Anticoagulatory and Procoagulatory Effects of Cannabinoids

Subjects: Hematology

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Abnormal blood coagulation or coagulopathy is a common manifestation of many pathological conditions. It occurs when there is an imbalance between the activities of the coagulation system and the fibrinolytic system, leading to excessive or impaired intravascular blood clot formation, which can disturb blood flow causing ischemia or hemorrhage in the affected tissues. A growing body of evidence has demonstrated blood coagulation abnormalities in association with cannabinoid use, suggesting the involvement of the endogenous cannabinoid system (ECS) in modulating blood coagulation. However, the evidence in the literature has been controversial on whether cannabinoids promote or inhibit blood coagulation.

cannabinoids endocannabinoids endocannabinoid system marijuana cannabis coagulopathy blood coagulation thrombosis hemorrhage

1. Introduction

The endogenous cannabinoid system (ECS) is a complex regulatory network involved in the homeostasis of the organism at the cell, tissue, and organ levels. It is involved in embryogenesis and neurodevelopment [1][2], neuromodulation and neuroprotection [3][4], learning and memory [5][6], motor control [7], pain modulation [8][9], metabolic and immune responses [10][11][12], autonomic regulation of organ functions [13][14][15], among others. Given its involvement in tuning a wide range of pathophysiological processes, the ECS has attracted many researchers to study its potential as a therapeutic target in many pathological conditions such as cancer, cardiovascular disease, neurological disorders, inflammatory conditions, obesity, and metabolic disorders [11][16][17][18].

The versatile ECS consists primarily of (i) cannabinoid receptors type 1 and 2 (CB1 and CB2); (ii) their endogenous activating ligands including arachidonoyl ethanolamide (AEA), also known as anandamide, 2-arachidonoylglycerol (2-AG), virodhamine (O-arachidonoyl ethanolamine (O-AEA), and N-Arachidonoyl Dopamine [19], the latter two being sometimes considered as endocannabinoid-like ligands; and (iii) the enzymes involved in the metabolism of these endocannabinoids, such as diacylglycerol lipase (DAGL), N-arachidonoyl phosphatidylethanolamine phospholipase D (NAPE-PLD), monoacylglycerol lipase (MAGL), and fatty acid amide hydrolase (FAAH) [20][21]. Both CB1 and CB2 receptors belong to the class A subfamily of G protein-coupled receptors (GPCRs). Activation of these receptors results in cellular signaling that (i) inhibits adenylyl cyclase causing a decrease in intracellular cyclic adenosine monophosphate (cAMP) and protein kinase A levels, (ii) inhibits voltage-dependent N and P/Q type Ca^{2+} channels leading to a decrease in calcium influx, (iii) stimulates type A K^{+} channels causing an increase

in potassium efflux, and (iv) stimulates mitogen-activated protein kinases (MAPK) [22]. The best characterized endogenous ligands of CB1/CB2 receptors, AEA and 2-AG, are eicosanoids that are synthesized on demand from phospholipid precursors. NAPE-PLD catalyzes the synthesis of AEA [23], while DAGL is involved in 2-AG synthesis [24]. AEA and 2-AG have a short activity in vivo that is followed by rapid cellular uptake and intracellular degradation into arachidonic acid (AA) through metabolic reactions facilitated by the catalytic activities of FAAH and MAGL, respectively [25][26]. With the activities of various enzymes, AA is further metabolized into other eicosanoids, such as thromboxane A_2 (TXA_2) and prostaglandins [27]. AEA can act as a partial or full agonist on CB1 receptors depending on the system, but it has low efficacy at CB2 receptors, whereas 2-AG is considered a full agonist for both receptors [28]. In addition to the endogenous ligands of CB1 and CB2, these receptors can be modulated exogenously by other compounds including various synthetic receptor agonists and antagonists, as well as by naturally occurring plant-derived cannabinoids (phytocannabinoids), such as Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabinol (CBN), and cannabigerol (CBG). Δ^9-THC represents the most abundant cannabinoid in marijuana and is considered the main constituent responsible for its psychoactive effects [29][30].

2. Anticoagulatory Effects of Cannabinoids

Anticoagulatory effects of cannabinoids have been reported in a few preclinical studies and clinical case reports. Recently, in 2018, a multistate outbreak of synthetic cannabinoid-associated coagulopathy was declared in the Midwest of the United States with a series of case reports indicating an association between the (over-)use of synthetic cannabinoids and the incidence of coagulopathic hemorrhage, which may suggest potential anticoagulatory effects of these cannabinoids. However, in many of these cases, the hemorrhage induced by synthetic cannabinoid consumption seems to be an indirect effect and attributed to contamination of these cannabinoids with Brodifacoum, a commonly used rodenticide that functions as a long-acting vitamin K-dependent antagonist, hence, has anticoagulatory properties [31][32][33][34][35]. In other cases, however, the reported coagulopathic hemorrhage was thought to be a result of drug–drug interaction. Patients were on anticoagulative warfarin therapy and presented to clinics with events of supratherapeutic INR with or without bleeding in association with therapeutic or recreational uses of phytocannabinoids. It has been suggested that these cannabinoids may potentiate the anticoagulative effect of warfarin through cytochrome P450 interaction, thus, close monitoring and adjusting of warfarin doses are necessary for patients who consume cannabinoids [36][37][38].

Some preclinical studies, however, have indeed demonstrated anticoagulatory effects of phytocannabinoids as well as endocannabinoids. Levendal and Frost [12] studied the metabolic and coagulatory effects of a plant-derived cannabinoid, organic *Cannabis sativa* L. extract, administered subcutaneously, in streptozocin-induced diabetic Wistar rats. Thrombin-induced clotting time showed a significant prolongation in cannabis-treated diabetic rats compared to a vehicle. A similar effect of the cannabis extract on thrombin-induced clotting time was observed in rats without diabetes compared to the vehicle group.

The coagulatory effects of the phytocannabinoids olivetol, CBG, CBD, CBN, and THC were also examined on human and rabbit platelets [39]. It has been found that ADP-induced platelet aggregation was inhibited by all these cannabinoids in a dose-dependent manner both in human and rabbit platelets. A partial primary inhibition and a

total secondary inhibition by these compounds were observed in human platelet aggregation induced by adrenaline. These cannabinoids also showed a dose-dependent inhibition of rabbit platelet aggregation when the aggregation was induced by PAF. Although these cannabinoids had inhibitory effects on human and rabbit platelet aggregation, their effects on serotonin [^{14}C]5-HT release did not correlate with the inhibition of aggregation.

3. Procoagulatory Effects of Cannabinoids

While some reports in the literature have linked cannabinoid actions with hemorrhage, others illustrate an association between cannabinoid use and thromboembolic complications, suggesting procoagulatory effects of cannabinoids. In one case [40], the patient over a period of nine months had presented with recurrent thromboembolism manifested as acute bilateral renal infarcts, a left renal infarct, a pulmonary embolism (PE), and an ischemic stroke on four separate occasions following synthetic cannabinoid smoking. Her past medical history and family history were negative for potential risk factors of coagulopathy. Furthermore, her clinical investigation did not reveal any results that could explain her condition. She was started on anticoagulative therapy after her first thrombotic event and, despite being on a prophylactic daily aspirin (ASA), she developed repeated thromboembolism. The fact that each of these thromboembolic events was preceded by heavy smoking of cannabinoids is strongly indicative of a procoagulatory response triggered by these cannabinoids that possibly led to the activation of inflammatory pathways or coagulation pathways, albeit the exact mechanisms remain unknown.

In vitro studies conducted to examine the effects of endogenous cannabinoids on platelet function may give insights into possible mechanisms underlying the cannabinoid-induced procoagulatory responses seen with the previously reported thromboembolism cases associated with cannabinoid use, although, as indicated above, other mechanisms might be implicated. A study examined the effects of the main endocannabinoids AEA, 2-AG, and virodhamide on platelet aggregation in human blood and platelet-rich plasma (PRP) samples using multiple electrode aggregometry showed that both 2-AG and virodhamide stimulated platelet aggregation in blood, and induced shape change and adenosine triphosphate (ATP) release that was followed by platelet aggregation in PRP, whereas AEA (600 µM) was inactive. In addition, the stimulatory effects of 2-AG and virodhamide on platelet aggregation in blood and PRP were dose-dependent. The synthetic cannabinoids ACEA, a CB1 agonist, and JHW015, a CB2 agonist, showed neither a stimulatory nor inhibitory effect on platelet aggregation. The platelet aggregation induced by 2-AG and virodhamide was inhibited by ASA, a COX-1 inhibitor, daltroban, a specific TXA_2-receptor antagonist, and JZL184, a MAGL inhibitor, suggesting that this aggregation resulted from the degradation of these endocannabinoids into free AA and its metabolite TXA_2, rather than direct CB1/CB2 activation [41].

On the other hand, a study on washed human platelets demonstrated a dose-dependent platelet activation by AEA (250–1300 µM) resembling the effects induced by AA. However, unlike the AA-induced platelet activation, the activation triggered by AEA was not inhibited by ASA. Furthermore, PMSF, an inhibitor of FAAH that degrades AEA into AA, did not affect platelet activation induced by AEA, suggesting that this activation is independent of the AA pathway with no evidence to support a CB1/CB2 activation-dependent mechanism [42]. Another in vitro study, however, was able to show the existence of both CB1 and CB2 cannabinoid receptor expression on human platelet surface using Western blot. It also investigated the effects of THC (final concentrations 10^{-7} to 10^{-5} M) on platelet

activation. Whole blood flow cytometric analyses revealed that THC increased the expression of activated platelet surface markers: fibrinogen receptor (glycoprotein IIb-IIIa) and P selectin in a dose-dependent manner [43].

4. Conclusions

As illustrated in the previous two sections, members of all classes of cannabinoids (synthetic, plant-derived, and endogenous), despite being vastly different in their structure, receptor affinity, potency, and metabolism can have pro- or anti-coagulatory effects (**Table 1**). The reported variations in the coagulatory effects of a particular cannabinoid often depends on the experimental conditions under which the cannabinoid was studied. In the case of synthetic cannabinoids, contamination with other substances might largely be responsible for the observed anti-/pro-coagulatory effects. Nonetheless, plant-derived cannabinoids have shown interactions with warfarin, a well-known vitamin K antagonist that is commonly prescribed as an anticoagulant for many clinical indications including stroke prevention and DVT treatment and other cardiovascular conditions. Studies have indicated that both phytocannabinoids, Δ^9-THC and CBD, are potential inhibitors for the enzymatic activity of the cytochrome P450 enzyme CYP2C9 [44][45][46], which is the primary metabolic site where the S-enantiomer of warfarin, the part of the warfarin medication that exhibits the most potent anticoagulative effect, undergoes significant oxidative metabolism in the liver [46]. Therefore, the anticoagulative effect of warfarin could potentially be potentiated using these cannabinoids. With the recent increase in the interest in exploring the clinical potential of cannabinoids and the medicinal use of marijuana, clinicians should be aware of such drug–drug interactions that affect blood coagulation like the one reported with an FDA-approved CBD-based drug for treating intractable epilepsy, (Epidiolex, Greenwich Biosciences) [37]. In addition to the indirect anticoagulatory effects of phytocannabinoids, some of them indeed have been shown to exhibit anticoagulatory effects in pre-clinical studies by inhibiting thrombin activity [12][47] or platelet aggregation [39][48]. It seems, however, that consuming phytocannabinoids (or sometimes synthetic ligands) by smoking is likely to be associated with procoagulatory effects [40][49][50][51][52]; whether smoking itself is responsible for inducing the procoagulatory effects of these cannabinoids remains to be elucidated. Reported coagulatory studies of endogenous cannabinoids have been mainly done in vitro and, except for one study that demonstrated an anticoagulatory effect of AEA by inhibiting platelet aggregation [48], most of these studies support a procoagulatory effect through stimulating platelet activation and aggregation, although the exact mechanisms by which this effect occurs are still controversial [41][42][53].

Table 1. Overview of the reported coagulatory effects of various classes of cannabinoids with potential underlying mechanisms.

Cannabinoid	Anticoagulatory Effects with Potential Underlying Mechanisms	Reference
Synthetic		
Synthetic Cannabinoids	Indirect anticoagulatory effect → contamination of cannabinoid with brodifacoum (Vitamin K antagonist).	[31][32][33][34][35]
Plant-derived		

Cannabinoid	Anticoagulatory Effects with Potential Underlying Mechanisms	Reference
THC, CBD, cannabis	Drug–drug interactions → cannabinoids may potentiate the anticoagulative effect of warfarin in patients taking warfarin therapy through cytochrome P450 interaction.	[36][37][38]
Cannabis extract	Prolongation of thrombin-induced clotting time in diabetic Wistar rats.	[12]
Cannabis extract, THC, CBN	Inhibition of thrombin-induced clotting formation in vivo and in vitro.	[47]
Olivetol, CBG, CBN, CBD, THC	Inhibition of human and rabbit platelet aggregation.	[39]
Cannabis smoking	Diffuse alveolar hemorrhage and hemoptysis (unknown mechanisms)	[54][55][56]
Cannabis sativa	Impairment of collagen-induced platelet aggregation and aggregate formation on immobilized collagen under flow ex vivo.	[48]
Endogenous		
AEA	Inhibition of platelet aggregation and aggregate formation under flow over collagen in vitro through inhibiting P selectin expression and limiting glycoprotein IIb/IIIa activation.	[48]
Cannabinoid	**Procoagulatory Effects with Potential Underlying Mechanisms**	**Reference**
Synthetic		
Synthetic cannabinoid smoking	Repeated thromboembolic events with possible activation of inflammatory or coagulative pathways.	[40]
Synthetic cannabinoid smoking (JWH-018)	Acute ischemic stroke in patients with no prior risk factors for stroke (unknown mechanisms).	[49]
Synthetic cannabinoid use	Acute ischemic stroke with other prior risk factors for developing stroke.	[57]
Plant-derived		
Chronic THC exposure	Increase in the risk of developing venous thromboembolic complications in adult and geriatric trauma patients (unknown mechanisms).	[58][59]
Acute marijuana smoking	Increase in the risk of M.I by 5 times over baseline during the 60 min following acute marijuana smoking. Potential mechanisms: Activation of CB1 receptors with increased oxidative stress at the cardiovascular tissue level that may ultimately lead to the activation of coagulative pathways.	[50][60][61][62][63]
THC	Stimulation of platelet activation via CB1/CB2-dependent mechanism through increasing fibrinogen receptor (glycoprotein IIb-IIIa) and P	[43]

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Cannabinoid	Anticoagulatory Effects with Potential Underlying Mechanisms	Reference
	selectin expression.	
Endogenous		
2-AG, Virodhamide	Stimulation of platelet aggregation in human blood and PRP samples through degradation of these endocannabinoids into AA metabolite (TXA_2).	[41]
2-AG	Stimulation of platelet activation accompanied by a robust TXA_2 release from these platelets leading to cytoplasmic Ca^2+ release, granule secretion, and platelet aggregation.	[53]
AEA	Stimulation of platelet activation through a mechanism independent of the AA pathway.	[42]

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