Peer reviewed article

Platelet activation as a universal trigger in the pathogenesis of acute coronary events after cocaine abuse[1]

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Numerous reports document the widespread use of cocaine in most parts of the world, which confers an increased risk of vascular morbidity and mortality. The mechanisms responsible for this association are multifactorial, but platelet activation might play a substantial role linking these events. Contradictory data exist regarding the cellular mechanisms of cocaine's effects on thrombocytes. In terms of therapeutic interventions, a possible activation of platelets would conceptually require more aggressive anti-platelet therapy with aspirin, clopidogrel or other compounds, however, no data exist to date to support this approach. Further studies elucidating these issues are warranted. This review summarizes the latest and often confusing data on the interaction between cocaine and platelets in certain in vitro, animal and clinical scenarios.

Key words: platelets; cocaine; coronary artery disease

Introduction

With limited resources and an ever-growing incidence of cocaine abuse, patients, academic centres, and community hospitals alike could benefit from an identifiable trigger of morbidity in cocaine use that can be targeted pharmacologically to prevent clinical manifestations. This article is intended to review the literature on cocaine induced platelet activation and its potential for therapeutic intervention in cocaine induced cardiac events.

Illicit drug trade touches millions of lives in both developed and developing countries. Its most deleterious impact is concentrated amongst the vulnerable and marginalized of our societies. The UN estimates that some 180 million people worldwide – 4.2% of people aged 15 years and above – were consuming drugs in the late 1990s; this figure includes 144 million consuming cannabis, 29 million people consuming amphetamine-type stimulants, 14 million people taking cocaine and 13 million people abusing opiates, 9 million of whom were addicted to heroin [1]. In 1997 an estimated 1.5 million Americans, or 0.7% of the population aged 12 and older, were current cocaine users [2].

In 2000, there were an estimated 601,776 drug-related emergency department (ED) episodes in the U.S. with an overall of 1,100,539 ED drug mentions (1.8 drugs per episode). From 1990 to 2000, total drug-related episodes increased 62%, from 371,208 to 601,776. Cocaine-related episodes constituted 29% (174,896) of all ED drug episodes in 2000, more than any other illicit substance [3]. Hence, cocaine remains the most common cause of illicit drug-related visits to the emergency department, and it is associated with a large abrupt but transient increase in the risk of acute myocardial infarction (MI) in patients who are otherwise at relatively low risk. As cocaine abuse has become widespread, it has been associated with various acute vascular complications, including angina pectoris, myocardial infarction, stroke and sudden cardiac death. There were 16,926 deaths from drug-induced causes in 1998 (legal and illegal drugs) (1998) [4].

Effects of cocaine on the cardiovascular system

As mentioned above, cocaine is associated with a large, but transient increase in the risk of acute MI in patients who otherwise would not be regarded as at risk [5, 6]. Moreover, cocaine abuse has been associated with many vascular complications involving the carotid, coronary or renal vas-

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cular beds, possibly enhancing platelet-endothelial interactions, and causing venous thrombosis [7]. Cocaine's direct effects on the cardiovascular system are primarily mediated via alpha-adrenergic stimulation. They include an increase in the determinants of myocardial oxygen demands through modulation of heart rate and alteration of systemic arterial pressure, as well as a concomitant decrease in myocardial oxygen supply presumably caused by vasoconstriction of the epicardial coronary arteries [8]. These transient structural changes of the coronary arteries as a result of cocaine abuse can trigger severe chest pain, angina, and even acute MI.

In addition, cocaine has proarrhythmic effects on the myocardium, with multiple mechanisms thought to be involved. The adrenergic mechanism appears to be a result of neurotransmitter uptake blockade, whereas the ionic disbalance often encountered is neurally independent [9]. In humans, intracoronary infusion of cocaine (sufficient in amount to achieve a high drug concentration in coronary sinus blood) causes a deterioration of left ventricular systolic and diastolic performance [10]. Intense alpha-adrenergic stimulation resulting from cocaine use combined with atherosclerotic coronary artery disease puts the patient at greater risk of having an acute ischemic event [11]. Taken together, cocaine has been shown to be responsible for the blockade of neurotransmitter reuptake causing arrhythmogenesis via increased intracellular calcium, myocardial ischaemia via vasospasm, and increased myocardial oxygen demand and contraction band necrosis via increased intracellular oxygen demand [12]. Cocaine inhibits neuronal epinephrine uptake, even with long duration of abuse, and may also influence directly or indirectly related enzymatic systems [13]. Pharmacological effects of cocaine are more diverse and include increased (central) neurotransmission by re-uptake inhibition of dopamine and serotonin [14, 15]. Existing data suggest that cocaine is able to increase vasoconstrictive endothelin-1 release in vitro and in vivo. Cocaine-induced vasoconstriction / vasospasm may therefore be facilitated by the release of endothelin-1 [16].

A hypothesis

Thus, myocardial infarction and other cardiovascular events are well-recognized complications of cocaine abuse. However, the pathophysiological basis for cocaine-induced acute coronary syndromes is not fully elucidated. One attractive hypothesis to explain the association of thrombosis with chronic cocaine ingestion is that cocaine either directly or indirectly induces platelet activation. In this context it has been reported that, using various *in vitro* experimental models, wide ranges of cocaine concentrations cause mostly pro-aggregatory effects on platelet function [17].

Cocaine: pathophysiological effects on platelet function

If cocaine indeed activates platelets, it does so via either direct or indirect pathways or both. It is well established that cocaine exposure causes platelet activation, alpha granule release, and enhanced formation of platelet microaggregates [18]. Cocaine has been found to induce fibrinogen binding to the platelet surface, implicating this narcotic agent as an agonist capable of non-specific platelet activation in whole blood. It has been noted that cocaine may stimulate the release of substances from the vascular endothelium or from circulating platelets, thus promoting thrombosis and/or inhibiting fibrinolysis. Intranasal cocaine use, at a dose of 2 mg/kg body weight, increased PAI-1 (plasminogen activator inhibitor) activity, a well-known inhibitor of clot lysis [19]. In addition, reported alterations in platelet-endothelial cross-talk predispose cocaine abusers to coronary artery thrombosis and ischaemia [20]. Chronic abusers who died of acute coronary thrombosis had moderate to severe coronary atherosclerosis and an increased number of adventitial mast cells. These particular cells may initiate a deleterious cascade of events leading to premature atherosclerosis, vasospasm, or acute thrombosis, and sudden death in selected individuals who habitually, i.e. chronically, use cocaine [21].

As mentioned before, animal models have supported the finding that administration of cocaine has a pro-thrombotic effect. In swine, cocaine increased the reactivity of platelets exposed to the subendothelium [22]. A study in rats concluded that cocaine exposure, in conjunction with other pathological conditions such as atherosclerosis, coronary vasopasm, or pre-existing ischemic events, may contribute to the onset of thrombotic phenomena by interfering with the prostaglandin system [23]. Indirect activation of platelets was confirmed in a study in dogs, maintaining that cocaine metabolites rather than the drug itself may induce platelet aggregation [24].

On the other hand, a few studies have suggested that cocaine may negatively affect hemostasis by decreasing platelet function under certain conditions [25]. Although a seemingly contradictory concept, cocaine may have a direct inhibitory effect on the ability of platelets to participate in thrombus formation. In vitro studies have shown that cocaine in high concentrations inhibits ADP- and arachidonic acid-induced platelet aggregability [26]. Cocaine modifies both Ca^{++} membrane binding and the extent of Ca^{++} influx, thereby increasing permeability to arachidonic acid and al-

tering the affinity of the membrane binding sites for aggregation agents. Cocaine use is associated with the loss of heterotrimeric G proteins that mediate the earliest step in cell responses to external events by linking cell surface receptors to intracellular signaling pathways. In one recent report it has been shown that deletion of the alpha subunit of G(z) in mice impairs platelet aggregation by preventing the inhibition of cAMP formation normally seen at physiologic concentrations of epinephrine, and causes the mice to be more resistant to fatal thromboembolism [27]. Recently, one report found that cocaine does not cause a hypercoagulable state and therefore cannot assist in explaining ischemic alterations in users [28].

In conclusion, while it is obvious that cocaine abuse is associated with increased vascular mortality, the mechanism of this association is definitely multifactorial and platelet activation might play a substantial role linking these events. Contradictory data exist regarding the cellular mechanisms of cocaine's effects on thrombocytes. Further studies elucidating these mechanisms are warranted. In terms of therapeutic interventions a possible activation of platelets would conceptually require antiplatelet therapy with aspirin, clopidogrel or other compounds, but no data exist to date to support this approach.

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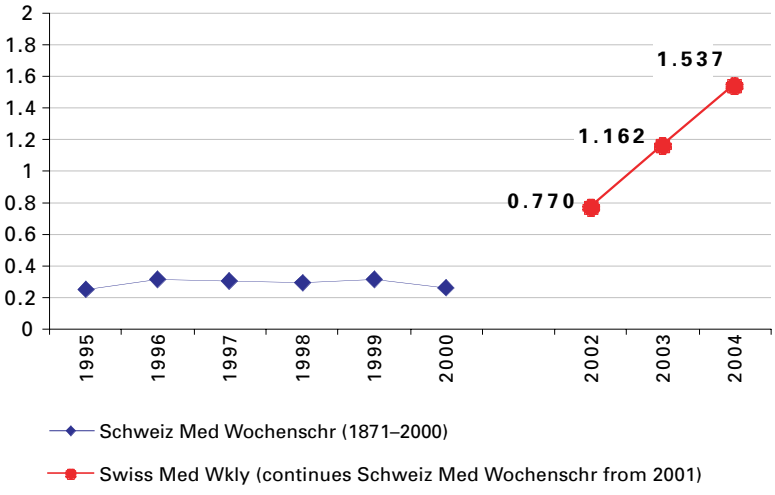

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