



Cannabinoids: Pivotal Role in Sepsis



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Introduction

Sepsis is a multifactorial disease with uncontrolled systemic production of inflammatory mediators ('cytokine storm') leading to systemic inflammatory response syndrome (SIRS) following microbial infection. It is characterized by vascular hyporeactivity, decreased tissue perfusion, tachypnoea, hyperthermia, systemic hypotension, multiorgans failure despite of antibiotic therapy, adequate fluid resuscitation and administration of vasopressors. Infections caused by bacteria (Gram +ve or Gram -ve), fungi, virus, parasites etc. or pathological conditions like ischaemia, burn, abdominal surgery, pancreatitis, haemorrhage etc. favour the development of niche for sepsis. In Indian context, hospital mortality and 28 days mortality of severe sepsis were found to be 65.2% and 64.6%, respectively, within the period between June 2006 and June 2009 [1], while in United States, sepsis ranks tenth leading cause of death with mortality rates varying between 30 to 70% among ICU patients [2]. The characteristic vascular hyporeactivity and persistent hypotension leading to multiple organs failure is considered to be the major cause of death in septic patients. It is well established that uncontrolled release of pro-inflammatory mediators like tumor necrosis factor (TNF α), interleukin-1, interleukin-6, chemokines, prostaglandins, leukotriens, proteases, platelet activating factor (PAF), histamine, endocannabinoids and nitric oxide are directly or indirectly involved in mediating endothelial dysfunctions and alteration in microcirculation resulting in tissue hypoxia and organ dysfunction [3].

Excess production and release of nitric oxide (NO) followed by stimulation of the soluble guanylyl cyclase (sGC) in smooth muscle cell (SMC) imparts an imbalance in the equilibrium between vasoconstriction and vasodilatation with a predominance of vasodilatation. Cannabinoids are synthesized from different types of phospholipids in peripheral tissues by enzymes diacylglycerol lipases (DAGL- α and DAGL- β). Fatty acid amide hydrolase (FAAH), a microsomal enzyme, hydrolyses cannabinoids. Cannabinoids are also metabolized by monoacyl glycerol lipase (MAGL) present in the presynaptic neurons. The cannabinoids being highly lipid soluble act through cannabinoid receptors CB1 and CB2 which are the member of rhodopsin family of G-protein coupled receptors. Cannabinergic system plays a pivotal role in regulation of cardiovascular system in certain pathological conditions associated with hypotension such as haemorrhagic shock, cardiogenic shock and

endotoxic shock. The fascinating possibility of using cannabinoids as antihypertensive agents came into light more than 30 years ago. CB1 receptor antagonists SR 141716 and AM251, in spontaneously hypertensive rats evoked a sustained increase in blood pressure and cardiac contractility without any change in heart rate, however, in normotensive rats no effect was observed on blood pressure and cardiac contractility. Similar evidence has also been found in angiotensin II-induced hypertensive rat, more likely due to increase in the expression of vascular and cardiac CB1 receptors in hypertensive rats compared to normotensive rats [4]. During septic insults, cannabinoids are released from macrophages and platelets and acts as a potent vasodilator. AEA, an agonist of cannabinoid receptors contributes to hypotension and bradycardia whereas 2-AG another agonist of cannabinoid receptors, plays a key role in development of tachycardia and transient decrease in blood pressure which contributes to haemodynamic changes in septic condition. Stimulation of CB2 receptors is mainly associated with anti-inflammatory effect.

Cannabinoids play a major role in immune cell function and in regulation of inflammation as they inhibit excess formation of cytokines, apoptosis of lymphocytes, migration of leukocytes, decrease in the expression of TLR-4 (antigen presenting cells) depending upon the stages of septic shock [5]. Inhibition of metabolic enzymes, FAAH and MAGL, results in increase in the activity of cannabinoids resulting in augmentation of inflammation [6]. Taken together, cannabinoids exerts differential action in sepsis. On the other hand, time -dependent vertical therapy is a critical approach in sepsis. Thus understanding of cannabinoids action during different stages of sepsis is very important to establishes cannabinoids-targeted therapy in sepsis.

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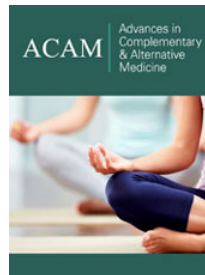
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