgonine, a tropane alkaloid, is a sodium channel blocker, which produces enhanced sympathetic activity at low doses [13,14] (Fig. 1, center box). At high doses, cocaine is markedly more dangerous than other central nervous system stimulants, including amphetamines [15], and can cause sudden cardiac death through its effect on sodium channels and local anesthetic actions [13,14,16]. Cocaine crosses the blood–brain-barrier perhaps better than other psychoactive chemicals and may even induce its breakdown [17,18]. In addition, cocaine blocks reuptake of catecholamines in the presynaptic neurons in the central and peripheral nervous systems, resulting in increased catecholamines, sympathetic output and stimulation [2,19]. There is also evidence that the cardiovascular actions of cocaine are mediated in part by dopamine [20], via central and peripheral mechanisms [21]. Stimulation of dopamine cells in the ventral tagmental area increases blood pressure and this effect is antagonized by the dopamine D2 receptor blockers [22].

4. Acute effects of cocaine

Cocaine's acute hematological effects on the vessel (Fig. 1, upper box) [10,23,24] center on the loss of the endothelium's protective functions, a common denominator in the pathogenesis of ischemic vascular disease [35,36]. Cocaine releases endothelin-1[45], which is found to be elevated in CUD and declines with detoxification [36,46,47]. When vessels are stressed, endothelin-1 (a vasoconstrictor protein produced by vascular endothelial cells) is elevated and nitric oxide (a blood vessel dilator) decreases, leading to vasoconstriction [35,36]. It was recently demonstrated that cocaine

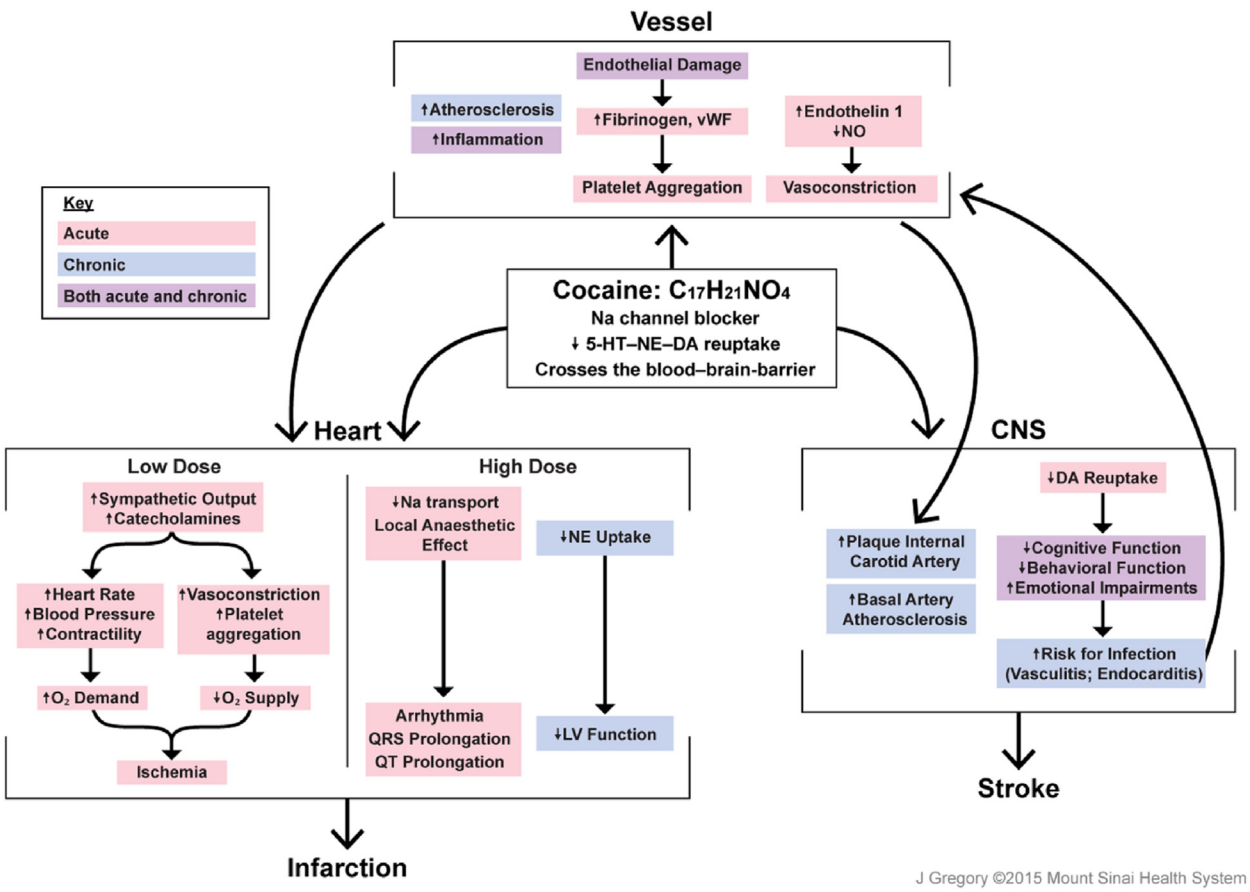

Fig. 1. Cocaine's acute and chronic toxicity mechanisms.
Cocaine's acute and chronic toxicity mechanisms on the vessel, heart, and the central nervous system (CNS), and their interactions. Carbon (C). Hydrogen (H). Nitrogen (N). Oxygen (O). Sodium (Na). Serotonin (5-HT). Norepinephrine (NE). Dopamine (DA). Nitric oxide (NO). Von Willebrand factor (vWF). Dioxygen (O_2). Left ventricular (LV). Heart mechanisms adapted from Ref. [13]; figure based on following references [2,5,6,10,13,15–19,23–44].

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