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Bitter Taste Receptor in Vascular Smooth Muscle: Expression, Functions and the Mechanisms

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Abstract

Bitter taste receptors (TAS2Rs) express in the vasculature. Recent evidence suggests that TAS2R agonists have different functions on vascular smooth muscles (VSMs) through variable mechanisms.

Keywords: Bitter taste receptor; Vascular smooth muscle; Expression; Function; Mechanism.

Introduction

TAS2Rs are initially found in epithelia on the tongue. Several recent studies have demonstrated the expression of TAS2Rs in VSMs. They exhibit distinct functions to the activation by different TAS2R agonists. Here, we discussed the expression and functions of TAS2Rs in VSMs and the underlying mechanisms.

Expression of TAS2Rs in the vasculature

TAS2Rs were originally identified in the taste bud. Further studies discovered TAS2Rs and their downstream signaling molecules in various types of non-gustatory systems, including digestive, respiratory, genitourinary and cardiovascular systems, as well as in the brain and immune cells [1-6]. Here, we reviewed the literature about TAS2Rs in VSMs of rats, mice, and pigs commonly used for cardiovascular research. **Table 1** showed the TAS2R expression in the vasculature of humans and different animals.

Upadhyaya et al. detected 21 of 25 subtypes of hTAS2R mRNA using RT-PCR except for hTAS2R16, 38, 40, and 41 in human pulmonary artery smooth muscle cells [7]. However, other studies using different primers and gene sequencing techniques, the nCounter platform, showed the hTAS2R40 mRNA expression [8, 9] Jaggupilli and colleagues found that hTAS2R3, 4, 5, 10, 13, 19, and 50 expressed at moderate levels and hTAS2R14, 20 expressed at a high level in human pulmonary artery smooth muscle [9]. Seven hTAS2R subtypes (hTAS2R3, 4, 7, 10, 14, 39, and 40) appeared in human omental arteries [2]. hTAS2R46 was found in human aortic smooth muscle cells [10].

Seven rat TAS2R subtypes (rTAS2R107, 108, 121, 123, 137, 139, 144) and their synonyms in the mouse (mTAS2R110, 108, 130, 114, 137, 139, 140) were identified in rat and mouse pulmonary arteries, respectively [8]. Seven rTAS2R subtypes, 39, 40, 108, 114, 130, 137, and 140, expressed in rat mesenteric arteries, and they all expressed in cerebral arteries except rTAS2R114 [2]. The mRNA of rTAS2R40, 108, 126, 135, 137, 143 expressed in endothelium-denuded rat thoracic aorta [11]. Three mTAS2R subtypes (mTAS2R116, 143, 108) expressed in the mouse aorta [10, 12]. TAS2R1 was found in porcine pulmonary artery smooth muscles [7].

Effects of TAS2Rs on the functions of VSMs

TAS2Rs could protect organisms from the intake of toxic substances, which is vital for animal and human survival. Moreover, TAS2Rs have various roles in different organs or tissues. Activation of TAS2Rs regulates the tension of the VSM and thus affects the blood pressure. To define the function of TAS2Rs in VSMs, phenylephrine- and high concentration of KCl pre-contracted vascular tissues are commonly employed. Two typical bitter compounds, denatonium and quinine, are promiscuous TAS2R agonists and commonly used in the TAS2R study [13, 14]. Chloroquine, dextromethorphan, noscapine, and 6-n-Propyl-2-thiouracil are also used as TAS2R agonists [4, 12, 13].

Chloroquine and noscapine relaxed phenylephrine-contracted human pulmonary arterial rings [4]. Denatonium and 6-n-Propyl-2-thiouracil also inhibited phenylephrine-induced contraction in mouse aortic smooth muscle [12] Chloroquine, denatonium, dextromethorphan, noscapine, and quinine could activate TAS2R1, 3, 4, 10, 14, and 40. They relaxed the phenylephrine-contracted aortic rings of guinea pigs; however, there was no direct evidence for the existence of these TAS2Rs [4]. On the contrary, saccharine, an agonist of TAS2R43 and TAS2R44, showed no effects, and this was in line with the absence of these two receptors in the guinea pig genome [15].

Chloroquine and quinine relaxed the KCl (60 mM) contracted human omental arteries in a concentration-dependent manner [2]. Chloroquine relaxed KCl (60 or 140 mM) constricted rat mesenteric and cerebral arteries and thoracic aortas [2, 16]. It also relaxed phenylephrine or high KCl (40 or 80 mM) contracted rat pulmonary arterial rings independently of the endothelium [8].

Some TAS2R agonists caused VSM constriction. Agonists for mTAS2R108 and 137 elicited a steady increase in perfused mouse hearts' aortic pressure [17]. Liu et al. reported that denatonium increased the tonic contraction in endothelium-denuded rat thoracic aortas in a concentration-dependent manner [11]. Upadhyaya et al. showed that dextromethorphan, acting through pTAS2R1, caused endothelium-independent constriction in piglet pulmonary artery [7].

Mechanisms

TAS2Rs are G protein-coupled receptors. Upon agonist binding, the G protein gustducin dissociates from βγ subunits, and they activate different downstream effectors [6]. Gustducin can activate

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Table 1: Species, origins, subtypes and detection techniques of TAS2Rs.

Species	Cell/Tissue	TAS2Rs	Techniques used
		hTAS2R1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 60	RT-PCR (7)
	Pulmonary artery	hTAS2R3, 4, 7, 10, 14, 39, 40	RT-PCR (8)
	smooth muscle cells	hTAS2R1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 16, nCounter sequencing	
Human		38, 39, 40, 41, 42, 30/31/43/45/46, 48, 49, 50, 60	RT-PCR (9)
	Pulmonary artery	hTAS2R3, 4, 10, 14	PCR (4)
	Omental artery	hTAS2R3, 4, 7, 10, 14, 39, 40	RT-PCR (2)
	Aortic smooth muscle cells	hTAS2R46	RT-PCR (10)
	Pulmonary artery	rTAS2R107, 108, 121, 123, 137, 139, 144	RT-PCR (8)
	Mesenteric artery	rTAS2R39, 40, 108, 114, 130, 137, 140	RT-PCR (2)
Rat	Cerebral artery	rTAS2R39, 40, 108, 130, 137, 140	
	Thoracic aorta	rTAS2R40, 108, 126, 135, 137, 143	RT-qPCR (11)
	Pulmonary artery	mTAS2R108, 110, 114, 130, 137, 139, 140	RT-PCR (8)
Mouse	Aortic smooth muscle cells	mTAS2R116, 143	RT-PCR (10)
	Thoracic aorta	mTAS2R108	RT-PCR (12)
Porcine	Pulmonary artery smooth muscle cells	pTAS2R1	qPCR (7)

phosphodiesterases (PDEs) and consequently suppress the intracellular cAMP signaling [18, 19]. Gβγ proteins could enhance the inositol triphosphate (IP_3) production and intracellular Ca^{2+} signals [6, 18].

The acknowledged TAS2R agonists, including chloroquine, denatonium and quinine, could activate more than one TAS2R subtypes. Previous studies cannot assert the particular subtypes of TAS2Rs that mediated the physiological functions due to the agonists or antagonists' lack of selectivity and specificity.

Foster et al. [17] used HEK293T-$G\alpha_{16/gust44}$ cells, which were transiently transfected with cDNA constructs coding for mTAS2Rs. They identified that the effective concentration range of TAS2R agonists were in the micro molar to milli molar range. They showed that sodium thiocyanate increased the aortic pressure, a function attenuated by Gαi and Gβγ inhibitors, pertussis, and gallein. Liu et al. [11] reported that six rTAS2Rs and the downstream signaling molecule, Gα-gustducin, expressed in the rat aorta. They showed that denatonium increased the tension of endothelium-denuded aorta rings via TAS2R-Gαgustducin-PDEs cascade, a phenomenon blocked by a bitter taste masking agent and PDE inhibitors. However, denatonium did not affect the total intracellular cAMP in the aorta. It was likely that the localized cAMP suppression mediated the denatonium-induced tonic contraction [18]. One limitation of this study was that they could not assert the function of specific TAS2R subtypes.

Upadhyaya et al. [7] reported that dextromethorphan induced porcine pulmonary artery vasoconstriction by increasing intracellular Ca^{2+} via TAS2R1 activation as demonstrated by TAS2R1 knockdown. Moreover, dextromethorphan increased IP_3 production in porcine pulmonary artery smooth muscle cells. The authors proposed that the calcium increased through TAS2R-Gβγ-PLCβ signaling pathway.

Conclusion and Future Perspectives

Cumulative evidence indicates that TAS2Rs mediate a variety of functions in VSMs. However, understanding the expression, functions and mechanisms of TAS2Rs is still in its early stage. Up to date, reports mostly show the TAS2R mRNA expression. The lack of specific antibodies challenges the detection of TAS2R proteins and the identification of their signaling cascade. The studies for determining the TAS2R functions often use bitter compounds in the micro molar to the millimolar range; however, the agonist at high concentrations could exert various off-target effects. The promiscuity of bitter receptor-ligand interactions is another issue. Thus, selective and specific agonists and antagonists are necessary for clarifying the role of the individual receptor. To overcome these obstacles, we may fully understand the biological basis of TAS2Rs in VSMs in the future.

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