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Role of thromboxane A_2 signaling in endothelium-dependent contractions of arteries

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ABSTRACT

Thromboxane A_2 (TxA_2) plays a very important role in various cardiovascular diseases through its action on platelet aggregation, vasoconstriction, and proliferation. The present article focuses on the role of TxA_2 signaling in endothelium-dependent contractions of arteries. Arachidonic acid (AA) is metabolized by cyclooxygenase (COX) to form the unstable prostaglandin H_2 which is further converted into TxA_2. After being produced by thromboxane synthase (TxAS), TxA_2 ultimately stimulates TxA_2/prostanoid (TP) receptor to induce vasoconstriction. The calcium ionophore A23187, the prostanoid precursor AA, or the muscarinic receptor agonist acetylcholine (ACh) can evoke endothelium-dependent contractions associated with TxA_2. The endothelium-dependent contractions shown in hypertension, diabetes, atherogenesis, and other cardiovascular diseases have been significantly reduced by antagonism of COX, TxAS, or TP receptor. So inhibition of the bioavailability and/or effect of TxA_2 may be promising therapeutic targets to prevent these diseases. Especially some bioactive compounds isolated from medicinal plants will provide new pharmacological approaches to promote vascular health.

1. Introduction

Furchgott and Zawadski observed that acetylcholine (ACh) produced marked relaxation in rabbit thoracic aorta and there were no vasodilatory responses after rubbing its intimal surface. Therefore they suggested that ACh stimulated the release of a substance in endothelial cells that could relax vascular smooth muscle [1]. In 1987 the substance was identified as nitric oxide (NO) [2,3]. Luscher and Vanhoutte found ACh caused endothelium-dependent contractions in thoracic aorta from spontaneously hypertensive rats (SHR), which was normalized by indomethacin, an unspecific cyclooxygenase (COX) inhibitor [4]. This implicated the release of endothelium-derived contracting factors, possibly COX-derived prostanoids. Endothelium might maintain vascular tone by controlling the balance between NO and COX-derived prostanoids.

Arachidonic acid (AA) is metabolized by COX to form the unstable prostaglandin H_2, which is further converted into prostacyclin (PGI_2), thromboxane A_2 (TxA_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by their respective synthases [5–7]. TxA_2 was first detected as an unstable intermediate in human platelets, whose half-life was about 30 s. [8] The generation of TxA_2 was significantly greater in platelets from male than female pigs [9]. After being produced by thromboxane synthase (TxAS), TxA_2 ultimately stimulates TxA_2/prostanoid (TP) receptor [10]. TxA_2 plays a very important role in various cardiovascular diseases through its action on platelet aggregation, vasoconstriction, and proliferation. The present article focuses on the role of TxA_2 signaling in endothelium-dependent contractions of arteries (Table 1).

2. The thromboxane A_2 signaling pathway

2.1. AA

The calcium ionophore A23187, the prostanoid precursor AA, the muscarinic receptor agonist ACh, or uridine adenosine tetraphosphate evoked endothelium-dependent contractions, which were significantly reduced by TxAS inhibitors [11–15]. These findings indicated that following an increase in the intracellular calcium concentration TxA_2 production was responsible for the vascular contraction. The intracellular increase of calcium ions is critical for phospholipase A_2 to release AA from membrane phospholipid, because selective inhibition of calcium-independent phospholipase A_2 didn't affect A23187-induced endothelium-dependent contractions whereas inhibition of both calcium-dependent and calcium-independent phospholipase A_2 abrogated the vasoconstriction [16].

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Table 1
Summary of representative antagonists of the TxA_2 pathway.

Groups	Representative Compound	Species	Vessel	Effect	Reference
Unspecific COX antagonist	Indomethacin (5 μM)	STZ-induced diabetic rats	Femoral arteries	Abolished contraction to A23187 (0.1–1 μM)	Shi et al. [18]
	Indomethacin (10 μM)	$ApoE^{-/-}$ mice	Mesenteric resistance arteries	Significantly improved dilation to ACh (10 μM)	Romero et al. [50]
	Meclofenamate (1 μM)	obese mice	Carotid arteries	Significantly reduced contraction to ACh (30 μM)	Traupe et al. [25]
	Indomethacin (10 μM)	Dogs	Basilar arteries	Abolished contraction to AA(0.01–10 μM)	Katusic et al. [14]
Specific COX-1 antagonist	Valeryl salicylate(3mM) and SC560(0.3 μM)	STZ-induced diabetic rats	Femoral arteries	Significantly reduced contraction to A23187(0.1–1 μM)	Shi et al. [18]
	SC560 (1 μM)	Spontaneously Hypertensive rats	Carotid arteries	Abolished contraction to sphingomyelinase (0.1 U/mL)	Spijkers et al. [22]
	SC560 (0.3 μM)	Spontaneously Hypertensive rats	Thoracic aortas	Prevented contraction to A23187 (1nM–1 μM)	Gluais et al. [11]
	Valeryl salicylate (1 mM)	6-month-old mice	Renal arteries	Significantly increased dilation to ACh (0.001–30 μM)	Gendron and Thorin [12]
Specific COX-2 antagonist	Paracoxib (1 μM)	Angiotension II-infused hypertensive rabbits	Renal afferent arterioles	Abolished contraction to ACh (1–1000 μM)	Wang et al. [19]
	NS398 (10 μM)	Zucker diabetic fatty (ZDF) rats	Mesenteric resistence arteries	Significantly increased dilation to Ang II(0.01 μM)	Retailleau et al. [47]
	NS398 (10 μM)	Old obese Zucker rats	Mesenteric resistence arteries	Significantly improved dilation to ACh (0.001–10 μM)	Vessieres et al. [54]
TxAS antagonist	Furegrelate (10 μM)	Zucker diabetic fatty (ZDF) rats	Mesenteric resistence arteries	Significantly increased dilation to Ang II (0.01 μM)	Retailleau et al. [47]
	Dazoxiben (10 μM)	STZ-induced diabetic rats	femoral arteries	Significantly reduced contraction to A23187 (0.1–1 μM)	Shi et al. [18]
	Furegrelate (10 μM)	6-month-old mice	Renal arteries	Significantly increased dilation to ACh (0.001–30 μM)	Gendron and Thorin [12]
	Dazoxiben (100 μM)	Dogs	Basilar arteries	Significantly reduced contraction to AA(0.01–10 μM)	Katusic et al. [14]
TP antagonist	GR32191	Type 2 diabetic mice (db/db)	Renal arteries	Completely inhibited U46619-induced contraction (1 μM)	Kuang et al. [26]
	SQ29548 (10 μM)	Old obese Zucker rats	Mesenteric resistence arteries	Significantly increased dilation to ACh (0.001–10 μM)	Vessieres et al. [54]
	SQ29548 (10 μM)	Obese mice	Carotid arteries	Significantly reduced contraction to ACh(30 μM)	Traupe et al. [25]
	SQ29548 (0.1 μM)	angiotension II- infused hypertensive rabbits	Renal afferent arterioles	Abolished contraction to ACh(1–1000 μM) and U46619(0.01 μM)	Wang et al. [19]
	Ifetroban (1 μM)	angiotension II- infused hypertensive rabbits	Renal afferent arterioles	Abolished contraction to U46619 (0.01 μM)	Wang et al. [19]
	S-18886 (100 nM)	Spontaneous hypertensive rats	Thoracic aortas	Abolished contraction to A23187 (1nM–1 μM)	Gluais et al. [11]
	SQ29548 (10 μM)	6-month-old mice	Renal arteries	Significantly reduced dilation to ACh (0.001–30 μM)	Gendron and Thorin [12]
Dual TxAS inhibitor and TP receptor antagonist	BM-573 (3 μM)	$ApoE^{-/-}$ mice	Mesenteric resistance arteries	Significantly improved dilation to ACh (0.1–10 μM)	Romero et al. [50]