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

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Introduction

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-
Platelet activation in acute coronary events after cocaine abuse

Platelet activation is a key event in the pathogenesis of acute coronary events. Cocaine abuse can trigger severe chest pain, angina, and acute MI, possibly due to 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 up-regulation due to increased (central) neurotransmission by re-uptake inhibition of dopamine and serotonin [14, 15]. Existing data suggest that cocaine is able to increase vasoconstrictive endothelin-I release in vitro and in vivo. Cocaine-induced vasoconstriction / vaso-spasm may therefore be facilitated by the release of endothelin-I [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, vasoospasm, 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 vasoconstriction, 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(0) 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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