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Review

TRP-channels as key integrators of lipid pathways in nociceptive neurons

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ABSTRACT

TRP-channels are the most prominent family of ligand-gated ion channels for pain perception. In sensory neurons, TRPV1–V4, TRPA1 and TRPM8 are expressed and are responsible for the conversion of external stimuli to painful sensations. Under pathophysiological conditions, excessive activity of TRP-channels leads to mechanical allodynia and thermal hyperalgesia. Among the endogenous TRP-channel sensitizers, activators and inhibitors, more than 50 arachidonic acid- and linoleic acid-metabolites from the COX-, LOX- and CYP-pathways, as well as lysophospholipids and isoprenoids can be found. As a consequence, these lipids represent the vast majority of endogenous TRP-channel modulators in sensory neurons. Although the precise mechanisms of TRP-channel modulation by most lipids are still unknown, it became clear that lipids can either bind directly to the target TRP-channel or modulate TRP-channels indirectly by activating G-protein coupled receptors. Thus, TRP-channels seem to be key sensors for lipids, integrating and interpreting incoming signals from the different metabolic lipid pathways. Here, we discuss the specific properties of the currently known endogenous lipid-derived TRP-channel modulators concerning their ability to activate or inhibit TRP-channels, the molecular mechanisms of lipid/TRP-channel interactions and specific TRP-regulatory characteristics of the individual lipid families.

Contents

1. Introduction

The mammalian ion channel family of transient receptor potential (TRP)-channels consists of six subfamilies, TRPC, TRPM, TRPP, TRPML, TRPA and TRPV [1,2]. In sensory neurons of the peripheral nervous system several members of the TRP channel family are expressed, most importantly TRPV1–TRPV4, TRPA1 and TRPM8, but also TRPC1 TRPC3 and TRPC6 [3–6]. Under physiological conditions TRP channels serve as transducers of external stimulations, such as heat (TRPV1–V4), low pH (TRPV1) noxious cold and cool temperatures (TRPA1 and TRPM8) osmotic and possibly also mechanical

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stimulations (TRPV4, TRPA1, TRPC3 and TRPC6). TRP channels contain six transmembrane domains and two intracellular N- and C-terminal domains. Among those TRP-channels expressed in sensory neurons, the most prominent and best investigated ones are TRPV1 and TRPA1, which are key molecules for sensing noxious stimuli and tissue damage [7].

Activation of TRP channels is achieved through different mechanisms. TRPV1 is activated by binding of exogenous ligands, such as capsaicin and many endogenous ligands to a vanilloid binding site located between the third and fourth transmembrane domain, involving Tyr511 as crucial regulatory residue [8,9]. In contrast, TRPA1 activation seems to be more promiscuous and unselective. Interaction of electrophilic moieties with regulatory cysteine residues in ankyrin repeat domains located at the intracellular N-terminus is sufficient to activate the channel [10,11].

Upon TRP activation, the opening probability of the channel increases resulting in calcium-flux through a calcium permeable pore between the fifth and sixth transmembrane domain and subsequent depolarization in sensory neurons [7,12,13]. Under pathophysiological conditions, TRP-channels are sensitized and their activation threshold is reduced, leading to an enhanced pain perception of painful (hyperalgesia) and normally non-painful (allodynia) stimulations. Mechanisms of sensitization involve posttranlslational modifications such as phosphorylation by protein kinases as PKA and PKCε, nitrosylation of the channels, and increased recruitment of TRP channels to the plasma membrane

Table 1
Lipid metabolites as sensory TRP-channel modulators. The labeled concentrations refer to the lipid or the TRP channel with the same label. Abbreviations: 15-d-PGJ_2: 15-deoxy-$^{\Delta 12,14}$-Prostaglandin J_2, RvD, RvE: Resolvin D, Resolvin E, PD1/NPD1: Protectin/Neuroprotectin D1, HPETE: Hydroperoxyeicosatetraenoic acid, HETE: Hydroxyeicosatetraenoic acid. LTB4: Leukotriene B4, RvD: Resolvin D, (h): human, (m): murine, EET: Epoxyeicosatrienoic acid, LPA: Lysophosphatidic acid, AEA: Arachidonyl ethanolamide (Anandamide), NAPE-PLD: N-acyl phosphatidylethanolamine phospholipase D, OAG: Oleoylacetylglycerol, DAG: Diacylglycerol, PLC: Phospholipase C, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, AA: Arachidonic acid, SA: stearic acid, cPLA2: cytosolic phospholipase A_2 $iPLA_2$: Calcium-independent phospholipase A_2, LPC: lysophosphatidylcholine, LPI: lysophosphatidylinositol, LPS: lysophosphatidylserine, FPP: Farnesyl pyrophosphate, IPP: Isopentenyl pyrophsphate, DMAPP: Dimethylallyl pyrophosphate, 4-HNE: 4-Hydroxynonenal, 4-ONE: 4-Oxononenal, ATRA: all-trans retinoic acid, 9-cis-RA: 9-cis retinoic acid, DH: Dehydrogenase, HODE: Hydroxyoctadecadienoic acid, Oxo-ODE: Oxooctadecadienoic acid. NADA: N-arachidonoyl dopamine, OLDA: N-oleoyl dopamine, FAAH: fatty acid amide hydrolase, NAPE-PLD: N-acyl phosphatidylethanolamine phospholipase D, OA-NO_2: Nitro-oleic acid, PIP_2: Phosphatidylinositol-4,5-bisphosphate, PI4K: Phosphatidylinositol 4-kinase, PIP5K: Phosphatidylinositol-4-phosphate 5-kinase. Detailed structural information about lipids is available at lipidmaps.org [176].

Lipid	Key enzyme	TRP-channel	Effect	Effective conc./dose	Reference
PGE_2[a]/PGI_2[b]	COX-2	TRPV1	Sensitizers	1 μM[a], 0.1–1 μM[b]	[31,33]
15-d-PGJ_2[a], 8-iso-PGA_2[b], PGA_2[c], PGA_1[d]	COX-2	TRPA1	Activators	8.9–22 μM[a], 22.4 μM[b], 24 μM[c], 15.1 μM[d]	[36,164]
RvE1	Acetylated COX-2	TRPV1	Inhibitor	1–50 pM	[40]
17(R)-RvD1	Acetylated COX-2	TRPV3	Inhibitor	1–30 μM	[37]
5-(S)-HETE[a], 12-(S)-HETE[b], 12-(S)-HPETE[c], 15-(S)-HPETE[d], LTB_4[e]	12-/15-LOX, 5-LOX (LTB_4)	TRPV1	Activators	9.2 μM[a], 10 μM[b], 8 μM[c], 8.7 μM[d], 12.5 μM[e]	[47,53]
Hepoxilin A_3	12-LOX, eLOX3	TRPA1/TRPV1	Sensitizer	1 μM, 1–10 ng (*in vivo*)	[24,46,48]
RvD2	15-LOX	TRPA1/TRPV1	Inhibitor	0.1 nM (TRPV1), 2 nM (TRPA1)	[30]
RvD1	15-LOX	TRPV3[a]/TRPV4[b]/TRPA1[c]	Inhibitor	28 nM[a], 8.1 nM[b], 63 nM [c]	[38]
Maresin 1	(h)12-LOX/(m) 12-/15-LOX	TRPV1	Inhibitor	0.5–100 nM	[49]
PD1/NPD1	15-LOX	TRPV1	Inhibitor	IC_{50} 0.4 nM	[51]
5,6-EET	CYP2C/CYP2J	TRPA1	Activator	100 nM–5 μM	[28]
5,6-EET[a], 8,9-EET[b]	CYP2C/CYP2J	TRPV4	Activator	150 nM[a], ?[b]	[62]
20-HETE	CYP4A/CYP4F	TRPV1	Sensitizer	10–30 μM	[27]
LPA 18:1	Autotaxin	TRPV1	Activator	5–10 μM	[29]
AEA	NAPE-PLD	TRPV1	Activator	10 μM	[53,75]
OAG [a], DAG [b]	PLC	TRPA1/TRPA1	Activator	43 μM[a], ?[b]	[84,165]
DHA[a], EPA[b]	$iPLA_2$	TRPA1 TRPV1 TRPM8	Activators Inhibitors Inhibitors	100 μM each 1.2 μM [a], 224 nM [b] 2 μM[a], 6.3 μM[b]	[87,30,89]
AA	$cPLA_2$	TRPM8	Inhibitor	3.2 μM	[89]
AA n-6, AA n-3, SA	$cPLA_2$	TRPA1	Activators	100 μM each	[87]
LPC, LPI, LPS	$iPLA_2$	TRPM8	Activators	3 μM each	[89]
PIP_2	PI4K, PIP5K [166] PLC-substrate	TRPA1[a] TRPM8[b] TRPV1[c]	Inhibitor/ activator Activator Inhibitor/ activator	2.6 μM–15 μM[a] 15 μM[b] 5–50 μM[c]	[53,85,167–171]
FPP	HMG-CoA reductase FPP synthase ?	TRPV3	Sensitizer	130 nM	[97]
IPP	HMG-CoA-reductase	TRPV3/TRPA1	Inhibitor	1–30 μM, 1 mM (*in vivo*)	[96]
DMAPP	HMG-CoA-reductase IPP isomerase ?	TRPV4	Sensitizer	2.5–30 μM, 3 mM (*in vivo*)	[72]
4-HNE	?	TRPA1	Activator	19.9–27 μM	[103,172]
4-ONE	?	TRPA1/TRPV1	Activator	1.9 μM	[104,172,173]
ATRA[a], 9-cis-RA[b], 13-cis-RA[c], retinol[d]	Retinol DH, Aldehyde DH Retinaldehyd DH? [174,175]	TRPV1	Activators	100–1000 μM[a], 3–300 μM[b], 10–100 μM[c], 30–100 μM[d]	[105]
9-HODE[a], 9-oxo-ODE, 13-HODE[b], 13-oxo-ODE	15-LOX ?, CYP2J ?, CYP3A1 ?	TRPV1	Activators	300 nM–100 μM[a] 800 nM–100 μM[b]	[25,26,59]
NADA[a], OLDA[b]	FAAH ?	TRPV1	Activator	65 μM[a], 36 μM [b]	[21,110]
OA-NO_2	?	TRPV1/TRPA1	Activator	1 μM	[109]
Unsaturated C18 N-acylethanolamines	NAPE-PLD ?	TRPV1	Activator	10–100 μM	[111]

[a,b,c] or [d] labeled concentrations refer to the lipid or the TRP channel with the same label.