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Pathophysiological mechanisms of catecholamine and cocaine-mediated cardiotoxicity

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Abstract Overactivation of the sympatho-adrenergic system is an essential mechanism providing short-term adaptation to the stressful conditions of critical illnesses. In the same way, the administration of exogenous catecholamines is mandatory to support the failing circulation in acutely ill patients. In contrast to these short-term benefits, prolonged adrenergic stress is detrimental to the cardiovascular system by initiating a series of adverse effects triggering significant cardiotoxicity, whose pathophysiological mechanisms are complex and only partially elucidated. In addition to the development of myocardial oxygen supply/demand imbalance induced by the sustained activation of adrenergic receptors, catecholamines can damage cardiomyocytes by fostering mitochondrial dysfunction, via two main mechanisms. The first one is calcium overload, consecutive to β-adrenergic receptor-mediated activation of protein kinase A and subsequent phosphorylation of multiple Ca^{2+}-cycling proteins. The second one is oxidative stress, primarily related to the transformation of catecholamines into "aminochromes," which undergo redox cycling in mitochondria to generate copious amounts of oxygen-derived free radicals. In turn, calcium overload and oxidative stress promote mitochondrial permeability transition and cardiomyocyte cell death, both via the apoptotic and necrotic pathways. Comparable mechanisms of myocardial toxicity, including marked oxidative stress and mitochondrial dysfunction, have been reported with the use of cocaine, a common recreational drug with potent sympathomimetic activity. The aim of the current review is to present in detail the pathophysiological processes underlying the development of catecholamine and cocaine-induced cardiomyopathy, as such conditions may be frequently encountered in the clinical practice of cardiologists and ICU specialists.

Keywords Catecholamines · Cocaine · Cardiomyopathy · Oxidative stress · Mitochondria · Signaling · Heart failure

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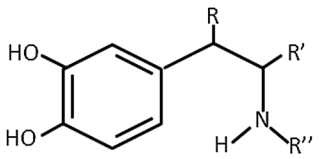
Introduction

Most critically ill patients disclose a hyperadrenergic state as a primary adaptive response to the acute stress imposed to their organism. In addition, exogenous catecholamines represent the first-line therapeutic agents to improve cardiovascular dysfunction in intensive care unit (ICU) patients. Whereas a prompt surge of sympathetic stimulation is essential for survival under conditions of acute circulatory failure, prolonged exposure to elevated levels of catecholamines may, by contrast, become maladaptive and can result in significant adverse effects [1]. Of primary concern, sympathetic overstimulation promotes cardiac toxicity, whose detrimental consequences have been well established in the field of chronic heart failure syndromes [2]. With respect to acute illnesses, this issue has recently begun to attract particular attention, with the publication of several studies reporting adverse cardiovascular effects, and possibly increased mortality, associated with catecholamine administration [3–5]. The mechanisms responsible for the cardiac toxicity of adrenergic agents remain only partly defined, but recent findings have highlighted the



Adrenaline	R=OH	R'=H	R''=CH_3
Noradrenaline	R=OH	R'=H	R''=H
Dopamine	R=H	R'=H	R''=H
Isoproterenol	R=OH	R'=H	R''=$CH(CH_3)_2$

Fig. 1 Structure of the main catecholamines

crucial role played by altered redox status and mitochondrial dysfunction in such toxicity [6]. The purpose of the present article is to review the current state of knowledge on this topic. Besides catecholamines, a section will also be dedicated to cocaine, since this frequently used recreational drug also promotes significant cardiac toxicity, via mechanisms depending, in part, on its sympathomimetic actions.

Catecholamines

Major pharmacological aspects of catecholamines

Catecholamines, released from the adrenal medulla and from the central and sympathetic nervous system, function as hormones and neurotransmitters playing crucial regulatory roles in the cardiovascular system. Structurally, catecholamines include a dihydroxybenzene ring (catechol) and a nitrogen group (amine). They are generated from the aminoacid L-tyrosine through successive hydroxylation, decarboxylation and methylation steps resulting in the sequential formation of dihydroxyphenylalanine (L-Dopa), dopamine, norepinephrine (NE, noradrenaline) and epinephrine (Epi, adrenaline) [6, 7] (Fig. 1). The pharmacological actions and the cell responses to catecholamines are mediated by two major types (α and β) of G proteins-coupled adrenergic receptors. The α-adrenoceptors are further subdivided into α_1 (α_{1A}, α_{1B}, α_{1D} subtypes) and α_2 (α_{2A}, α_{2B} and α_{2C} subtypes) receptors, while the β-adrenoceptors comprise the β_1, β_2 and β_3 subtypes [8, 9].

The α_1 receptors are coupled to pertussis-insensitive G protein ($G_{q/11}$) to activate phospholipase C, promoting an increase in cytosolic Ca^{2+} ($[Ca^{2+}]_i$) via the formation of diacylglycerol and inositol triphosphate [6]. In cardiac myocytes, α_{1A} and α_{1B} adrenoceptors mediate positive inotropic effects and hypertrophic responses, respectively, whereas in vascular smooth muscle cells, α_{1D} adrenoceptors elicit arterial vasoconstriction, notably in the coronary arteries [6, 10]. The α_2 receptors are coupled to inhibitory G proteins (G_i and G_0) and inhibit adenylyl cyclase signaling. They are essentially expressed at the nerve terminals from noradrenergic neurons, where they regulate neurotransmitter release via an inhibitory presynaptic feedback loop [6, 11]. The β_1 and β_2 receptors activate a G_s-adenylyl cyclase-cAMP-protein kinase A (PKA) cascade, leading to an increase in $[Ca^{2+}]_i$. In the heart, this translates into positive inotropic, chronotropic, bathmotropic and lusitropic effects, resulting in an increase in heart rate, cardiac output, stroke work and cardiac relaxation (mainly mediated by β_1 receptors) [6, 12]. In vascular smooth muscle, both β_1 and β_2 receptors mediate relaxant responses and vasodilation [13]. The β3 receptors, expressed by cardiac myocytes, trigger a G_i–NO–cGMP pathway, which produces a negative effect on cardiac contractility [14]. Finally, in addition to α and β adrenoceptors, five types of dopaminergic receptors exist ($D_{1–5}$). D_1 and D_5 are coupled to G_s and activate adenylyl cyclase, whereas $D_{2–4}$ inhibit adenylyl cyclase via G_i signaling. In the heart, only D_1 and D_4 are expressed, mediating some inotropic actions [10, 15]. The affinity of catecholamines for the different receptors is indicated in Table 1.

Table 1 Affinity of the different adrenoceptors to endogenous and synthetic catecholamines and sympathomimetic agents

	α_1	α_2	β_1	β_2	β_3	$DR_{1–5}$
Adrenaline	+++	+++	++++	+++	+	0
Noradrenaline	++++	+++	+++	+	+	0
Dopamine	++	?	++++	++	?	++++
Dobutamine	+	+	++++	++	0	0
Isoproterenol	–	–	+++	+++	+	0
Phenylephrine	++++	0	0	0	0	0
Ephedrine	+++	+++	++	++	?	0

Endogenous catecholamines are represented by adrenaline, noradrenaline and dopamine. Dobutamine and isoproterenol are synthetic catecholamines with predominant β-adrenergic actions. Phenylephrine is a sympathomimetic compound acting as a selective α_1 agonist. Ephedrine is a synthetic sympathomimetic agent with mild direct β-agonist activity and with indirect α-agonist activity produced by displacement of noradrenaline from nerve terminals. The table has been drawn from [10, 85–87]

DR dopamine receptors

The pharmacological actions of catecholamines are terminated by two major mechanisms, including reuptake (both presynaptic and extraneuronal) and metabolism [6]. The later depends primarily on oxidative deamination by neuronal mono-amine oxidase (MAO) to form dihydroxyphenylglycol, which is in turn *O*-methylated by extraneuronal catechol-*O*-methyl-transferase (COMT) into methoxhydroxyphenylglycol (MHPG). Catecholamines may also be first *O*-methylated into metanephrine and normetanephrine and secondarily deaminated into MHPG. MHPG is oxidized in the liver by alcohol and aldehyde dehydrogenases to form vanillylmandelic acid, the major

end-product of norepinephrine and epinephrine metabolism, which is excreted in the urine [7].

Catecholamine-induced cardiotoxicity

Increased levels of endogenous catecholamines occur acutely to provide a short-term adaptation to stressful conditions, which is known as the *fight-or-fly response* [16]. Similarly, the exogenous administration of catecholamines is life-saving in clinical situations associated with reduced cardiac output and/or hypotension [17]. In contrast to these short-term benefits, sustained elevation of catecholamines is detrimental to the cardiovascular system by initiating significant cardiotoxicity [6], as observed in chronic heart failure [18], pheochromocytoma [19], stress-induced ("takotsubo") cardiomyopathy [20] and during prolonged therapy with high doses of exogenous catecholamines [1]. According to this last condition, the administration of the synthetic β-adrenoceptor agonist isoproterenol to laboratory animals has been used for decades as a well-recognized model of cardiac injury [21].

The morphological features of such injury, already described by Richard M. Pearce in the early twentieth century, reproduce many aspects of myocardial infarction [22]. They include various degrees of cardiomyocyte necrosis and apoptosis, myocardial infiltration with polymorphonuclear and mononuclear leukocytes, interstitial edema, subendocardial and subepicardial hemorrhages, and the progressive development of distinct foci of fibrosis over time [6, 21]. On an ultrastructural viewpoint, the main alterations of catecholamine-induced cardiac toxicity comprise myofibrillar injury, mitochondrial swelling and dilatation of the sarcoplasmic reticulum [6, 21].

Multiple mechanisms have been postulated to explain the cardiotoxicity of catecholamines. The overstimulation of catecholamine receptors enhances cardiac contractility and heart rate, with secondary increase in myocardial oxygen demand that may outweigh oxygen delivery, creating areas of "functional" hypoxia which can be exacerbated by vasoconstriction in the coronary macro- and micro-circulation and which reduce the supply of high-energy phosphates [6]. The later can be further aggravated by metabolic changes, such as the stimulation of lipolysis with deposition of neutral lipid droplets in cardiomyocytes [23], resulting in an uncoupling of oxidative phosphorylation [24]. Changes in membrane permeability leading to various electrolytic imbalances (hypokalemia, hypomagnesemia with reduced intracellular Mg^{2+}) disturb multiple cellular homeostatic processes fostering additional myocardial toxicity [25].

Notwithstanding the aforementioned processes, there is now substantial evidence to incriminate intracellular calcium overload, oxidative stress and mitochondrial dysfunction as the major mechanisms accounting for the cardiotoxicity of catecholamines. A hallmark of sustained catecholamine exposure is a significant rise in Ca^{2+} both in the cytosol ($[Ca^{2+}]_i$) and mitochondria ($[Ca^{2+}]_m$) from cardiomyocytes, whose importance in triggering myocardial cell death has been identified more than 40 years ago by Fleckenstein and colleagues [26, 27]. The "Fleckenstein hypothesis" of Ca^{2+}-mediated cardiotoxicity of catecholamines is nowadays described as the mitochondriocentric signal transducer–effector (MSTE) pathway: Mitochondrial Ca^{2+} overload (signal) triggers mitochondrial oxidative stress (transducer) and mitochondrial permeability transition (effector), eventually leading to cell death via apoptotic and necrotic pathways [28].

Myocardial $[Ca^{2+}]_i$ and $[Ca^{2+}]_m$ build up in response to β-adrenergic receptor-mediated activation of PKA, resulting in the downstream phosphorylation of multiple Ca^{2+}-cycling proteins, including sarcolemmal L-type Ca^{2+} channels, phospholamban and sarcoplasmic reticulum ryanodine receptor Ca^{2+} release channels (RyR2) [16]. PKA-dependent phosphorylation of troponin and myosin binding protein C further participates to increase $[Ca^{2+}]_i$, by reducing Ca^{2+} affinity of myofilaments [6, 16]. Persistent activation of β-adrenoceptors also promotes the activation of Ca/calmodulin-dependent protein kinase II (CaMKII), both via PKA-dependent and PKA-independent mechanisms [29]. Activated CaMKII phosphorylates multiple protein targets, which comprise voltage-gated Ca^{2+} channels, RyR2 Ca^{2+} release channels and voltage-gated Na^+ channels, with resulting increase in $[Ca^{2+}]_i$ [30]. Following the rise in $[Ca^{2+}]_i$, a progressive increase in $[Ca^{2+}]_m$ occurs, leading to a rapid change in the permeability of the inner mitochondrial membrane, followed by swelling of the mitochondrial matrix, loss of respiratory control and generation of reactive oxygen species (ROS) which further exacerbates the Ca^{2+}-induced mitochondrial dysfunction [28].

The pathophysiological events triggered by elevated $[Ca^{2+}]_m$ are considerably amplified by the oxidative stress that develops upon sustained exposure to high levels of catecholamines, in connection with the following identified mechanisms. First, MAO-dependent oxidative deamination of catecholamines forms hydrogen peroxide (H_2O_2), which may be converted to the highly reactive hydroxyl radical ($OH^{\cdot}$) through metal catalysis (Fenton chemistry) [6]. Secondly, activation of α_1-adrenoceptors by catecholamines induces the activation of NADPH oxidase, with ensuing generation of the superoxide anion radical ($O_2^{\cdot-}$) in cardiac myocytes [31]. Third, and most importantly, catecholamines are readily oxidized into toxic compounds termed "aminochromes" (due to their colored appearance in solution) [24]. This process occurs spontaneously at a low rate (autooxidation), but it is markedly accelerated in

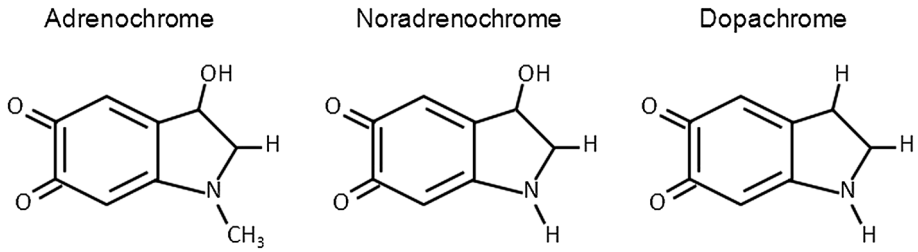


Fig. 2 Structure of aminochromes formed from the oxidation of catecholamines

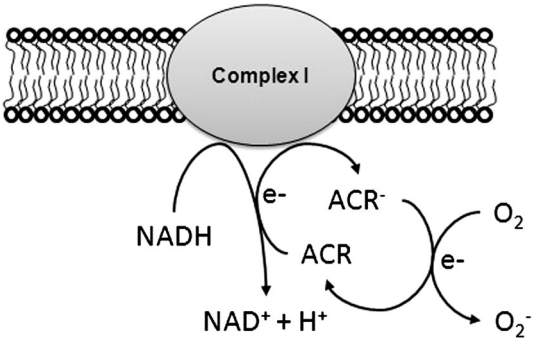


Fig. 3 Formation of superoxide via redox cycling of aminochromes. Aminochromes (ACR) are reduced to aminochrome semiquinones (ACR^-) in the presence of NADH by complex I in the inner mitochondrial membrane. Auto-oxidation of ACR^- back to ACR induces the generation of the superoxide anion radical ($O_2^{\cdot-}$). The transfer of electrons is indicated by e^-

the presence of oxidants and free radicals such as $O_2^{\cdot-}$, redox metals (especially iron and copper) and by enzymatic catalysis (notably by xanthine oxidase, myeloperoxidase and cytochrome oxidase) [24, 32–34]. Catecholamine oxidation is a two-electron process forming ortho-quinone derivatives, followed by cyclization into leukoaminochromes which are further oxidized into aminochromes [32], whose chemical structure is indicated in Fig. 2.

Aminochromes exert direct toxic effects on the coronary arteries (vasoconstriction) and the myocardium, including inhibition of oxidative phosphorylation and depression of calcium binding, with the overall result to reduce contractile force and to produce extensive necrotic damage, as shown in both ex vivo [35–37] and in vivo [38] experimental models. Besides their direct toxicity, aminochromes also induce the formation of large amounts of ROS via redox cycling processes occurring primarily in mitochondria [39]. The first step of this cycle is the one-electron reduction to aminochrome semiquinone in the presence of NADH, catalyzed by complex I from the respiratory chain [39, 40]. In the second step, the semiquinone immediately regenerates the native aminochrome by auto-oxidation in the presence of oxygen, releasing one molecule of $O_2^{\cdot-}$ (Fig. 3). The cycle is then renewed, promoting an explosive enhancement of $O_2^{\cdot-}$ generation, which, in turn, triggers the further oxidation of catecholamines within their respective aminochromes, whose concentrations is thereby exponentially increasing [39].

When the formation of free radicals and oxidants outweighs the endogenous antioxidant capacities, a state of oxidative stress develops with profound cytotoxic consequences related to oxidative damage in lipids, proteins and nucleic acids [41, 42]. The "oxidative stress theory" of catecholamine cardiotoxicity is supported by a myriad of studies showing considerable benefit of antioxidant therapies, including melatonin [43], quercetin [44], ascorbic acid [45] or *N*-acetylcysteine [46], to name only a few. It is particularly noticeable that the oxidative stress elicited by catecholamines, in conjunction with the marked $[Ca^{2+}]_i$ and $[Ca^{2+}]_m$ overload, fosters the opening of the mitochondrial permeability transition pore (mPTP) in cardiac myocytes, as recently well demonstrated in a model of isoproterenol-induced cardiac injury [47]. Opening of the mPTP promotes mitochondrial depolarization and cessation of oxygen transport. This triggers the secondary generation of free radicals, a process termed "ROS-induced ROS release" (RIRR), which amplifies mitochondrial oxidative stress and mPTP opening, leading to permeabilization of the outer mitochondrial membrane and efflux of pro-apoptotic molecules [48, 49]. Depending on the degree of mPTP opening, cells may either recover (minimal opening) or die by apoptosis (moderate opening) or necrosis (massive, irreversible opening) [50, 51].

In summary, a sustained high level of catecholamine can exert major toxic effects on the myocardium, leading to morphological alterations similar to those produced by myocardial infarction, including primarily cardiomyocyte cell death and progressive focal myocardial fibrosis. Such toxicity stems from a multiplicity of catecholamines' actions on the heart, most significantly calcium overload, oxidative stress and mitochondrial dysfunction, as illustrated in Fig. 4.

Cocaine

Pharmacological basis of cocaine effects

Cocaine (benzoylmethylecgonine), derived from the leaves of *Erythroxylon coca*, is a commonly used illicit drug with

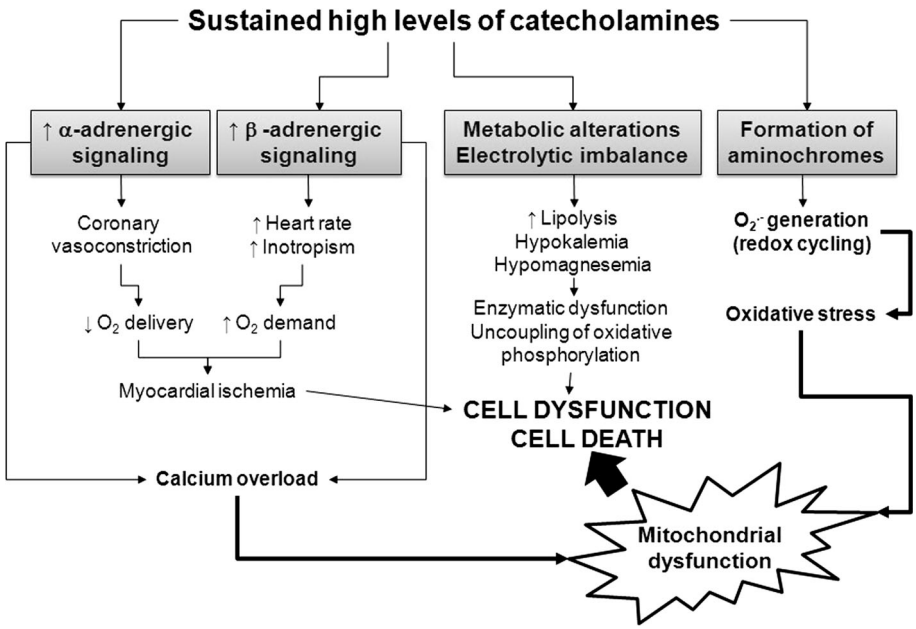


Fig. 4 Mechanisms of catecholamine-induced cardiotoxicity. The major pathways of cardiotoxicity are indicated with the *black arrows*

potent stimulant actions. It is generally used by nasal insufflation or by inhalation ("crack"), reaching peak plasma concentrations after 30–60 min or within seconds to minutes, respectively. Its serum half-life is about 60 min, being rapidly cleared via tissue uptake and metabolism by plasma and liver esterases into two major water-soluble active metabolites, benzoylecgonine and ecgonine methylester, excreted in the urine [52, 53]. The effects of cocaine are related to the blockade of the presynaptic reuptake of dopamine and norepinephrine, with resulting increase in their concentration in the synaptic cleft and enhanced postsynaptic transmission, as well as enhanced central sympathetic outflow [54, 55]. The psychostimulant actions of cocaine mainly result from enhanced dopamine neurotransmission, whereas the cardiovascular effects of the drug are related primarily to its sympathomimetic actions. In addition, cocaine also blocks the fast Na^+ channels in membranes, reducing the phase 0 of the action-potential, thereby inducing a local anesthetic effect [56, 57].

Cardiovascular consequences associated with cocaine use

Cocaine use is associated with numerous acute and chronic cardiovascular complications, which comprise chest pain, hypertension, acute myocardial infarction, arrhythmias, sudden death, aortic dissection, stroke (both ischemic and hemorrhagic) and cardiomyopathy leading to chronic heart failure [53, 55]. The primary mechanism of cocaine's cardiovascular toxicity relates to its marked sympathomimetic effect. Increased α_1-adrenergic stimulation promotes arterial vasoconstriction with subsequent elevation of blood pressure and reduced microvascular blood flows, whereas enhanced β-adrenergic stimulation increases heart rate and cardiac contractility [54]. The vasoconstrictive action of cocaine is further amplified by two additional properties, namely inhibition of nitric oxide synthesis [58] and increased formation of endothelin-1 [59] by the endothelium. Furthermore, cocaine induces a prothrombotic state by activating platelets (via elevated P-selectin expression, increased release of platelet factor 4, thromboglobulin, NAP-2 and CD40 ligand) [60] and coagulation (via an increase in plasminogen-activator inhibitor, fibrinogen and tissue factor, together with decreased expression of tissue factor inhibitor, antithrombin and protein C) [56, 61, 62]. Over time, these various effects promote accelerated atherosclerosis and endothelial dysfunction, which further increase the risk of cardiovascular events (notably myocardial infarction and ischemic stroke) in cocaine users [55].

The significant increase in blood pressure due to α_1-adrenergic-dependent vasoconstriction is the major mechanism responsible for acute complications such as cerebral hemorrhage and aortic dissection in cocaine users [53, 55]. The α_1-mediated coronary vasoconstriction, together with the β_1-adrenergic-induced tachycardia and increased contractility, leads to an imbalance between myocardial oxygen demand and supply, triggering myocardial ischemia and acute myocardial infarction [53, 55], the risk of which being increased 24-fold in the 60 min following cocaine use [63]. Importantly, coronary vasoconstriction may initially resolve when serum cocaine concentration decreases, but may backslide after several hours due to the effects of cocaine metabolites, producing recurrent, delayed

myocardial ischemia [53, 55]. Coronary thrombus formation due to platelet activation is an additional factor that may precipitate myocardial infarction [57]. Cocaine can further promote major arrhythmias and sudden cardiac death, both via its sympathomimetic effects (increased ventricular irritability) and its blocking effects on Na^+ channels, which prolongs QRS duration and QT interval and favors the development of reentrant circuits, similarly to class I antiarrhythmic agents [53, 55, 57].

In the long term, chronic use of cocaine may result in a particular form of cardiomyopathy with various degrees of systolic and diastolic dysfunction, cardiac hypertrophy and dilatation, resulting in chronic heart failure [53, 55]. Histological characteristics include loss of myofibrils, multiple foci of contraction band necrosis, fibrosis and interstitial infiltrates with inflammatory cells [57, 64], which are similar to the cardiac lesions described following sustained catecholamine exposure (for instance, during pheochromocytoma) [55]. In a limited number of cases, evidence of inflammatory myocarditis has been noted, characterized by perivascular eosinophilic infiltrates and absence of necrosis, attributed to an hypersensitivity reaction to cocaine itself or any contaminants added to adulterate the drug, such as amphetamine, sugars or talc [57].

Role of oxidative stress and mitochondrial dysfunction in cocaine cardiotoxicity

Recent observations support a key role of myocardial oxidative stress and mitochondrial dysfunction in the pathogenesis of cocaine-induced cardiomyopathy [65–67]. Indeed, substantial evidence of cardiac oxidative damage, including depletion of antioxidants and lipid peroxidation, has been obtained both in laboratory animals [65, 66, 68] and humans [69, 70] exposed to cocaine. Underlying mechanisms include (1) indirect, catecholamine-induced, oxidative stress, due to formation of aminochromes and redox cycling compounds (see above), (2) the activation of the $O_2^{\cdot-}$-generating enzymes NADPH oxidase [65, 66, 71, 72] and xanthine oxidase [73], (3) the induced formation of ROS by dysfunctional mitochondria [67, 73, 74] and (4) the generation of pro-oxidant derivatives of cocaine metabolites [74, 75].

Activation of NADPH oxidase (Nox) by cocaine in cardiac myocytes has been linked with an α_1-adrenergic-G protein-PKC-coupled mechanism, leading to phosphorylation of the $p47^{phox}$ cytosolic subunit of the enzyme [71]. The dependence on α_1-adrenoceptor was notably demonstrated by the abrogation of Nox activation in the heart of cocaine-treated rats after administration of the α_1 antagonist prazosin [71]. Fan and co-workers then demonstrated that cocaine could also activate Nox in rat myocardium via PKC-dependent but α_1-independent upregulation of the expression of Nox-2, one of the two Nox isoforms (with Nox4) present in cardiac tissue [72]. The activation of Nox appears to be a critical event for the propagation of ROS generation in hearts exposed to cocaine, as supported by Isabelle et al. [65]. These investigators found, in a model of chronic cocaine administration to rats, that $O_2^{\cdot-}$ formed in response to Nox activation induced the secondary activation of xanthine oxidase (XO) [76], leading to further $O_2^{\cdot-}$ formation, which initiates a cycle of progressive amplification of oxidative stress [65]. In addition, the intense generation of $O_2^{\cdot-}$ by co-activation of Nox and XO targets mitochondria to produce additional ROS via the RIRR mechanims (ROS-induced ROS release) [49], contributing to this amplification cycle [73].

An additional pathway of cocaine-mediated oxidative stress which has received little attention may be related to the formation of oxidative metabolites [75]. Besides the major degradation pathway of cocaine by ester hydrolysis, a minor *N*-oxidative pathway process also exists, in which cocaine is demethylated to norcocaine, and then oxidized to *N*-hydroxynorcocaine and norcocaine nitroxide [77, 78]. Evidence has been obtained that *N*-hydroxynorcocaine and norcocaine nitroxide form a couple transferring electrons from NADPH and generating $O_2^{\cdot-}$ during redox cycling, a mechanism notably incriminated in the liver toxicity elicited by cocaine [77, 79]. In addition to promote ROS formation, these oxidized metabolites of cocaine have also been associated with direct toxic effects on mitochondria, by suppressing state 3 and 4 respiration, resulting in suppression of ATP generation [74].

The primary target of cocaine-mediated oxidative stress is the mitochondria, with various established consequences, including formation of ROS (see above), impaired electron transfer and suppression of ATP production [67, 73, 74], as well as membrane permeabilization with release of cytochrome C and subsequent cell death [80–82]. The mitochondrial impairment elicited by cocaine has been particularly well addressed in a recent work by Vergeade et al. [67]. In this study, the administration of cocaine for seven consecutive days to rats resulted in significant left ventricular dysfunction. At the cellular level, cocaine led to an increase in oxygen consumption in cardiac fibers together with increased ROS generation and decreased ATP synthesis, indicative of an uncoupling of oxidative phosphorylation. The changes were selectively noted in the interfibrillar fraction, but not the subsarcolemmal fraction of mitochondria, pointing to differential susceptibility of distinct mitochondrial fractions to pathological stimuli. Co-treatment with cocaine and MitoQ, a mitochondrial-targeted antioxidant [83, 84], suppressed these mitochondrial abnormalities and completely prevented cardiac dysfunction, thereby providing strong support to the role of a mitochondrial defect in cocaine-mediated cardiotoxicity [67].

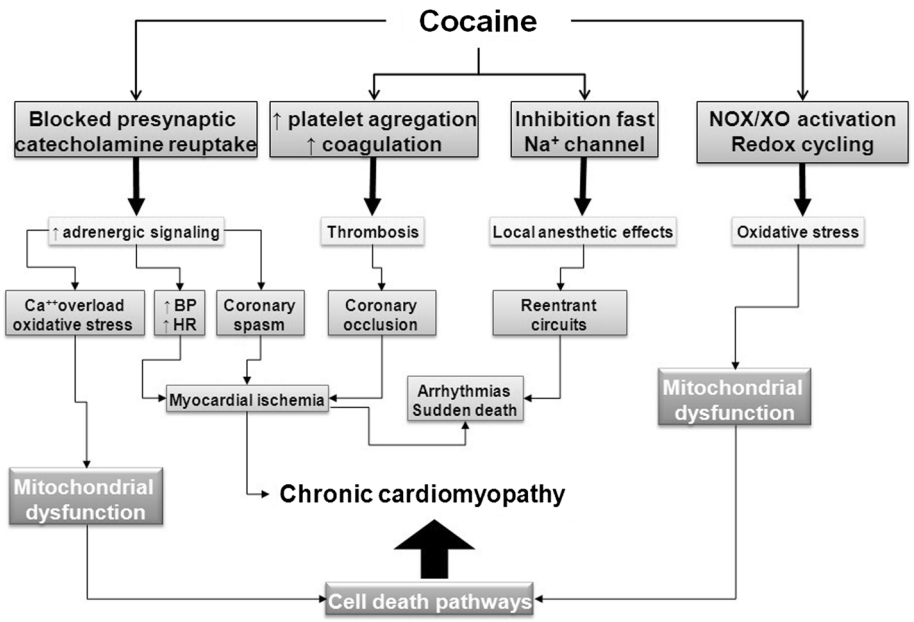


Fig. 5 Major mechanisms of cocaine toxicity in the cardiovascular system. *BP* blood pressure, *HR* heart rate, *NOX* NADPH oxidase, *XO* xanthine oxidase

Figure 5 summarizes the mechanisms involved in cardiovascular toxicity associated with cocaine use. Besides its considerable sympathomimetic effects resulting in catecholamine-mediated adverse actions, cocaine also fosters the generation of significant amounts of ROS within cardiomyocytes, whose major consequence is mitochondrial dysfunction with subsequent activation of cell death processes.

Conclusions

Although catecholamines are essential to support life in conditions of acute cardiovascular failure, sustained adrenergic stimulation exposes to the risk of significant cardiotoxicity. In addition to the direct role of sustained stimulation of adrenoceptors, catecholamines promote profound mitochondrial dysfunction in cardiac myocytes by inducing intracellular calcium overload and, most importantly, by initiating mitochondrial oxidative stress following their transformation into toxic aminochromes. Mitochondria also play a central role in the cardiac toxicity of cocaine, which acts, partly, through its sympathomimetic actions, but also through its ability to disturb redox balance in cardiac myocytes. Clinicians should be aware of these dangerous side effects in order to prevent the detrimental consequences of hyperadrenergic stress, notably by a cautious use of exogenous catecholamines. Furthermore, future studies should evaluate whether antioxidant molecules efficacious in laboratory animals, such as the recently developed mitochondrial-targeted antioxidants, can protect the heart from the toxicity of catecholamines and cocaine in the clinical setting.

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