

# Cocaine Dependence and Stroke: Pathogenesis and Management

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**Abstract:** Cocaine abuse remains a devastating medical problem for our society. Current concepts suggest that both hemorrhagic and ischemic stroke, particularly in young people, can result as a consequence of cocaine exposure. We provide an analysis of mechanisms of injury and a discussion of the pharmacological management of stroke following cocaine use. Preclinical research suggests that the cause of cocaine-mediated stroke is multifactorial and involves vasospasm, changes in cerebral vasculature, and platelet aggregation. We suggest that drugs able to induce vasospastic, thrombogenic, or neurotoxic effects of cocaine could be suitable as therapeutic agents. In contrast caution should be exerted when using anti-platelet and thrombolytic agents in cocaine users with stroke.

**Keywords:** Cocaine, hemorrhagic stroke, ischemic stroke, antineurotoxic agents, antithrombogenic agents, antivasospastic agents.

## 1. INTRODUCTION

Despite the importance of psychosocial factors, at its core, drug addiction involves a biological process: the ability of repeated exposure to a drug of abuse to induce changes in a vulnerable organism, driving the compulsive seeking and taking of drugs, and loss of control over drug use, that define a state of addiction. Although the brain and the circuitry cerebellum are the main target of chronic cocaine use (Fig. 1) [1, 2] other organs are not spared and neither is the cerebrovascular system. In fact it has been recently published that astrocytes may represent the first cells displaying acute cocaine toxicity; therefore antioxidant drugs able to reduce this early toxicity in astrocytes could be useful in the management of cocaine-induced brain damage [3]. Moreover, a glucagon-like peptide 1 receptor expressed in GABAergic neurons of the dorsal lateral septum may be involved in the function driving behavioural responses to cocaine-use [4].

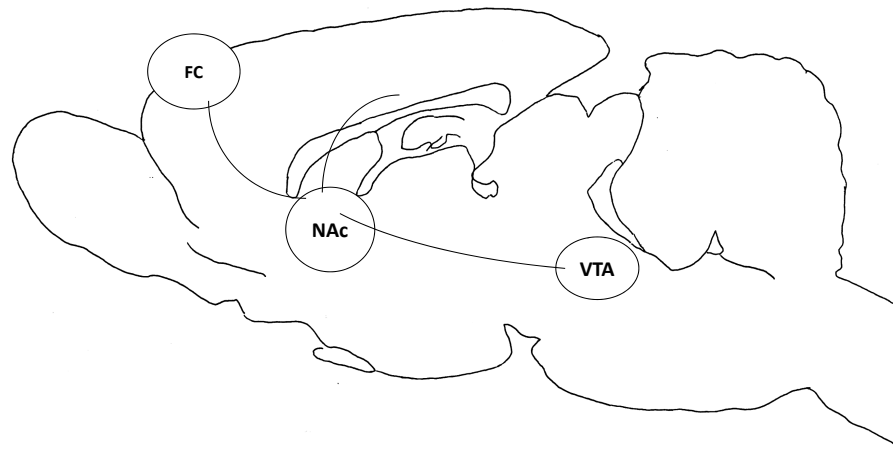
Stroke represents the largest cause of severe disability and the third most common cause of death in developed countries [5]. Recently, strokes have become more prevalent in younger people. About 5% of strokes occur in people between 18 and 44 years [6]. They appear to occur more in men more than women [7] and blacks also have been reported to have a high incidence of strokes in this age range

[8]. In young people, thromboembolism and intracranial small vessel disease occurs less and so stroke tends to be caused by other factors, such as substance abuse [9-11].

Increasing evidence supports the relationship between substance abuse and stroke [12, 13]. In cocaine users, the probability of stroke is up to 14 times greater than that in non-drug users [14] and genetic factors may be involved in the death related to cocaine-use [15]. In agreement with this statistic, Silver and coworkers [8], using a urine toxicology screen, documented that 11% of 420 patients recruited in a single tertiary care stroke center were positive for cocaine (19% were younger than 50 years, while 9% were older, commonly black  $P < 0.01$ ). Of these cocaine users patients with ischemic strokes, 44% were due to large-artery atherosclerosis, 11% to cardioembolism, and 22% to small-vessel occlusion. Fehnel and coworkers [16] reported that 2.2% of 4073 acute ischemic stroke patients had a history of cocaine use and/or a positive toxicology. Moreover, the authors showed that in cocaine users the most common cause of ischemic stroke was cardioembolism (43%) respect to large-artery atherosclerosis (18%) and small-vessel occlusion (21%).

Cocaine induces hemorrhagic and ischemic stroke, with the incidence of hemorrhagic stroke prevailing over ischemic stroke [17]. Active cocaine users appear to be more likely to have intracerebral hemorrhage compared with previous users (37.7% v 8.6%) and less likely to have ischemic stroke or transitory ischemic attack (36.1% v 65.7%). In an observational study of 1,924,413 patients admitted for myocardial infarction, cocaine was reported to be a significant comorbidity associated with the highest risk of cerebrovascular disease in post-myocardial infarction [18]. Several mecha-

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**Fig. (1).** The major cellular pathways affected by cocaine in the brain. Dopaminergic projection from the ventral tegmental area (VTA) provide the major source of dopamine to frontal cortex (FC) and nucleus accumbens (NA).

nisms may be responsible for the cerebrovascular complications (Table 1). A sudden rise in systemic arterial pressure may cause haemorrhages, frequently in association with an underlying aneurysm. Vasospasm, vasculitis, myocardial infarction with cardiac arrhythmias and increased platelet aggregation also may provoke infarcts [19]. Cocaine-use induces apoptosis of endothelial and/or smooth muscle cells, with dysfunction of the vascular wall, resulting in a dissection of extra-cranial artery responsible of ischemic stroke [20]. In ischemic stroke, about 80% of the cerebral infarcts in cocaine-users occur in the regional distribution of the middle cerebral artery [21], typically in young adults without pre-existing vascular diseases [22]. Cocaine can reduce cerebral blood perfusion before the development of clinically detectable symptoms in the central nervous system [23, 24], which may persist for 6 months [25] or longer [26] in abstinent cocaine addicts.

Moreover, use of cocaine increases blood pressure and risk of aneurysms rupturing [27], and has a close association with hemorrhagic stroke [28]. Here we will review the relationship between cocaine use and cerebrovascular pathologies that often afflict the lives of cocaine addicts and complicate their health problems, beyond the behavioral dysfunctions caused by cocaine use.

## 2. COCAINE AND STROKE

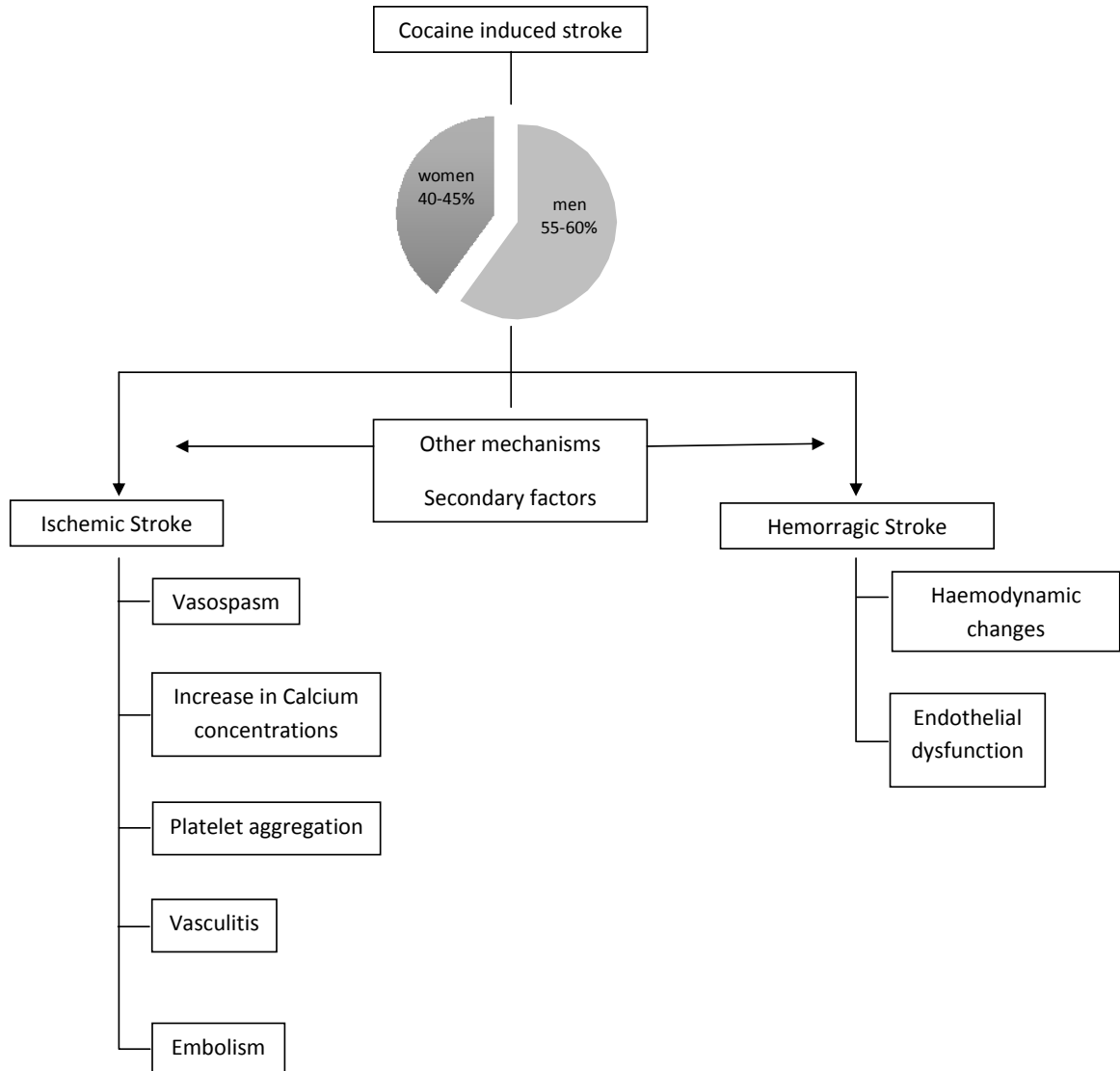
### 2.1. Incidence and Onset of Stroke

Cocaine-associated stroke was first reported in 1977 [29]. During the 1980s, increased production of alkaloidal “crack” cocaine and the subsequent epidemic of crack use led to a significant increase in the number of case reports of cocaine-related stroke. Epidemiologic studies indicate that the incidence of major cerebrovascular abnormalities in hospital admissions associated with cocaine abuse was low 24 years ago (0.35%-3%) [30, 31]. However, the incidence has been gradually increased as more cases of cerebrovascular complications in cocaine users have been reported in recent years, and incidents seem to have reached epidemic proportions [32].

The use of cocaine is associated with both ischaemic and haemorrhagic stroke. In particular, crack cocaine seems to be associated with both ischemic strokes and hemorrhage strokes, whereas cocaine hydrochloride causes mainly intracerebral and subarachnoid bleeding [33]. Early studies also suggested a higher proportion of cerebrovascular events related to cocaine use [19, 34]. Toossi and co-workers [35] retrospectively reviewed 5,142 clinical records of neurovascular service and identified 96 cocaine-users (61 active users and 35 previous users). They found that 47% of the 96 cocaine users developed ischemic stroke/transient ischemic attack, 27% developed intracerebral hemorrhage, and 26% developed subarachnoid haemorrhage. Daras *et al.* [19], conducted a 6-years study involving 54 cocaine-users with neurovascular events. Amongst these patients, 25 patients developed cerebral infarcts and 29 developed cerebral haemorrhages. The difference in route of cocaine administration (e.g. smoked, snorted or injected) was not relevant to the pathophysiology of stroke [19]. Moreover, cerebral infarcts or haemorrhage occurred within 3 hours of cocaine use in 15 of 25 and 17 of 29 stroke patients, respectively. Infarcts occurred overnight after use of cocaine in 10 of 29 patients. Similarly, the onset of stroke symptoms was usually found immediately or within 3 hours after cocaine use [19, 30, 34, 36]. For example, intramuscular administration in a male user was followed 1 h later by aphasia and right sided hemiparesis [29]. Taken together, these data suggest that a much higher risk of stroke occurs shortly after use of cocaine.

### 2.2. Brain Lesions

Cocaine-induced ischaemic stroke has been reported in both anterior and posterior arterial territories; moreover, cocaine can induce retinal and spinal cord infarctions, as well as transient ischaemic attacks. Haemorrhage can be found in brain parenchyma (i.e. basal ganglia, hemispheric and brain stem), cerebroventricles and subarachnoid space. In a review of the records of 3,712 drug abusers, 13 patients were identified with neurologic deficits attributable to the use of cocaine; in 7 of the 13 patients, ischemic manifestations were the most frequent, while three patients had subarachnoid haemorrhage, and three had intracerebral haemorrhage [30].

**Table 1. Patho-physiological mechanisms of stroke induced by cocaine.**

Klonoff and co-workers [36] reported 47 patients (8 reported in a case report and 39 reviewed from the literature) in whom cocaine use was related to stroke. The authors documented that intracranial aneurysms or arteriovenous malformations were present in 17 patients and intracranial haemorrhages were more common with respect to cerebral infarction. Acute cocaine use was associated with higher risk of aneurysm rupture in patients with subarachnoid hemorrhage [8]. In addition, cocaine users with an intracerebral hemorrhage had worse functional outcomes and higher in hospital mortality, compared with cocaine-negative patients [11].

### 2.3. Cerebral Ischemia – Mechanisms of Action

Cocaine may cause vasospasm and then cerebral ischemia by several mechanisms: (1) inhibition of serotonin reuptake [20, 37]; (2) potentiation of norepinephrine-induced vasoconstriction [21] (3) increasing calcium flux into vascular smooth muscle [22] (4) through active metabolites benzoylecgonine and ecgonine [23] and (5) endothelin-1-mediated endothelial activation.

#### 2.3.1. Vasospasm

The presence of cerebral vasospasm has been documented in patients with cocaine-related ischaemic strokes by cerebral angiography. Levine and co-workers [34] studied 28 individuals with stroke temporally related to the use of alkaloidal cocaine (during or within 72 hours of use) in four medical centers. In these patients, the authors documented the presence of cerebral infarction in the middle cerebral artery (n = 10), anterior cerebral artery (n = 3), posterior cerebral artery (n = 1), and vertebrobasilar arteries (n = 4); subarachnoid hemorrhage (n = 5); intraparenchymal hemorrhage (n = 4); and primary intraventricular hemorrhage (n = 1). Moreover, the authors described that 18 patients presented acute neurologic symptoms immediately, or within one hour, of using cocaine, showing a strong temporal association between cocaine use and cerebrovascular events. Mehta *et al.*, [38] reported a case of a 53-year-old female with a medical history of hypertension, dyslipidemia, and cocaine abuse that developed neurological signs of acute ischemia and chronic infarcts, in the border zones of the

right anteriorcerebral artery and middle cerebral artery. Clinical and radiological evaluation revealed that neurological signs were multifocal vasospasm related to cocaine abuse rather than an impending thromboembolic infarct and intravenous thrombolytic therapy induced an improving of symptoms in about 3 weeks. The mechanism of cocaine-induced vascular failure has also been documented by observing isolated cat cerebral arteries, where the administration of benzoylecgonine, the primary cocaine metabolite, induced a 50% decrease in a cross sectional area.[39]. Volkow *et al.*[23] reported the presence of cerebral areas with decreased cerebral blood flow in chronic cocaine users compared to healthy volunteers. A double-blind study, performed in 24 healthy individuals, also reported that intravenous cocaine administration (0.4 or 0.2 mg/kg) induced dose-related angiographic changes, indicative of cerebral vasoconstriction [32]. In agreement with this observation, administration of cocaine (0.2 or 0.4 mg/kg) in twenty-three healthy adult males with a history of recreational cocaine use (3-40 lifetime exposures), caused a decrease in cerebral blood volume. This decrease was measured by dynamic susceptibility contrast magnetic resonance imaging, also suggesting that cocaine is able to induce vasospasm and cerebrovascular adverse events[40]. Moreover, another mechanism of vasospasm may be related to a decrease in cerebral metabolism that induces a down-regulation of blood flow [41].

London *et al.*, [42] used a double-blind, placebo-controlled, crossover study to evaluate the effects of cocaine hydrochloride (40 mg, intravenously) on regional cerebral metabolic rates by measuring glucose metabolism in eight poly-drug abusers using positron emission tomography. The authors documented that cocaine reduces the regional cerebral metabolic rate for glucose in twenty-six of 29 brain regions (all neocortical areas, basal ganglia, portions of the hippocampal formation, thalamus, and midbrain). In addition, cocaine induces cerebral vasospasm and cellular damage in brain dopamine rich areas, suggesting that dopamine modulates cerebral blood flow [6]. Interestingly, a direct neuronal impairment could be caused by repeated cocaine exposure. For instance, cocaine disturbs calcium signalling in medium spiny neurons by enhancing and prolonging the stimulation of both dopamine D1 and D2 receptors (D1R/D2Rs) [29, 43-45]. Moreover, in an experimental study performed in rat nucleus accumbens neurons, Perez *et al.*, [46] documented that cocaine induces dysregulation of Ca<sup>2+</sup> homeostasis with involvement of D2R, showing that D2R stimulation reduced Ca<sup>2+</sup> influx preferentially via the L-type Ca<sup>2+</sup> channels and evoked intracellular Ca<sup>2+</sup> release.

### 2.3.2. Calcium

Cocaine has direct effects on calcium channels, promoting intracellular calcium release from the sarcoplasmic reticulum in cerebral vascular smooth muscle cells [47, 48]. Moreover, when canine cerebral vascular smooth muscle cells are exposed to cocaine, a significant increase in free calcium concentration occurs [49]. Furthermore, cocaine's vasospastic effects on smooth muscle can persist beyond its half-life, due to the prolonged presence of its major metabolites (benzoylecgonine and norcocaine) that are also potent vasoconstrictors [50].

### 2.3.3. Endogenous Peptides

Bradykinin-mediated endothelium-dependent relaxation is impaired in chronic cocaine abusers [17]. In addition to bradykinin, endothelin-1 (ET-1), a potent and efficacious spasmogen of smooth muscle [51], may be involved in cocaine induced vasospasm. Interestingly, acute changes in cerebral blood flow have been documented in experimental study after intravenous and intracranial injections of ET-1 [52]. The involvement of ET-1 in cocaine-induced vasospasm has been suggested by Fandino and co-workers [53] that in an experimental study performed in rabbit, demonstrated that the infusion of cocaine into the cisterna magna of rabbits induced a time- and concentration-dependent spasm, inhibited during the co-infusion of PD145065, an non-selective ET-receptor antagonist.

### 2.3.4. Platelet Aggregation and Blood Viscosity

A decrease in cerebral blood flow in cocaine-dependent patients has been associated with an increase in platelet aggregation [54, 55]. Acute platelet rich thrombi have been observed in fatal cocaine related infarcts, in both normal and atherosclerotic coronary vessels [56]. In chronic cocaine users, the release of cell growth factors by activated platelets might promote atherosclerosis, predisposing users to thrombosis and ischemia in the absence of acute intoxication, despite a young age [56]. The cause of this condition is supported by the finding that advanced atherosclerosis is observed in the renal arteries and aorta of cocaine users [57]. The arteriosclerotic toxicity of cocaine has also been demonstrated in rabbits [58], in which the same pathophysiological process may also occur in intracerebral vessels, leading to cocaine-induced lacunar infarction. Similarly, cocaine consumption is able to induce platelet activation, granule release, reversible stomatocytosis of red blood cells and an increase in plasma von Willebrand factor, with a decrease in bleeding time, in healthy volunteers [59-61].

Cocaine induces vasospasm resulting in platelet aggregation, with the release of smooth muscle growth factor and obstructive intimal hyperplasia [27]. Angiographic and pathological data suggests that vasospasm with secondary thrombus formation are major causes of stroke in cocaine users [50]. Histological analysis revealed small calibre intracerebral arteries with infolded and irregular internal elastic lamina in multiple territories, related to cocaine-induced vasoconstriction. An *in vitro* study revealed that cocaine increases the platelets' response to arachidonic acid, leading to enhanced thromboxane A2 production and platelet aggregation [62]. Protein C antithrombin III depletion additionally contributes to cocaine's pro-coagulant effects [17, 54, 63, 64].

### 2.3.5. Cerebral Vasculitis

Cerebral vasculitis has been attributed to cocaine misuse and has been diagnosed based on angiography findings of arterial beading. One case was described in a previously healthy 22-year-old man with a history of cocaine abuse [65]. Krendel *et al.* [66] also described two cases of cerebral vasculitis associated with cocaine use that were histologically confirmed by brain biopsies. Angiography was normal

in one patient, and in the other one showed multiple large vessel occlusions, without the described pattern of vascular beading. In another case, a woman was reported to have cerebral vasculitis following intravenous and intranasal administration of cocaine [67]. She was brought to the emergency room, and later a psychiatric facility, due to abnormal behaviours. Brain biopsy revealed vascular changes involving primarily small arteries with lymphocytic infiltration, endothelial thickening, and deposition of proteinaceous amorphous material within and around vessel walls.

Vasculitis represents a controversial pathophysiological mechanism in patients with cocaine-associated stroke and may be related to other drugs or excipients. Drug-associated cerebral vasculitis has been well reported during amphetamines abuse causing an inflammatory vasculopathy with vessel wall necrosis leading to vessel wall rupture [27]. Amphetamines have a similar mechanism of action of cocaine - increase of catecholamines availability at nerve terminals - therefore there are similarities in the aetiology of vasculitis. Moreover, amphetamines may also be present as adulterants in cocaine preparations.

More recently, other cases of vasculitis, related to the use of cocaine mixed with levamisole, an immunomodulating agent, have been reported and the production of antineutrophils cytoplasmic antibodies was detected in the patients with visible skin lesions [68-72].

### 2.3.6. Embolism

Petty *et al.*, [73] reported a case of a 39-year-old woman, without history of hypertension, hypercholesterolemia, heart disease, alcohol abuse, intravenous drug use, syphilis, or collagen vascular disease, that developed left hemiparesis caused by embolic occlusion of the upper division middle cerebral artery branch 3 hours after smoking crack cocaine. Cerebral emboli with subsequent infarction can originate from cardiac thrombi made during a cocaine induced myocardial infarction [74, 75] or during cocaine related cardiomyopathy [27]. Experimental studies in cultured fetal rat myocardial cells [76] and in cultured human endothelial cells [20, 77] documented a time and concentration-dependent increase of apoptosis after cocaine administration. Moreover, in neonatal rats, prenatal cocaine exposure induces abnormal apoptosis and myocyte hypertrophy, leading to an increased susceptibility to ischemic insults in postnatal life [78].

Both myocardial infarct and cardiomyopathy are established causes of cardiac arrhythmia that may also predispose to cardioembolism. Prolongation of the QT interval has been reported in patients presenting with cocaine toxicity [79], and experiments on isolated myocytes exposed to cocaine resulted in a modest prolongation of the transmembrane action potential, showing a possible mechanism for cocaine arrhythmogenesis [80]. Contaminants mixed with cocaine may provide a further cause of cardioembolism due to arrhythmia. As with any substance injected intravenously, cocaine administered by this route can result in embolic vessel occlusion due to endocarditis. Stroke resulting from endocarditis may also be haemorrhagic, following rupture of a septic aneurysm [81-83].

## 2.4. Cerebral Hemorrhage – Mechanisms of Action

Cocaine use is associated with intracerebral haemorrhage [84]. As with ischaemic stroke, the exact mechanism involved is not fully understood. Martin-Schild *et al.* [11] evaluating 3,241 stroke patients admitted to their stroke service from 2004 to 2007, reported that 132 were positive for cocaine metabolites and of those, 45 had intracerebral haemorrhage. These cocaine-positive patients, respect to cocaine-negative patients showed higher blood pressure and severe intracerebral haemorrhage and have a 3 fold higher probability of dying during hospitalization. In a prospective autopsy-based study, Nolte *et al.*, [85] documented positive toxicity of cocaine in 59% of 17 non-traumatic haemorrhagic strokes.

### 2.4.1. Cocaine-Induced Haemodynamic Changes

Autopsy studies demonstrated a higher incidence of hypertensive cardiovascular disease in cocaine-induced haemorrhagic stroke [85, 86], suggesting that haemorrhagic stroke could be a consequence of haemodynamic effects of cocaine in a susceptible subgroup of individuals. Previously, Green and co-workers [84] presenting a case of intracerebral haemorrhages in a patient with a history of cocaine and ethanol abuse reported that 78% of patients with cocaine-related subarachnoid haemorrhage and 48% of patients with cocaine-related intracerebral haemorrhage have underlying vascular abnormalities. In agreement more recently, Chang and co-workers, [44] reviewing data of patients with a diagnosis of aneurysmal subarachnoid hemorrhage admitted to the Johns Hopkins Medical Institutions between 1991 and 2009, documented that recent cocaine use represents an independent predictor of in-hospital mortality. The mechanism of cocaine-induced the aneurysmal rupture is not clearly evaluated even if it may be related to an acute increase of blood pressure, mediated by inhibition of reuptake of dopamine and norepinephrine from the synaptic cleft. Finally, cocaine use is an independent risk factor for cerebral vasospasm after aneurysmal subarachnoid haemorrhage [87].

### 2.4.2. Loss of Cerebral Autoregulation

Cocaine blocks reuptake of catecholamines at pre-synaptic nerve endings, resulting in tachycardia, acute hypertension [88, 89], and increasing the risk of aneurysm rupture [90, 91]. An experimental study in rats documented that cocaine exposure induces a dysfunction in cerebral autoregulation, increases the levels of hypertension (mean arterial blood pressure > 145 mmHg), and predisposes to vascular rupture [92]. Cocaine-induced disturbance of cerebral autoregulation may also result in reperfusion injury and haemorrhagic transformation of an infarct [93].

### 2.4.3. Endothelial Dysfunction

In human aortic endothelial cells, cocaine increases endothelin-1 production and ET-1 receptor type-A expression [94]. It has been hypothesized that vasospasm is mediated through endothelin-1 in patients with cocaine-related subarachnoid haemorrhage from aneurysm. As mentioned earlier, an endothelin-receptor antagonist has been shown to block

spasms induced by cocaine in rabbits [53] and more recently, has been used to treat vasospasm during subarachnoid haemorrhage [95].

### 2.5. Other Mechanisms in Cocaine – Induced Stroke: Secondary Factors

The mechanism of cocaine related stroke is confounded by contaminants, such as procainamide, quinidine and antihistamines, which are often mixed with the cocaine. These chemicals, may contribute to clinical effects and symptoms in ischemic and hemorrhagic stroke. Vasospastic effects of cocaine can persist beyond its half-life [39]. The major metabolites of cocaine (i.e., benzoylecgonine and norcocaine) are also potent vasoconstrictors [50]. These metabolites also induce endothelial von Willebrand factor release and this phenomenon could explain the thrombotic risk after cocaine ingestion [60]. In addition, chronic cocaine use impairs bradykinin-mediated endothelium-dependent relaxation [17]. All of these secondary factors may contribute to the high occurrence of stroke in cocaine users.

### 3. Pharmacological Therapies of Stroke

Acute ischemic stroke causes irreversible injury in ischemic core, but reversible injury in the peri-focal zone, the penumbra, if the stroke is treated quickly [96, 97]. Neurons within the penumbra become functionally impaired, but are not yet dead and are sufficiently active to sustain membrane potentials [98]. Although both timing and cellular pathways involved in neuronal death after ischemia are not fully understood, several mechanisms (e.g. glutamate-mediated excitotoxicity, oxidative stress, nitric oxide overproduction, release of inflammatory cytokines, expression of adhesion molecules, matrix metalloproteinase production, protein synthesis and apoptosis) may be involved [97, 99]. Apoptosis is considered the prototypical form of cell death in the penumbra [97]. Therefore, the primary pharmacological target for acute ischemic stroke treatment should be rescuing the cells in the penumbra area, in order to maintain blood flow and brain activity [96, 97].

Although ischemic stroke has been rigorously investigated for more than two decades, thrombolytic treatment using recombinant tissue plasminogen activator (r-tPA) is still the only FDA-approved pharmacological treatment for acute ischemic stroke [100]. The use of tPA is limited to selective patients with a narrow therapeutic window [101]. Several experimental drugs with anti-inflammatory, antioxidant, and anti-apoptotic actions have been used to provide vascular protection in patients with ischemic stroke [102]. Therefore, in this section, we will describe several medications that have potential uses to reduce cocaine's vasospastic, thrombogenic, or neurotoxic effects.

#### 3.1. Calcium Channel Blockers

Du *et al.*, [48] reported that cocaine-mediated vasoconstriction is related to an increase of intracellular calcium concentrations. Experimental studies documented the effects of calcium antagonist dihydropyridine (isradipine) to reduce cerebral ischemia and neuronal cell damage [103-105].

Sauter and colleagues [106] reported that several dihydropyridine calcium antagonists (i.e., darodipine, nimodipine, nitrendipine, and isradipine) are effective in the management of ischemic damage caused by occlusion of the middle cerebral artery in the rat. The authors further attributed the greatest anti-ischemic and antivasospastic effects of isradipine to the blockade of dopamine release from cortical neurons in the cerebral vasculature. In another experimental study, 60 minutes of cerebral ischemia was induced in spontaneously hypertensive male rats through carotid artery occlusion. Isradipine treatment significantly reduced dopamine, but not glutamate, release [107]. Ooboshi and colleagues [108] reported that pre-treatment with isradipine (200 µg/ml) produced a 37% decrease in dopamine release in the forebrain, but not in the striatum of rats. Similarly, isradipine pretreatment also significantly reduced forebrain ischemia (i.e., improved blood flow), but had no effect on striatal blood flow. Together, these results suggest that isradipine is a potent cerebral vasodilator, particularly in dopamine-innervated brain regions. Similar results were observed in an animal model of cocaine use, in which isradipine (10 mg orally), administered 60 min before intravenous cocaine (0.33 mg/kg), prevented cocaine-induced ischemia in dopamine-rich brain areas such as the inferior parietal, putamen, and superior temporal lobe [109]. These data support the use of calcium channel blockers as a strategy to treat and improve brain damage after cocaine abuse.

#### 3.2. Antithrombogenic Agents

As stated above, cocaine-dependent patients have multiple focal decreases in regional cerebral blood flow. Enhanced platelet activation and aggregation is thought to be one cause of the reduced cerebral blood flow pathophysiology that leads to thrombus formation. Based on this platelet activation, we propose that aspirin, an irreversible inhibitor of cyclooxygenase-1 in platelets, or amiloride, vasodilator and an inhibitor of P-selectin expression (a cell adhesion molecule on the surfaces of activated endothelial cells that activates platelets), may be suitable as antithrombogenic agents. Kosten and co-workers reported a significant improvement in regional cerebral blood flow after amiloride (10 mg daily), but not aspirin (325 mg/daily), treatment in 77 cocaine-dependent subjects [110]. The lack of effect in regional cerebral blood flow by aspirin may be due to platelet thrombi dislodging from larger blood vessels, which blocks circulation of smaller down-stream blood vessels. Moreover, amiloride can induce vasodilatation through inhibition of carbonic anhydrase and improves the areas of hypoperfusion induced by cocaine [110]. Ritanserin, a 5-HT<sub>2</sub> receptor antagonist, also has antiplatelet aggregation properties [111, 112]. However, its use for this indication in cocaine addicts remains to be determined.

As stated above, cocaine may cause acute cerebrovascular disorders such as ischemic stroke and intracranial hemorrhage [17]. Acute cocaine-induced ischemic stroke has been associated with arrhythmias, cardiomyopathies, septic emboli from endocarditis, postmyocardial infarction-related thromboembolism, vasospasm, and vasculitis in intravenous drug abusers [27, 59]. Several of these mechanisms may

pose an increased risk for intracerebral hemorrhage after intravenous administration of tissue plasminogen activator (tPA). In addition, cocaine causes acute hypertension, which may also pose an increased risk of intracerebral hemorrhage after intravenous tPA. Indeed, intracerebral hemorrhage has been reported in patients with cocaine-associated acute coronary syndromes, treated with thrombolytic drugs [113]. Given these concerns, physicians are recommended to be cautious and avoid using tPA for treating acute ischemic stroke associated with cocaine [114].

By comparing cocaine-positive and cocaine-negative patients in thrombolytic treatment with intravenous tPA, Martin-Schild *et al.* [114] found no complications in tPA-treated patients with acute ischemic stroke associated with cocaine. Cocaine-positive and cocaine-negative treated patients had similar stroke severity and safety outcomes. Patients with acute ischemic stroke associated with cocaine treated with tPA had more severe strokes on the baseline National Institutes of Health Stroke Scale and similar safety outcomes compared with non tPA-treated patients with acute ischemic stroke associated with cocaine. In contrast, a young patient with a history of cocaine and ecstasy abuse associated with coma caused by acute basilar artery occlusion. The endovascular thrombo-aspiration method was used to induce a complete recanalization of the basilar artery and allowed positive patient recovery, without risk for intracerebral hemorrhage [115]. Therefore, thrombolytic therapy for acute ischemic stroke associated with cocaine may provide a safe alternative treatment for physicians.

### 3.3. Glutamate Antagonists

Another approach that has been suggested to reduce cocaine's neurotoxic effects is the use of glutamate NMDA (N-methyl-D-aspartate) receptor antagonists, such as phencyclidine and MK-801 [20, 37, 116] and AMPA receptors antagonists [72] to prevent glutamate excitotoxicity from causing neuronal death. These medications should also, potentially, reduce the effects of excitatory amino acids released during neuronal degeneration. However, their other psychoactive effects (such as psycho stimulating, rewarding, or hallucination), limit their extensive use in humans. For instance, these medications not only reduce the seizure threshold, but also are hallucinogenic. Other compounds that modulate glutamatergic transmission through ionotropic glutamate receptors include the non-competitive NMDA receptor antagonists, i.e. amantadine and memantine, the partial NMDA receptor agonist D-cycloserine, [75, 117] and the anticonvulsants topiramate and perampanel [2]. They have shown efficacy in treating cocaine dependence or reducing relapse in humans, as well [3, 4, 118]. Accordingly, glutamate agents with less unwanted side-effects should have greater ability to prevent or treat cocaine-induced cerebral ischemia. In addition, evidence has shown that kappa opiate receptor agonists may also modulate glutamate transmission and, therefore, prevent ischemic damage [17]. For example, the kappa opiate antagonist buprenorphine was reported to decrease cocaine-induced perfusion abnormalities [119]. However, results of this study has been disputed because of the lack of a placebo control. Thus, more research is required to elucidate the role of kappa opiate antagonists in treating cocaine-induced cerebral ischemia.

## CONCLUSION AND DIRECTIONS FOR FUTURE RESEARCH

Abuse of illicit drugs is a major cause of stroke in young patients. The risk of stroke is higher in cocaine users, compared to age-matched nonusers [14]. Cocaine users have additional risk factors for stroke, including tobacco use, heavy alcohol intake, high prevalence of arrhythmias and other health conditions (i.e. cardiomyopathies, hypertension, cerebral vascular malformations) [10, 61].

Moreover, amphetamines co-use, as well as the presence of other adulterant ingredients in cocaine preparations may represent an additional risk factors during cocaine hydrochloride users. Cessation of cocaine use is critical to reduce the risk of stroke. Cocaine induces hemorrhagic stroke, and the incidence of hemorrhagic stroke is higher than ischemic stroke [17]. Caution should be exercised before using thrombolytic agents in these patients due to the higher risk of intracranial bleeding, although Martin-Schild *et al.* [114] showed in a small-scale study that thrombolytic therapy for acute ischemic stroke associated with cocaine appears to be safe. Therefore, more studies are needed to determine the safety and efficacy of intravenous thrombolysis.

Cocaine use induces a cerebral artery vasospasm rather than thrombosis as aetiology of ischemic stroke. Mehta *et al.*, [38] recently reported the benefits of CT angiography/CT perfusion imaging in cases of cocaine abuse. This type of imaging differentiates multifocal vasospasm-induced hypoperfusion/ischemia from focal thromboembolic ischemia/infarct, allowing for appropriate medical management in the crucial hyperacute time period. Experimental studies showed that exposure to cocaine induced neuronal death via multiple apoptosis-regulating mechanisms [120]. Apoptosis is an active process in the penumbra after stroke, contributing to the evolution of ischemic lesions [97]. Therefore, the apoptotic effects of cocaine may induce neuronal death to occur even more rapidly in the penumbra. There is insufficient evidence to evaluate the clinical utility of screening tests for drug abuse in primary care settings, including toxicology tests of blood or urine, or the use of standardized questionnaires to screen for drug use or misuse [121]. However, it is reasonable to screen young patients, particularly men, for drug use when they present with cryptogenic stroke. In addition, every effort should be made to encourage cessation of cocaine use, particularly, in the presence of other specific factors that increase the risk of stroke.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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