Oxidative Stress and Cocaine Intoxication as Start Points in the Pathology of Cocaine-Induced Cardiotoxicity. A Systematic Review

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Abstract

**Background:** Psychomotor stimulants are the most commonly used prohibited substances after cannabis. Globally, their use reaching epidemiological proportions and is one of the most common causes of death in many countries. In recent years, more research, define drug use as the leading cause of serious cardiovascular pathologies ranging from abnormal heart rhythms to heart attack and sudden cardiac death. The reactive oxygen species generation, toxic metabolites formation and oxidative stress play a significant role in cocaine-induced cardiotoxicity.

**Main body:** In the present review, we discuss various studies related to dopamine neurotransmission and oxidative stress, with a focus on the cardiotoxicity of the cocaine molecule and the cardiovascular complications that occur after cocaine use.

**Conclusion:** Hypothetically, this study can serve as a basis for developing a rapid and effective method for determining oxidative stress levels by monitoring changes in the redox status of patients with cocaine intoxication.

**Background**

Cocaine, together with amphetamine and its analogues, belongs to the group of psychomotor stimulants with different pharmacological and pathophysiological properties and with a well-described synergy between them [Howell and Kimmel 2008]. Despite the wide range of serious medical consequences, the effects that stimulants have on the brain make them one of the most widely used illicit substances worldwide [Ciccarone 2011]. The effect of various drugs on dopamine regulation and the role of the dopamine molecule in the development of drug dependence and addiction have been well studied. As a central nervous system (CNS) stimulant, cocaine causes a feeling of euphoria, increased motor activity, and a reduced feeling of fatigue and hunger [Klimas 2012]. In response, leads to addiction and dependence develop, leading to chronic use, and increases the risk of damage to the whole organism [Phillips et al. 2009]. In addition to its effects on the CNS, its use can lead to significant cardiovascular complications and sudden cardiac death (SCD). SCD is characterized as a dynamic event and represents the sudden and unexpected death of cardiac etiology. It is defined as a sudden, unexpected pulseless condition, usually occurs within $≤ 1$ h of the onset of symptoms, and is often due to cardiac arrhythmia [Zipes and Wellens 2000; Chugh et al. 2008].

The drug seriously affects the cardiovascular system by directly participating in increasing sympathetic stimulation and causing excessive catecholamines secretion. Moreover, it indirectly exerts its cardiotoxic effect on the heart muscle by inducing acute or chronic cardiovascular damage. Cocaine exposure is potentially associated with structural and functional changes in cardiomyocytes, as evidenced by several clinical manifestations of cardiomyopathy and congestive heart failure [Yeo et al. 2007]. Acute intoxication and chronic administration cause pathological changes throughout the cardiovascular system, and cocaine-induced cardiotoxicity can lead to various structural and functional damage to
cardiac tissue [Kim and Park 2019]. Depending on the dose and the presence of concomitant cardiovascular disease, the clinical effects vary widely and include vasoconstriction, arrhythmia, tachycardia, aortic dissection, heart attack, myocardial ischemia, etc. [Ghuran and Nolan 2000]. Not only are the harmful effects of cocaine well-known, but also those of its metabolites [Reese 1984], which can cause serious and irreversible damage to the entire cardiovascular system [Schindler et al. 1995].

Cocaine exerts its toxicity on the human body by generating ROS, such as hydrogen peroxide, hydroperoxides, alkyl peroxides, superoxide, hydroxyl, and others [Kovacic 2005]. Therefore, ROS production and oxidative damage are considered a major factor in cocaine-induced cardiotoxicity [Cerretani et al. 2012] and are a leading cause in the pathogenesis of cardiovascular damage [Graziani et al. 2016].

In this review, we examine the detrimental effects of cocaine and its metabolites on the cardiovascular system. Moreover, we accent on the role of OS in the pathology of cocaine-induced cardiotoxicity. The review aims to develop methods for diagnosing acute and chronic cocaine toxicity by determining OS levels in biological samples used mainly in emergency medicine and toxicology clinics.

**Main Text**

**Methods**

To ensure the accuracy and completeness of this systematic review, we searched for relevant scientific articles in PubMed, Academic Search Complete, and Scopus. An in-depth analysis of the English scientific literature in the period from 1983 to 2019 inclusive was conducted, which contains in its titles the keywords "drug, cocaine, neurotransmitters, cardiotoxicity, oxidative stress, sudden cardiac death" and managed to include studies according to PRISMA guidelines [Moher et al. 2009]. Over 1000 clinical, laboratory, epidemiological studies and literature reviews related to stimulant use and cocaine-induced cardiotoxicity were studied, from which we selected 80 articles directly related to our topic.

**Cocaine action of brain system**

Cocaine belongs to the group of psychomotor stimulants and is considered one of the most addictive drugs. Its narcotic effect consists of increasing extracellular dopamine (DA), and dopamine dysregulation underlies the addictive behavior [Ashok et al. 2017]. The mechanism involves inhibition of dopamine reuptake in the CNS [Ghuran and Nolan 2000]. The cocaine molecule acts on the presynaptic transporters of monoamines and facilitates the activity of the monoamine neurotransmitters dopamine, norepinephrine (NE), and serotonin (SE), in the central (CNS) and peripheral nervous system [Afonso et al. 2007; Howell and Kimmel 2008]. Depending on the stimulant, the pathophysiological mechanisms of drug action include direct toxicity, neurohormonal activation, altered calcium homeostasis, and oxidative stress. There are three main brain systems involved in drug reward - dopamine, opioid, and γ-amino butyric acid/aminobutyric acid receptor (γ-GABA/GABA). Therefore, reward systems for the brain have a multidetermined neuropharmacological basis with separate neurochemical processes involving different,
albeit overlapping, neuroanatomical patterns [Koob 1992]. Experimental data show that the Nucleus accumbens septi (limbic region) and the dorsal caudal nucleus are the two main target areas in CSN in which increases in extracellular concentrations of DA are observed [Di Chiara and Imperato 1988]. In addition to the limbic region, stimulants exert their effects on the brain by increasing the release of norepinephrine in the prefrontal cortex [Dela Peña et al. 2015].

**Dopamine transporter - the main target of stimulants**

The main target of cocaine in the human body is the dopamine transporter (DAT). Cocaine blocks the action of the transporter, preventing the DA absorption in the CNS and thus allows its accumulation at the synapse. Initially, the pharmacological effect it exerted was DAT blockade, followed by an increase in DA concentration and dopamine receptors activation [Volkow et al. 2004]. Through a synaptic mechanism, the drug directly amplifies the mesolimbic dopaminergic signal at the DA receptor, increasing synaptic dopaminergic concentrations and thus mediating certain behavioral effects [Adinoff 2004]. Dopamine accumulates in the synaptic cleft and causes increased activity of postsynaptic receptors and elicits an enhanced response in the host cell (Figure 1) [Fowler et al. 2007]. In cocaine users, catecholamines can be increased up to 5 times [Ghuran and Nolan 2000]. Retention of the cocaine molecule by DAT leads to overstimulation of dopaminergic neurons and excessive synaptic metabolism of the neurotransmitter [Dackis and Gold 1985]. Increasing the DA absolute concentration at the synapse and the time interval in which the neurotransmitter remains at the site of the postsynaptic receptor disturbs the balance between the release of DA and the reuptake of the dopamine molecule [Adinoff 2004]. The sympathomimetic effects of cocaine are manifested not only by the binding of the cocaine molecule to the dopamine transporter, but also to the serotonin (SERTPR) and norepinephrine transporter (NET). Increases sympathetic stimulation, which causes vasoconstriction, hypertension, and increased myocardial oxygen demand [Heard et al. 2008]. Cocaine inhibits the reuptake of the monoamine neurotransmitter 5-hydroxytryptamine (5-HT) by blocking the action of SERTPR, increases the secretion of adrenaline and noradrenaline from the adrenal cortex, which enhances the effect of norepinephrine. As a result, sustained, supraphysiological extracellular levels of various catecholamines have been observed [Grewen et al. 2014], which defines the drug as a potent sympathomimetic agent with a direct cardiotoxic effect [Pramanik and Vidua 2018].

Especially important for the drugs amplified effects is the way they are administered (intravenous, intranasal and smoking). Volkow et al. determine the rate at which cocaine enters the brain as a key parameter in its effectiveness in blocking DAT. Using [11C]-labeled cocaine and positron emission tomography (PET), they found significant blockade of the dopamine transporter in all modes of cocaine administration. A dose-dependent effect was observed with intravenous and intranasal administration, but not with cocaine smoking [Volkow et al. 2000]. Its rapid absorption by the brain leads to rapid changes in DA levels. Moreover, for the enhancing properties of the drug, the involvement of a “phasic” dopamine firing is particularly important, which is characterized by sharp fluctuations in neurotransmitter levels [Grace 2000]. Like cocaine, amphetamine (AMPH) acts on DAT by activating the mesolimbic dopaminergic pathway. The mechanism involves an increase in extracellular dopamine and prolongation
of DA-receptor signaling in the striatum [Calipari and Ferris 2013]. Both cocaine and amphetamines increase the time interval in which DA remains at the postsynaptic receptor [Adinoff 2004].

Cocaine works mainly by blocking the dopamine transporter, while amphetamine competitively prevents the reuptake of dopamine by the DAT. It is assumed that the action of methylphenylamine also depends on its concentration; what’s more the dose is crucial for determining the effects of abuse of amphetamine and/or its analogues. Thus, at low concentrations, AMPH acts primarily as a DAT blocker, while high concentrations increase and promote DAT-mediated back transport of dopamine from the cytoplasm to the synaptic cleft [Ashok et al. 2017; Fleckenstein et al. 2007].

Effects of stimulants on the cardiovascular system Cocaine-related sudden cardiac death

The heart muscle is one of the main targets of many drugs and various chemicals, and cardiovascular diseases (CVDs) are the leading cause of death worldwide. Various cardiovascular pathologies are directly dependent on constant drug intake [Bachi et al. 2017] and characterized by complex heterogeneous pathophysiological mechanisms [Senoner and Dichl 2019]. Stimulant abuse is a major cause of new or exacerbation of pre-existing cardiac pathology, which increases morbidity and mortality in general [Rangel et al. 2014]. Cocaine is a very powerful biologically active molecule that affects various cellular receptors and entire systems, which is why cocaine intoxication is one of the most common causes of various cardiovascular events, such as myocardial infarction. Furthermore, cocaine causes some severe complications, and its cardiotoxic effects are associated with the development of cardiac contractile dysfunction, high blood pressure [Ghuran and Nolan 2000], tachycardia, arrhythmia [Afonso et al. 2007] and sudden cardiac death (SCD) [Zaitsu et al. 2016]. Its use can lead to myocardial infarction, causing vasoconstriction of the coronary artery [Darke et al. 2006]. Hemorrhagic stroke, infective endocarditis, myocarditis, acute pulmonary edema, and aortic dissection are common side effects associated with hypertension in cocaine addicts [Schwartz et al. 2010]. The sudden rise in blood pressure and weakening of the vessel wall leads to local dilation of blood vessels (arteries or veins), which can cause aneurysms [Bolla et al. 1998]. Smoking crack or cocaine causes the drug accumulation in the heart tissue and causes acute cardiotoxicity directly affecting the myocardium [Volkow et al. 1996]. The pathophysiology of cocaine-related myocardial ischemia and infarction involves one or a combination of several factors. On the one hand, increasing heart rate, blood pressure and contractility increase the need for oxygen in the myocardium. On the other hand, the supply of oxygen to the myocardium is insufficient, as a result of which its balance in the myocardial tissue is disturbed [Schwartz 2010]. Another mechanism characteristic of cocaine cardiotoxicity involves conduction disturbances [Crumb and Clarkson 1990]. Blocking sodium channels and increasing calcium flow with a subsequent vasoconstrictor reaction is thought to be one of the leading mechanisms of cocaine cardiotoxicity [Kloner et al. 1992]. By affecting myocardial electrical impulses, there is an increase in the contractility and electrical conductivity of cardiomyocytes [Ghuran and Nolan 2000] as well as a change in cardiac conduction [Schwartz et al. 2010]. At low doses, cocaine blocks sodium channels and produces enhanced sympathomimetic activity. Due to its direct effects on cardiac ion channels, inhibition of I – type calcium current Ca$^{2+}$ delayed rectifier potassium (K) currents, and sodium (Na) current in
cardiomyocytes has been observed. This leads to increased PR, QRS and QT intervals and disruption of the coordinated electrical activity of the heart [O'Leary and Hancox 2010]. Inactivation of the sodium and potassium channels by cocaine results in decreased myocardial contractility, intracardiac conduction delay, and myocardial suppression. Prolongation of the cardiac ventricular depolarization period leads to reentrant arrhythmia and reduced left ventricular ejection fraction [Pramanik and Vidua 2018]. Thus, the drug exerts direct toxicity on the heart muscle, which is associated with arrhythmias, due to secondary blockade of sodium channels and elevated levels of norepinephrine [Lange and Hillis 2001]. Besides, circulating catecholamines effect on the coronary vasculature as vasoconstrictors and can cause ischemia and myocardial infarction (MI) [Isner and Chokshi 1991]. Cocaine use has also been associated with a large rapid and transient increase in the risk of acute myocardial infarction in patients who are otherwise at relatively low risk [Mittleman et al. 1999]. Chronic cocaine use causes irreversible structural damage to the heart, including arterial endothelial damage, vascular damage, and progression of atherosclerosis [Minor et al. 1991]. Individuals with an initially low risk of atherosclerosis, cocaine use led to sudden death in 76% of cases. The mechanism involves thrombus formation due to increased platelet aggregation at sites of atherosclerotic narrowing and enhanced coronary arterial vasoconstriction [Richard et al. 2010]. Therefore, chronic drug use and subsequent left ventricular hypertrophy are considered to be the leading cause of myocarditis, dilated cardiomyopathy, and heart failure [Phillips et al. 2009]. Forty-three percent of emergency room visits are associated with cocaine use, with the highest percentage of male users between the ages of 35 and 44 [Abuse 2017]. Mortality associated with cocaine use is also common in 30-year-old men and most commonly occurs at home and on weekends [McCord et al. 2008].

Metabolites of cocaine with expressed cardiotoxicity

Cocaine is metabolized mainly in two different ways. The main chemical reactions to cocaine that produce toxic metabolites include hydrolysis and decarboxylation. Of greater importance for the toxic manifestations and reactions of the drug is the oxidation pathway, which involves electron transfer, as a result of which free radicals are generated. The metabolites involved in this mechanism are norcocaine, norcocaine nitrooxide, N-hydroxynorcocaine, norcocaine nitrosonium, cocaine iminium [Kovacic 2005]. Besides, highly toxic formaldehyde is formed at a significant rate [Dahl and Hadley 1983]. Benzoylecgonine and ecgonine methyl ester are the two major metabolites known to cause hypertension [Pramanik and Vidua 2018]. Benzoylecgonine can be detected in the urine for 1 to 2 days after intravenous administration of 20 mg of cocaine and 2 to 3 days at a higher dose administered intranasal. In chronic users, the maximum time for detection of benzoylecgonine in urine is 22 days after the last use [Verstraete 2004]. Norcacaine, a metabolite known for its vasoconstrictive effects, has also been shown to be highly cardiotoxic [Kovacic et al. 1988; Zheng et al. 2019].

Intravenous administration of norcocaine to rats at a dose of 1 mg/kg caused a decrease in heart rate and an increase in plasma adrenaline levels. This suggests that cocaine –like norcocaine may be implicated in cocaine cardiovascular toxicity [Mahlakaarto et al. 1998]. Ecgonine is detected in the urine [Fish and Wilson 1969] up to 8 days after a single dose [Rezkalla and Kloner 2007]. The metabolites
Egonine methyl ester and norcocaine can remain in the blood for up to 1-2 weeks [Johanson and Fischman 1989]. Ecgonine and benzoylecgonine are used as markers for cocaine use in forensic practice [Reese 1984].

Countless interactions have been reported between cocaine, alcohol and other substances. The drug transesterification in the presence of ethanol (EtOH) results in the formation of a potent pharmacologically active metabolite cocaethylene (ethylbenzoylecgonine) (Figure 2) [Bencharit et al. 2003], which shows direct cardiotoxicity, with a proven high risk of heart attack [Farooq et al. 2009]. Ethanol enhances and prolongs the effects of cocaine on the cardiovascular system, and the combination of cocaine and ethanol is more cardiotoxic than any other. Their combination significantly increases heart rate and can lead to myocardial depression, decreased coronary arterial blood flow, dysrhythmias, and sudden cardiac death, probably due to cocaethylene toxicity [Henning et al. 1994]. Concomitant use of cocaine and nicotine significantly exacerbates the harmful effects of the drug on the heart by disrupting the supply of oxygen to the myocardium by potentiating coronary arterial vasoconstriction [Moliterno et al. 1994]. Cocaine has been reported as a strong vasoconstrictor and can be detected in the blood and urine even 4 days after use. The time to peak blood concentration varies and depends on the route of administration (smoking, oral administration, nasal inhalation and intravenous injection). When smoking or intravenously injected, the maximum concentration of the drug is reached from 1 to 5 minutes, and orally between 60-90 minutes [De Giorgi et al. 2012]. The time to peak subjective effect of cocaine averaged 14.6 minutes after insufflation compared with 3.1 minutes after injection [Ciccarone 2011].

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**Free radicals, oxidative stress, mitochondrial dysfunction, and cocaine-induced cardiovascular toxicity**

Oxidative stress (OS) occurs when the production of reactive oxygen and nitrogen exceeds the antioxidant defense systems of cells [Ye et al. 2015]. Important sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) include enzymatic reactions involving cytochrome P450 enzymes,
NAD(P)H oxidase (NOX), myeloperoxidase, and eosinophil peroxidase [Graziani et al. 2016]. For example, neutrophil type NAD(P)H oxidases are a major ROS source in cardiovascular cells and are involved in the production of superoxide radical (O$_2^\cdot$) in cardiac myocytes in cases of hypoxia or myocardial infarction and play an important role in angiotensin II-induced cardiac hypertrophy [Moritz et al. 2003]. As a result of an imbalance between the generation and elimination of ROS and RNS, changes in redox homeostasis are achieved [Uys et al. 2014].

In recent years, there have been increasing scientific reports of cocaine-induced cardiac dysfunction as a result of nitrosative/oxidative stress after cocaine use and mitochondrial dysfunction as a result of oxidative damage to cellular structures [Kovacic P 2005; Fan et al. 2009; Cerretani et al. 2012; Stankowski et al. 2015]. Cocaine directly inhibits the mitochondrial electron transport chain by increasing intramitochondrial Ca$^{2+}$ overload and depleting adenosine triphosphate (ATP) production. High levels of catecholamines disrupt calcium homeostasis and increase the activity of NAD(P)H oxidase and xanthine oxidase. As a result, additional amounts of ROS and RNS are generated in the mitochondria, which cause mitochondrial dysfunction. As additional sources of ROS with high cardiotoxicity, various aminochromes (adrenochromes, dopachrome, and noradrenochrome) are mentioned, which are produced during the catabolism of catecholamines [Graziani et al. 2017]. High ROS levels damage cellular macromolecules (DNA, lipids, and proteins) and adversely affect myocardial calcium function, causing arrhythmias, increasing cardiac remodeling, and leading to hypertension, necrosis, and apoptosis [Senoner and Dichtl 2019]. Lipid peroxidation is a major cause of myocardial membrane phospholipid damage and leads to glutathione depletion in chronic cocaine use [Frustaci et al. 2015]. Lipid peroxidation is a major cause of myocardial membrane phospholipid damage and leads to glutathione depletion in chronic cocaine use [Frustaci et al. 2015]. Cardiac oxidative stress after cocaine use is a precursor to cocaine-induced apoptosis in cardiomyocytes, leading to cardiovascular pathologies such as cardiac ischemia-reperfusion [Zorov et al. 2000]. Calcium and OS overload cause cardiomyocyte death in both the apoptotic and necrotic pathways. In cell line studies, ROS was found to have a primarily direct effect on cardiac cells by activating mitogen-activated protein kinase (MAPK) and NOX2. These results in acute myocardial oxidative stress, oxidative damage to cardiomyocytes, and cell death in a mouse model [Fan et al. 2009].

The first mechanism is the activation of the MAPK-beta-adrenergic receptor after calcium overload and subsequent phosphorylation of multitude calcium-containing cyclic proteins. The second mechanism is based on the redox cycle and takes place in the mitochondria. [Liaudet et al. 2014]. In addition to the relationship between oxidative stress and the generation of free radicals in oxidative myocardial damage, special attention is paid to the compromise of the antioxidant defense system of the heart in the pathogenesis of cardiotoxicity in the administration of illicit substance [Liaudet et al. 2014; Frustaci et al. 2015]. By ROS generation, cocaine severely compromised the antioxidant defense system in the heart by depleting non-enzymatic antioxidants such as glutathione in the myocardium. This thesis is confirmed by the study of Turillazzi et al. They reported depletion of the antioxidant reserve expressed in the GSH/GSSG ratio, and decreased ascorbic acid (AA) levels, and increased MDA concentrations in myocardial cells [Turillazzi et al. 2017]. Due to the strong cardiotoxicity of the cocaine molecule as a
result of oxidative stress elevated levels, compromised antioxidant defense system in cells, oxidative damage to cell structures and myocardial tissue as a whole is observed.

**Reactive oxygen species as a result of dopamine transmission**

Cocaine cardiotoxicity involves various direct and indirect mechanisms such as blockage of sodium, and potassium channels and altered calcium flow across the myocyte cell membrane and inhibition of reuptake and increased levels of the neurotransmitters dopamine, and norepinephrine. Acute toxicity and drug dependence have been associated with impaired energy and amino acid metabolism, oxidative stress increased levels, and altered dopamine neurotransmission [Womersley et al. 2019]. Elevated levels of plasma and interstitial catecholamines and generated ROS and RNS cause prolonged adrenergic stress and a series of adverse effects with significant cardiotoxicity detrimental to the cardiovascular system [Costa et al. 2011]. Cocaine exposure leads to increased oxygen radicals production, high levels of malondialdehyde MDA and nitrites in the prefrontal cortex and nucleus accumbens, oxidation of macromolecules and oxidative damage to the brain. An in vivo study in rats showed a significant increase in ROS levels, an increase in the enzymes superoxide dismutase (SOD), glutathione peroxidase and an increase in catalase activity (CAT) in the cerebral cortex and striatum [Pomierny – Chamiiołlo et al. 2013]. Oxidative stress due to drug abuse is mediated primarily by dopamine, which is why neurotransmitters are considered an important source of ROS in the brain [Kalivas and Volkow 2005]. Dopamine molecule oxidation by the enzyme monoamine oxidase produces superoxide radicals, hydrogen peroxide ($H_2O_2$) and reactive dopamine quinones [Cunha-Oliveira et al. 2013]. Enzymatic and non-enzymatic degradation of catecholamines and stimulation of adrenergic receptors generate intracellular ROS in high concentrations. As a result of oxidative stress and abundant ROS, catecholamines are transformed to aminochromes and in particular to highly toxic adrenochromes. It demonstrates direct cardiotoxicity to cardiomyocytes through disturbances in cellular Ca$^{2+}$ homeostasis and disruption of oxidative phosphorylation, including an oxidation-reduction cycle with subsequent generation of ROS [Graziani et al. 2016]. Adrenochrome, which is involved in this redox cycle, is responsible for the depletion of cellular antioxidants such as reduced ascorbate (AA) and glutathione (GSH), intracellular Ca$^{2+}$ overload, lipid peroxidation, and cardiomyocyte damage by a ROS-dependent mechanism [Fineschi et al. 2001].

**Conclusion**

Drug abuse has caused serious pathological changes and irreversible damage to the entire cardiovascular system. The picture is often complicated by the fact that people who abuse drugs often take them with other drugs and or alcohol, the combination of which can put the user in life-threatening situations. High awareness of the harmful effects of drug use, early diagnosis, knowledge of life-threatening cardiovascular conditions, and timely medical care are the main points in the successful treatment and saving of human life. Globally, deaths from stimulant use are skyrocketing. This requires additional preclinical and clinical studies to allow the development of a methodology for rapid qualitative and quantitative analysis of individuals with cocaine intoxication. As cocaine use leads to the generation
of free radicals, future methods for the analysis of acute and chronic drug intoxication should be based on changes in redox status and appropriate spin probes.

**Abbreviations**

**AA**: ascorbic acid  
**AMPH**: amphetamine  
**ATP**: adenosine triphosphate  
**CAT**: catalase  
**CNS**: central nervous system  
**CVDs**: cardiovascular diseases  
**DA**: dopamine  
**DAT**: dopamine transporter  
**DNA**: deoxyribonucleic acid  
**EPR**: electron paramagnetic resonance  
**EtOH**: ethanol  
**GSH/GSSG**: reduced/oxidized glutathione  
**GSH**: glutathione  
**MAPK**: mitogen-activated protein kinase  
**MDA**: malondialdehyde  
**MI**: myocardial infarction  
**NE**: norepinephrine  
**NET**: norepinephrine transporter  
**NOX**: nicotinamide adenine dinucleotide phosphate oxidase, NAD(P)H oxidase  
**NOX2**: nicotinamide adenine dinucleotide phosphate oxidase 2, NAD(P)H type 2  
**OS**: oxidative stress
**PET**: positron emission tomography

**RNS**: radical nitrogen spices

**ROS**: radical oxygen spices

**SCD**: sudden cardiac death

**SERT**: serotonin

**SERTPR**: serotonin transporter

**SOD**: superoxide dismutase

**γ-GABA/GABA**: γ-amino butyric acid/aminobutyric acid receptor

**5-HT**: 5-hydroxytryptamine

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Figures

Figure 1

Mechanism of cocaine-induced DAT blockade in presynaptic neurons [Fowler et al. 2007]. Cocaine binds tightly to the dopamine transporter to form a complex and interfere with normal DAT activity. It thus inhibits the reuptake of neurotransmitters from the extracellular space. The transporter is unable to perform its function, leading to increased levels of neurotransmitter in the postsynaptic space and enhanced postsynaptic transmission [Fowler et al. 2007].

Figure 2

Cocaine and major metabolites The time to detect cocaine and its metabolites in the blood, urine, saliva, sweat and hair depends on the dose, duration of use, sensitivity of the methods used, etc.