Endocannabinoids and Vascular Function

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ABSTRACT

Marijuana is used by humans for its psychoactive and medicinal effects. The active constituents of marijuana, the cannabinoids, exert effects via a G protein-coupled receptor, CB1. Two arachidonic acid analogs, N-arachidonylethanolamine and 2-arachidonylglycerol are hypothesized to function as endogenous ligands of the CB1 receptor. The cannabinoids exert significant vascular effects in humans and laboratory animals. In particular, the cannabinoids produce vasodilation and hypotension. The possible mechanisms for these effects are inhibition of transmitter release from sympathetic nerve terminals, direct effects on vascular smooth muscle cells, and effects on endothelial cell function. The data regarding these effects of the cannabinoids and possible sources of endocannabinoid ligands in the vasculature are the subjects of this review.

The biologically active principal of marijuana, Δ⁹-tetrahydrocannabinol (Δ⁹-THC), is a partial agonist of a G protein-coupled receptor. This receptor, named the CB1 receptor, is selectively activated by Δ⁹-THC and other cannabinoids (for review see Pertwee, 1999). The CB1 receptor has been characterized at a molecular level and is expressed in high amounts in the central nervous system (CNS). Antagonist studies (Dutta et al., 1994) and studies using CB1 receptor knock-out mice (Zimmer et al., 1999) provide evidence that most of the biological effects of i.v. doses of 10 mg/kg or less of Δ⁹-THC are mediated by the CB1 receptor.

Our understanding of the mechanism of activation of the CB1 receptor and its role in cellular function has come largely through studies of the effects of synthetic cannabimimetic compounds. These include: CP55940 and HU210, bicyclic and tricyclic derivatives of Δ⁹-THC; and Win 55212-2, an aminoalkylindole that binds the CB1 receptor with high affinity. Two competitive antagonists of the CB1 receptor have been identified. The first, SR141716A, binds to the CB1 receptor with high affinity and is selective for the CB1 receptor at concentrations below 1 μM (Rinaldi-Carmona et al., 1994). SR141716A is not completely specific for the CB1 receptor at concentrations above 1 μM. A second antagonist for the CB1 receptor LY320135 has lower affinity for the CB1 receptor and is less potent than SR141716A (Felder et al., 1998).

Mechoulam and coworkers discovered that a minor constituent of brain lipid extracts, N-arachidonylethanolamine (AEA; anandamide) bound and activated the CB1 receptor (Devane et al., 1992). Because AEA mimics the biochemical and physiological effects of Δ⁹-THC, these investigators suggested that AEA was the endogenous agonist of the CB1 receptor. Although considerable evidence has accumulated to support this hypothesis (Hillard and Campbell, 1997), it has not been definitively proven. For example, evidence that links an AEA-synthesizing cell in a synaptic or other close anatomical relationship with a cell expressing the CB1 receptor is lacking. In addition, questions remain regarding the regulation of the cellular syntheses of AEA and its putative precursor, N-arachidonylphosphatidylethanolamine. However, the evidence in support of AEA as an “endocannabinoid” is mounting as tools and techniques for its measurement improve. Some of the most exciting studies involve the relationships between AEA and the CB1 receptor in the vascular system. These studies are the subject of this review.

A second possible endogenous ligand of the CB1 receptor is the arachidonate ester, 2-arachidonylglycerol (2-AG) (Sugiura et al., 1997). 2-AG is an agonist of both the CB1 and CB2 receptors, and its concentration in brain is an order of magnitude higher than AEA. In spite of this, 2-AG has received...
less attention, possibly because it has poor stability both in vitro and in vivo. 2-AG spontaneously rearranges to 1-AG, which has lower affinity for the CB1 receptor than the parent compound (Sugiura et al., 1999). In addition, 2-AG is rapidly catalyzed by a number of cellular esterases that are not easily inhibited (Bisogno et al., 1997). This has hampered ligand binding studies and led to the conclusion that 2-AG has low affinity for the CB1 receptor. In fact, studies using whole cells demonstrate that 2-AG has both full efficacy and high affinity for the CB1 receptor (Sugiura et al., 1999).

CB1 receptors couple to several signal transduction cascades through activation of heterotrimeric G proteins (Pertwee, 1999). The major effects of activation of the CB1 receptor are pertussis toxin sensitive, evidence that the G proteins involved are of the G\textalpha_{i/o} family. CB1 receptor agonists inhibit the influx of calcium through N- and P/Q-type voltage-operated calcium channels, increase the open probability of several types of potassium channel, inhibit the activity of adenylyl cyclase, and initiate mitogen-activated protein kinase-mediated cascades. This spectrum of CB1-mediated cellular effects results in important functional changes, particularly in excitable cells such as neurons. Among other outcomes, the combination of decreased calcium channel activity and increased probability of potassium channel opening would be expected to have profound effects on neuronal neurotransmitter release. This is indeed the case in the hippocampus where CB1 receptors located on axon terminals exert significant inhibitory effects (Shen et al., 1996).

Cardiovascular Effects of the Cannabinoids In Vivo

It has been long recognized that the cannabinoids produce cardiovascular effects in vivo. In humans, the most consistent cardiovascular effects of both marijuana smoking and i.v. administration of Δ9-THC are peripheral vasodilation and tachycardia (Dewey, 1986). These effects manifest themselves as an increase in cardiac output, increased peripheral blood flow, and variable changes in blood pressure.

In anesthetized rats and dogs, Δ9-THC produces a transient pressor response followed by long-lasting hypotension and bradycardia (Dewey, 1988). The hypotensive effect of Δ9-THC is mimicked by various cannabinoids, including those with a rank order of potency that correlates well with the affinity of the same ligands for the CB1 receptor (Lake et al., 1997). The transient pressor effect of Δ9-THC is not mediated by the CB1 receptor. Administration of the endocannabinoid AEA to anesthetized rats also produces a brief pressor response that is followed by a more prolonged decrease in blood pressure (Varga et al., 1995). The depressor response to AEA is inhibited by coadministration of SR141716A (Varga et al., 1995) and is absent in CB1 receptor null mice (Jarai et al., 1999).

Activation of the CB1 Receptor Results in Decreased Sympathetic Outflow

The hypotensive effect of the cannabinoids in anesthetized animals requires intact sympathetic outflow from the CNS, and the hypothesis was put forward many years ago that the hypotensive and bradycardic effects of the cannabinoids resulted from inhibition of sympathetic outflow (Hardman et al., 1971; Vollmer et al., 1974). For example, the hypotensive effect of the synthetic cannabinoid 1-hydroxy-3(1,2-dimethylheptyl)-6,6,9-trimethyl 7,8,9,10-tetrahydro-6-dibenzopyran (DMHP) was lost in cats with spinal cord transections at the first cervical vertebra (Hardman et al., 1971). Furthermore, dogs treated with a very low dose (0.05 mg/kg) of DMHP lost the pressor reflex induced by occlusion of the common carotid artery. Because the pressor response to epinephrine was preserved in DMHP-treated dogs, these authors suggested that DMHP must interrupt sympathetic innervation of the blood vessels. Other investigators came to the same conclusions and suggested that the site of cannabinoid action was at the cardioregulatory centers in the CNS (Vollmer et al., 1974), although their data are also consistent with cannabinoid inhibition of the release of norepinephrine from sympathetic nerve terminals.

Recent studies using AEA in anesthetized rats (Varga et al., 1995) and Win 55212-2 in pithed, conscious rabbits (Niederhoffer and Szabo, 1999) eliminate a CNS site for the depressor effect of the cannabinoids. In rats, AEA increases activity in the sympathetic premotor neurons in the rostral ventrolateral medulla, an obligatory outflow pathway for centrally mediated sympathomodulatory effects (Varga et al., 1996). Similarly, Win 55212-2, administered into the cisterna cerebellomedullaris of rabbits, produces sympathoexcitation and activation of cardiac vagal fibers (Niederhoffer and Szabo, 1999). Thus, the cannabinoids induce a CNS-mediated increase in sympathetic and parasympathetic nerve activity, which would increase blood pressure and decrease heart rate. Therefore, this effect does not explain the observed depressor effects of the cannabinoids although it may underlie their bradycardic effects.

Cannabinoid inhibition of sympathetic innervation of the peripheral vasculature is due to CB1 receptor-mediated inhibition of norepinephrine release from sympathetic nerve terminals. Support for this conclusion comes from several studies. First, mRNA for the CB1 receptor is detected in a sympathetic ganglion, the superior cervical ganglion of the rat, which would be expected if a receptor was present on sympathetic nerve terminals (Ishac et al., 1996). Second, Win 55212-2 decreases the spillover of norepinephrine into the plasma in pithed, conscious rabbits with continuously stimulated sympathetic nerve terminals (Ishac et al., 1996). Third, treatment of isolated atria and vasa deferentia with AEA and Δ9-THC reduces the release of [3H]norepinephrine in response to electrical field stimulation (Ishac et al., 1996).

Nonneuronal Sites of Cannabinoid Action

Studies in isolated preparations of vascular tissue and cells provide evidence that the cannabinoids also affect vascular function through actions on nonneuronal cells. Although the majority of these studies report that the cannabinoids produce vasodilation of isolated vessels, it is unlikely that a common mechanism underlies all of these effects. Two nonneuronal cellular sites of cannabinoid action are supported by experimental evidence: vascular smooth muscle cells where cannabinoids alter influx, release, or sensitivity to calcium; and endothelial cells where cannabinoids alter the release of endothelial-derived factors.
Nonneuronal Sites of Cannabinoid Action: Vascular Smooth Muscle Cells

The most convincing evidence for CB1-mediated vasorelaxation resulting from a direct effect of the cannabinoids on vascular smooth muscle cells comes from studies in cat cerebral artery (Gebremedhin et al., 1999). At concentrations of 10 to 300 nM, AEA produces vasorelaxation of cat cerebral arteries contracted with either serotonin or KCl. This effect is mimicked by Win 55212-2 and inhibited by SR141716A. Cerebrovascular smooth muscle cells from cat express the CB1 cannabinoid receptor, and electrophysiological data demonstrate that Win 55212-2 and AEA decrease the opening of L-type calcium channels in these cells. This effect is blocked by both pertussis toxin pretreatment and by low concentrations of SR141716A, which support involvement of the CB1 receptor. Although it is not yet known whether smooth muscle cells in other vascular beds also express the CB1 receptor protein, message for the CB1 receptor has been detected in human aortic smooth muscle cells (Sugiura et al., 1998).

In rat mesenteric artery, AEA induces vasorelaxation that is independent of the presence of endothelium, attenuated by high potassium concentrations (Randall et al., 1996) and associated with membrane hyperpolarization (Plane et al., 1997). These studies have led to the suggestion that AEA activates a vascular smooth muscle cell potassium channel that results in hyperpolarization and relaxation. Experiments with potassium channel blockers have provided conflicting results regarding the identity of the potassium channel involved in this effect (Plane et al., 1997; White and Hiley, 1997; Ishioka and Bukoski, 1999).

The role of the CB1 receptor in AEA-induced vasorelaxation in the mesenteric artery has been approached with pharmacological studies that do not consistently demonstrate a receptor-mediated mechanism. First, the high affinity CB1 receptor agonists CP55940 and Win 55212-2 do not mimic AEA completely (Plane et al., 1997). Second, CB1 receptor antagonists do not consistently block the effect of AEA. Several studies report attenuation of AEA vasorelaxation by micromolar concentrations of SR141716A (Randall et al., 1996; White and Hiley, 1997; Ishioka and Bukoski, 1999), whereas others report no effect of SR141716A in the same concentration range (Plane et al., 1997; Wagner et al., 1999). Some of the discrepancy in the pharmacological data could be explained by variable expression of the CB1 receptor throughout the mesenteric bed. For example, Ishioka and Bukoski (1999) have demonstrated that the mesenteric branch arteries are particularly sensitive to relaxation by AEA. However, support for this and other explanations awaits further investigation.

AEA produces endothelial-independent vasodilation in rat hepatic artery without affecting resting membrane potential of vascular smooth muscle cells (Zygmunt et al., 1997). Data from single cell electrophysiological studies suggest that AEA inhibits calcium release from caffeine-sensitive intracellular stores in these cells. Because micromolar concentrations of AEA are required to produce this effect, it is not likely that the CB1 receptor plays a role.

R-Methanandamide inhibits forskolin-stimulated accumulation of cyclic AMP in rat carotid artery smooth muscle cells at very low concentrations (Holland et al., 1999). R-Methanandamide is a derivative of AEA that binds to the CB1 receptor with affinity similar to AEA but is not catalyzed by AEA amidohydrolase (Abadji et al., 1994). This effect is lost in pertussis toxin-treated vessels and may be mediated by the CB1 receptor, although the pharmacological data are not entirely consistent with this conclusion. Interestingly, R-methanandamide does not affect vessel tone in the preparation, except to inhibit forskolin-induced vessel relaxation slightly.

In summary, the contribution of direct effects on smooth muscle to the vasodilatory effects of the cannabinoids varies among vascular beds, as does the mechanism of action. In the cerebral circulation, vascular smooth muscle cells express the CB1 receptor that inhibits calcium entry through L-type calcium channels. It is not known whether this mechanism exists in other vascular beds. Endothelial-independent vasorelaxation in rat mesenteric vessels likely involves vascular smooth muscle cell hyperpolarization; however, whether this effect is mediated by the CB1 receptor and which potassium channel(s) are involved remain open questions. In carotid artery, R-methanandamide inhibits forskolin-stimulated adenyl cyclase but does not affect vessel tone. In light of other cellular data demonstrating that the CB1 receptor couples to inhibition of adenyl cyclase, this mechanism is plausible. However, it is not clear that the cannabinoids affect smooth muscle contractility via this mechanism.

Nonneuronal Sites of Cannabinoid Action: Endothelial Cells

In some vascular beds, endocannabinoid-induced changes in vascular tone include an endothelial component. The regulation of vascular smooth muscle cell contractility by endothelial-derived factors is well known. There are several studies describing AEA effects on the release of a variety of endothelial-derived vasoactive substances that occur through diverse mechanisms.

Nitric oxide (NO) is synthesized by endothelial cells and induces vasodilation as a result of activation of guanylyl cyclase in the adjacent vascular smooth muscle cells. In rat kidney, AEA-induced vasodilation is abolished by the NO synthase inhibitor, L-nitroarginine methyl ester (L-NAME) (Deutsch et al., 1997). Furthermore, AEA increases the synthesis of NO in renal endothelial cells (Deutsch et al., 1997) and human endothelial cell lines (Fimiani et al., 1999). AEA treatment also induces an increase in the release of intracellular calcium, which precedes and may be causally related to the increase in NO (Fimiani et al., 1999; Mombouli et al., 1999).

The role of the CB1 receptor in the effect of AEA on NO synthesis in renal endothelial cells is not clear. Positive evidence includes demonstration of a polymerase chain reaction product amplified from renal endothelial cell mRNA using primers specific for the CB1 receptor (Deutsch et al., 1997). The polymerase chain reaction product was the expected size and hybridized to an internal oligonucleotide sequence; however, the entire message for the receptor was not sequenced, which leaves open the possibility that a cannabinoid receptor is expressed that is not identical with the CB1 receptor. In fact, the high affinity of AEA relative to other CB1 receptor agonists reported in this study hints to an alternate cannabinoid receptor subtype. In the human endothelial cells studies, the effects of SR141716A were inconsistent. In one study,
SR141716A (1 μM) inhibited the effect of AEA on calcium mobilization (Fimiani et al., 1999), whereas in the other, 5 μM SR141716A itself elicited calcium mobilization and inhibited calcium mobilization induced by both AEA and histamine (Mombouli et al., 1999).

An alternative, non-CB1 receptor for AEA has been suggested by the work of Kunos and coworkers carried out using isolated, buffer-perfused mesenteric arterial bed in rats and mice (Jarai et al., 1999; Wagner et al., 1999). In rats, submicromolar concentrations of AEA and R-methanandamide produced endothelial-dependent vasodilatation that was competitively inhibited by 500 nM SR141716A (Wagner et al., 1999). However, the synthetic CB1 receptor agonist Win 55212-2 and HU210 were without effect. These data suggest that the effects of AEA, if receptor-mediated, are not due to activation of the CB1 receptor. This conclusion is supported by data from CB1 receptor knock-out mice in which mesenteric vasodilatation induced by AEA is preserved, as is its sensitivity to inhibition by SR141716A (Jarai et al., 1999). Structure activity studies suggest that the non-CB1 receptor-mediated effects of AEA are endothelial in origin and are mediated by a receptor; however, the identity of this receptor is not yet known. The vasodilatation induced by AEA is inhibited by the potassium channel blockers, apamin and charybdotoxin, added in combination but not by either when added alone. These data suggest that the novel endothelial receptor for AEA regulates the synthesis of an endothelial-derived hyperpolarizing factor (EDHF) and thereby affects vascular tone. This very testable hypothesis has yet to be proven.

It is clear that the cannabinoids, particularly AEA, also produce endothelial-dependent effects that are not mediated by the CB1 receptor. For example, in bovine coronary arteries, AEA serves as a precursor of eicosanoids in endothelial cells (Pratt et al., 1998). AEA is accumulated by endothelial cells, catabolized intracellularly to arachidonic acid by AEA amidohydrolase, and arachidonic acid is converted to vasodilator eicosanoids such as prostacyclin or epoxyeicosatrienoic acids. This effect of AEA is not mediated by the CB1 receptor and is abolished by an inhibitor of AEA amidohydrolase.

AEA and R-methanandamide produce endothelial-dependent relaxation in rabbit mesenteric artery at micromolar concentrations that is inhibited noncompetitively by the gap junction inhibitor 18α-glyceryrhrhetic acid (50 μM) and by a blocking peptide to connexin 43 (Chaytor et al., 1999). The authors hypothesize that AEA acts intracellularly to promote the diffusion of an EDHF from the endothelium to the vascular smooth muscle cell through gap junctions. A high concentration of SR141716A (10 μM) inhibited the effects of AEA, but also blocked dye transfer through gap junctions in a model system that does not express CB1 receptors. Thus, these studies provide an example of the nonselectivity of SR141716A for the CB1 receptor at high concentrations. They are an example of the pitfalls inherent in using inhibition by high concentrations of SR141716A as the only evidence for the involvement of the CB1 receptor in an effect proposed to be mediated by AEA.

In summary, AEA has effects on endothelial cells that result in changes in vascular tone. One of the more exciting mechanistic possibilities suggested by several studies is that endothelial cells may express a novel receptor that binds AEA and SR141716A with high affinity but does not bind as well to other high affinity CB1 receptor agonists. As with the effects of the endocannabinoids on smooth muscle cells, it is possible that some of the endothelial effects of AEA, particularly at concentrations above 1 μM are not cannabinoid receptor-mediated.

**Sensory Nerves as a Site of a Noncannabinoid Effect of AEA**

A recent study raises the intriguing possibility that AEA may exert its vascular effects via activation of vanilloid receptors on perivascular sensory nerves (Zygmunt et al., 1999). These investigators have reported that AEA, at concentrations above 1 μM, induces vasodilatation in rat hepatic, mesenteric and basilar artery preparations. The pharmacology of the response is consistent with AEA acting as an agonist of the VR1 vanilloid receptor and is inconsistent with a role for the CB1 receptor. The vasodilatory mechanism suggested by these results is that AEA, via VR1 receptors, induces the release of calcitonin-gene-related peptide, a potent vasodilator. Interestingly SR141716A, at a concentration of 10 μM, inhibits the vasodilator response to capsaicin in these vessels, which also acts via release of calcitonin-gene-related peptide. These data support the data cited above that AEA vasodilatation is not always explained by CB1 receptor effects. Because it is likely that the vessels used in most tissue bath experiments contain intact perivascular sensory neurons, it is possible that the endothelial-independent component of AEA-induced relaxation seen by other investigators occurs via this mechanism.

**Sources of Endocannabinoids in the Vasculature**

There is convincing evidence that the cannabinoids regulate vascular tone at a site or sites that are outside of the CNS. If we make the assumption that the physiological role of the receptor(s) for the endocannabinoids is to transduce signals from endogenously produced ligands, then the question of the cellular source of the endocannabinoids arises. This question is only beginning to be addressed as techniques capable of measuring low quantities of the endocannabinoids are developed. Three cell types have been suggested as the source of endocannabinoids in the vasculature: endothelial cells, perivascular neurons, and circulating cells, including platelets, polymorphonuclear leukocytes, and macrophages.

Based on the data obtained in mesenteric artery preparations, Randall et al. (1996) hypothesized that AEA is produced by endothelial cells and functions as an EDHF. Although subsequent studies from a number of laboratories have disproved the claim that AEA is EDHF (Plane et al., 1997; White and Hiley, 1997; Zygmunt et al., 1997), the question of whether endothelial cells are a cellular source of AEA remains open. Deutsch et al. (1997) have reported that endothelial cells from the kidney contain small but measurable amounts of endogenous AEA and its phospholipid precursor. They did not determine whether cellular AEA content or AEA release were altered by any stimuli. In contrast, our laboratory was unable to detect the synthesis of radiolabeled AEA by bovine coronary endothelial cells preloaded with radiolabeled arachidonic acid (Pratt et al., 1998). Human vascular endothelial cells generate and release 2-AG, but not
1-AG, in response to stimulation by thrombin and the calcium ionophore A23187 (Sugiura et al., 1998).

Both AEA and 2-AG have been shown to be synthesized and released by neurons derived from the CNS (Di Marzo et al., 1994; Stella et al., 1997). Therefore, a logical source of endocannabinoids in the vascular system is neurons innervating the adventitial surface of the vessels. Support for this hypothesis comes from recent studies demonstrating that activation of perivascular sensory nerve endings in the mesenteric circulation induces vasodilation that is inhibited by 0.3 μM SR141716A (Ishioka and Bukoski, 1999). An explanation of these data is that the sensory nerve endings release a vaso dilatory substance that is an endocannabinoid.

The possibility that endothelial cells express receptors for endocannabinoids invites the suggestion that cells in the blood are the source of ligand for these receptors. Indeed, AEA is synthesized and released from macrophage-derived cell lines in response to treatment with a calcium ionophore (Di Marzo et al., 1996) and platelet-activating factor (Pestonjamp and Burstein, 1998). Furthermore, macrophages taken from rats in shock induced by either hemorrhage (Wagner et al., 1997) or lipopolysaccharide (Varga et al., 1998) contain increased amounts of AEA compared with macrophages from control animals. Lipopolysaccharide treatment also increases the biosynthesis of 2-AG in rat macrophages (Di Marzo et al., 1999) and rat platelets (Varga et al., 1998). Recent studies have demonstrated that human platelets take up AEA where it serves as a substrate for 12-lipoxygenase (Edgemon et al., 1998). The resulting product (12(S)-hydroxy-arachidonyl ethanolamide) binds to the CB1 receptor with approximately the same affinity as AEA itself and is metabolically more stable. These studies suggest that the biosynthesis of AEA by circulating cells may be complex and result in the synthesis of several endocannabinoid species.

**Summary and Therapeutic Implications**

The cannabinoids have significant and complex effects on the vascular system that are not explained by a single mechanism or a single site of action. Some of these effects result from activation of CB1 receptors and therefore share the pharmacological specificity of the psychoactive effects of marijuana. It is likely that the CB1 receptors involved are located on axon terminals of sympathetic neurons and that activation of CB1 receptors results in decreased norepinephrine release. The physiological consequence of this mechanism is dependent upon the sympathetic tone of the subject. In anesthetized animals with high sympathetic tone, the outcome is hypotension. In conscious, healthy humans, the outcome is an increase in peripheral blood flow accompanied by tachycardia resulting from baroreceptor activation. There are forms of essential hypertension resulting from excessive and erratic activation of sympathetic outflow that theoretically could be treated by a CB1 receptor agonist.

In the cerebral circulation, cannabinoids reduce vascular smooth muscle cell calcium influx and cause vasodilation directly through CB1 receptors. This finding is consistent with evidence that marijuana produces an increase in cerebrovascular blood flow in humans that is not due to changes in sympathetic regulation of the cerebral circulation (Mathew and Wilson, 1993). It may also be the mechanism by which marijuana impairs cerebral autoregulation in response to changes in posture (Mathew and Wilson, 1993). There are several possible physiological roles for this receptor. Perhaps an endocannabinoid serves to couple cerebral blood flow with the metabolic activity of the surrounding neurons. Very few therapeutic interventions are available to treat cerebral vasospasm, the unique mechanism of action of the cannabinoids may be useful in this regard.

Recent studies using rodent models of hemorrhagic and endotoxin-induced shock suggest that endocannabinoids are synthesized by activated circulating macrophages and platelets (Varga et al., 1998). Furthermore, these investigators find that SR141716A inhibits the hypotension induced by both interventions, suggesting that the endocannabinoids contribute to the hypotension. If this also occurs in humans, a cannabinoid receptor antagonist could be very useful in the management of the profound hypotension that occurs during shock.

**References**


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