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Mechanisms of Vasodilation Induced by Medicinal Plants: A Mini-Review

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ABSTRACT

Medicinal plants are commonly used for the treatment of cardiovascular diseases; however, there is a paucity of information on their mechanisms of action. Some antihypertensive medicinal plants have been reported to act like vasodilator drugs, through a variety of cell signalling processes involving modulation of endothelial and vascular smooth muscle functions. Since endothelial dysfunction as well as increased peripheral vascular resistance are known to be associated with hypertension, this review highlights key cell signalling processes involving endothelium-derived factors as well as cellular Ca^{2+} homeostasis that may be used to characterize the vasodilator actions of medicinal plants.

Introduction

Medicinal plants have continued to be a vital source of natural products for the management of diseases. The use of medicinal plants in the treatment of cardiovascular diseases[1] has gained significant prominence in recent times, for a number of reasons, including the following: it is cheaper than orthodox medicines and has fewer harmful side effects.[2,3] Herbal medicines are commonly classified as Complementary and Alternative Medicine (CAM); indeed, they are widely used in both developed and developing countries.[4] They also constitute a rich source of bioactive metabolites for drug development in the pharmaceutical industries.[5, 6]

A major determinant of increased arterial blood pressure in hypertension is the rise in peripheral vascular resistance, resulting from abnormal vasoconstriction and increased vascular tone. This is also associated with impaired ability of vessels to dilate.[7, 8] Vasodilator drugs constitute a class of drugs commonly used in antihypertensive conditions.

In this presentation, we discuss possible cellular mechanisms, based on experimental findings, by which some commonly used medicinal plants ameliorate blood pressure through vasodilator mechanisms involving relaxation of vascular smooth muscle.

Vasodilator mechanisms

The mechanistic pathways for the action of vasodilator agents involve the interplay of a variety of cell signalling processes which regulate endothelial as well as vascular smooth muscle function.

Vascular endothelium

Endothelial dysfunction has been widely implicated in the pathogenesis of arterial hypertension. Endothelium-derived vasoactive substances include the following: vasodilators (nitric oxide prostacyclin, endothelium-derived hyperpolarizing factors, adrenomedullin, bradykinin, thrombin) and vasoconstrictors (angiotensin II, endothelin-1, vasoconstrictor prostanoids).

Agents which elicit endothelium-dependent vasorelaxation do so by causing vasodilation or inhibition of vasoconstriction through the release of endothelium-derived nitric oxide or other vasodilators released from the endothelium. Endothelium-derived relaxing factors (EDRFs) as well as endothelium-derived contracting factors (EDCFs) elicit their vascular actions through interaction between the endothelium and vascular smooth muscle cells. [8] Responses elicited by endothelium-derived relaxing factors are usually studied, *in vitro*, in arterial rings precontracted with phenylephrine or noradrenaline. In endothelium-denuded rings, endothelium-dependent relaxation response to acetylcholine (Ach) is impaired.[8, 9] It has been extensively reported that in endothelium-intact rings, Ach-induced relaxation is completely reversed by NG-nitro-L-arginine-methylester (L-NAME); a selective inhibitor of nitric oxide synthase.[1]

In vascular tone regulation, both endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDCFs) produce their effect via interaction between the endothelium and vascular smooth muscle cells. Endothelial factors that are most commonly held to account for the actions of vasodilator drugs, which may also explain the actions of vasodilator medicinal plants (Table 1), include: nitric oxide (NO) produced by endothelial NO synthases (eNOS), prostaglandins (PGI_2 and PGE_2), and endothelium-derived hyperpolarizing factors (EDHF). Endothelium-derived hyperpolarizing factors consist of a group of molecules, including: C-natriuretic peptide, hydrogen peroxide, carbon monoxide, hydrogen sulphide, epoxyeicosatrienoic acids and K^+.

Vascular smooth muscle

The contraction/relaxation process in vascular smooth muscle is dependent on changes in cytosolic Ca^{2+} levels $[Ca^{2+}]_i$. Drugs which alter transmembrane Ca^{2+} movement are commonly employed therapeutically, for the management of cardiovascular disorders. Also, a number of medicinal plants reduce vascular smooth muscle tone through interference with Ca^{2+} homeostasis (Table 1). Cell signalling pathways (mediating the actions of vasodilator drugs), which have been extensively investigated include the following: Voltage-operated calcium channel, VOCC; receptor-operated calcium channel, ROCC; store-operated calcium channel, SOCC; as well as the Sarco(endo)plasmic Reticulum Calcium ATPase, SERCA.[8, 20-22]

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Table 1: Selected medicinal plants with vasodilator activity.

Medicinal Plant	Classsification	Active Ingredients	Experimental Model	Effective Dose	Mode of Action
Allium sativum	Alliaceae or Liliaceae	Allicin., S-allyl cysteine	Adult rat cardiomyocytes	10 and 20µl / 4ml cell culture medium	Stimulates NO production; increase cellular levels of H_2S.[10]
Artocarpus altilis	Family: Moraceae; Common name: Breadfruit.	flavonoids, stilbenoids, arylbenzofurons and Jacalin	Isolated guinea pig aortic rings	0.71–4.26 mg/mL	α-adrenoceptor and Ca^{2+} channel antagonism.[11]
Capparis cartilaginea	Family: Capparaceae; Common name: Lasaf.	Flavonoids, glucosiolates and rutin	Anaesthetized rats.	1–10 mg/kg	Direct vasorelaxation and cardio-inhibition; non-adrenergic, non-cholinergic.[12]
Carum copticum	Family: Umbelliferae; Common name: Ajwain	calcium antagonists	Isolated rabbit aorta	0.1-3.0 mg/ml	Ca^{2+} channel antagonism.[13]
Daucus carota	Family: Umbelliferae; Common name: Carrot.	coumarin glycosides coded as DC-2 and DC-3.	NMT anesthetized rats; rabbit aorta	1–10 mg/kg; 10–200 µg/ml	Ca^{2+} channel antagonism.[14]
Hibiscus sabdariffa	Family: Malvaceae; Common name: Roselle	phenolic acids and anthocyans	Experimentally induced hypertensive rats.	20 mg/kg	Endothelium-dependent vasorelaxation.[15]
Moringa oleifera	Family: Moringaceae; Common name: Murungai	thiocarbamate and isothiocyanate glycosides	Normotensive anesthetized Wister rats	3 and 10 mg/kg),	Direct hypotensive effect.[16]
Musanga cecropiodes	Family: Cecropiaceae; Common name: Umbrella tree, Cork Wood	flavonoids, alkaloids, tannins, phlobatannins, glycosides,	Anesthetized Sprague-Dawley rats Isolated rat aorta	10 mg/kg and 40 mg/kg	ACE Inhibition; endothelium-dependent vasorelaxation.[9, 17]
Ocimum basilicum	Family: Lamiaceae; Common name: Sweet basil.	Rutin, quercetin, and quercitrin (flavonoids); caffeic, chlorogenic, and gallic acids	Biochemical enzyme assay	IC_{50}: 29.44 µg/mL	ACE Inhibition.[18]
Phyllanthus amarus	Family: Euphorbiaceae; Common name: Nela nelli.	Phenolic Acid	anesthetized NMT male rabbits	5-80 mg/kg	muscarinic receptor-mediated vasorelaxation; Ca^{2+} channel antagonism.[19]

Vasorelaxants which act through interference with Ca^{2+} influx via VOCC or ROCC are usually differentiated using relaxation responses of isolated arterial rings precontracted with high K^+ (VOCC) or phenylephrine (ROCC).[22] Some studies have reported that medicinal plants may induce vasodilation by inhibiting Ca^{2+} influx, as well as the release from intracellular stores.[23]

In rat mesenteric arteries, baicalin, a flavonoid compound isolated from *Scutellaria baicalensis*[22] was shown to significantly reduced the increase in Ca^{2+} induced by stimulation with Angiotensin II, vasopressin and endothelin, by a mechanism linked with inhibition of lipoxygenase biosynthesis and release of vasoconstrictor prostaglandins. It was also shown to abolish contractions induced by large-conductance Ca^{2+}-activated K^+ channel (BKCa channel), VOCC activator, Bay K8644 and protein kinase C activator PMA-induced contractions. Other important signalling transducers through which drugs modulate vascular smooth muscle contraction include cAMP and the cGMP pathways; their levels are known to be elevated by vasorelaxants.[24]

The use of inhibitors of Ca^{2+} release from intracellular stores is of great value in assessing signalling processes involved in the action of vasodilator compounds. Commonly used inhibitors include gandolinium, which inhibits SOCC and tharpsigargin, which inhibits SERCA.[8] Inhibition of the SERCA pump[25] results in an increase in intracellular Ca^{2+}.

Conclusion

In conclusion, mechanisms of vasodilation induced by medicinal plants are reasonably characterized through techniques that evaluate endothelial and vascular smooth muscle cell signalling processes. The use of appropriate pharmacologic antagonists and modulators of endothelial and vascular smooth muscle functions provides specific insight into the involvement of endothelium-derived factors as well as cellular Ca^{2+} homeostasis.

Conflict of interest

The authors declare no conflict of interest.

Authors declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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