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Review

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Terpenes and Lipids of the Endocannabinoid and Transient-Receptor-Potential-Channel Biosignaling Systems

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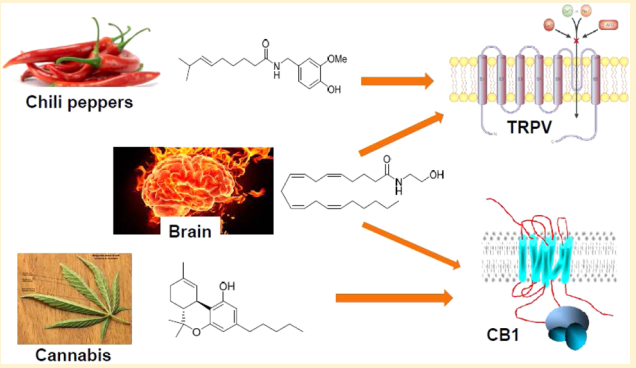
ABSTRACT: Endocananbnoid-system G-protein coupled receptors (GPCRs) and transient receptor potential (TRP) cation channels are critical components of cellular biosignaling networks. These plasma-membrane proteins are pleiotropic in their ability to interact with and engage structurally diverse ligands. The endocannabinoid and TRP signaling systems overlap in their recognition properties with respect to select naturally occurring plant-derived ligands that belong to the terpene and lipid chemical classes, the overlap establishing a physiological connectivity between these two ubiquitous cell-signaling systems. Identification and pharmacological profiling of phytochemicals engaged by cannabinoid GPCRs and/or TRP channels has inspired the synthesis of novel designer ligands that interact with cannabinoid receptors and/or TRP channels as xenobiotics. Functional interplay between the endocannabinoid and TRP-channel signaling systems is responsible for the antinocifensive action of some synthetic cananbinoids (WIN55,212-2 and AM1241), vasorelaxation by the endocannabinoid *N*-arachidonylethanolamide (anandamide), and the pain-relief afforded by the synthetic anandamide analogue *N*-arachidonoylaminophenol (AM404), the active metabolite of the widely used nonprescription analgesic and antipyretic acetaminophen (paracetamol). The biological actions of some plant-derived cannabinoid-receptor (e.g., Δ^9-tetrahydrocannabinol) or TRP-channel (e.g,, menthol) ligands either carry abuse potential themselves or promote the use of other addictive substances, suggesting the therapeutic potential for modulating these signaling systems for abuse-related disorders. The pleiotropic nature of and therapeutically relevant interactions between cananbinergic and TRP-channel signaling suggest the possibility of dual-acting ligands as drugs.



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At the cellular level of biological organization, a fundamental paradigm for communication utilizes plasma-membrane proteins (receptors, ion channels, transporters, etc.) as components of organized signaling circuits that interact with molecules (ligands) for the purpose of transmitting information from the external milieu to the intracellular compartment, thus enabling the target-cell to respond to its environment.[1] This core principle of signal transduction is well exemplified by two ubiquitous mammalian signaling systems, one of which employs cannabinoid (CB) receptors; the other, transient receptor potential (TRP) cation channels.

Discovery and molecular characterization of the first CB receptor to be cloned (CB1) was spurred by identification and synthesis of the major psychotrophic component of marijuana, (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC), a plant-derived CB ("phytocannabinoid") (Figure 1A). A second CB receptor, designated CB2, was subsequently identified through homology cloning, and other putative CB receptors have been suggested. Both CB1 and CB2 are class-A G-protein coupled receptors (GPCRs) featuring characteristic 7-transmembrane helical domains, significant homology with one another in their transmembrane domains, and distinct distributions: CB2 is found mainly in peripheral tissues (principally immune-associated), whereas CB1 is a major GPCR in the central nervous system at presynaptic neurons and is also expressed in the periphery.[2] CB1 and CB2, along with a growing family of their endogenous activators ("endocannabinoids") and the enzymes that synthesize and inactivate those agonists, are constituents of the endocannabinoid system, a biosignaling network ubiquitous in mammals.[3] The best-studied endocannabinoids, 2-arachidonoylglycerol (2-AG) and *N*-arachidonylethanolamide (or anandamide) (AEA), are lipid mediators

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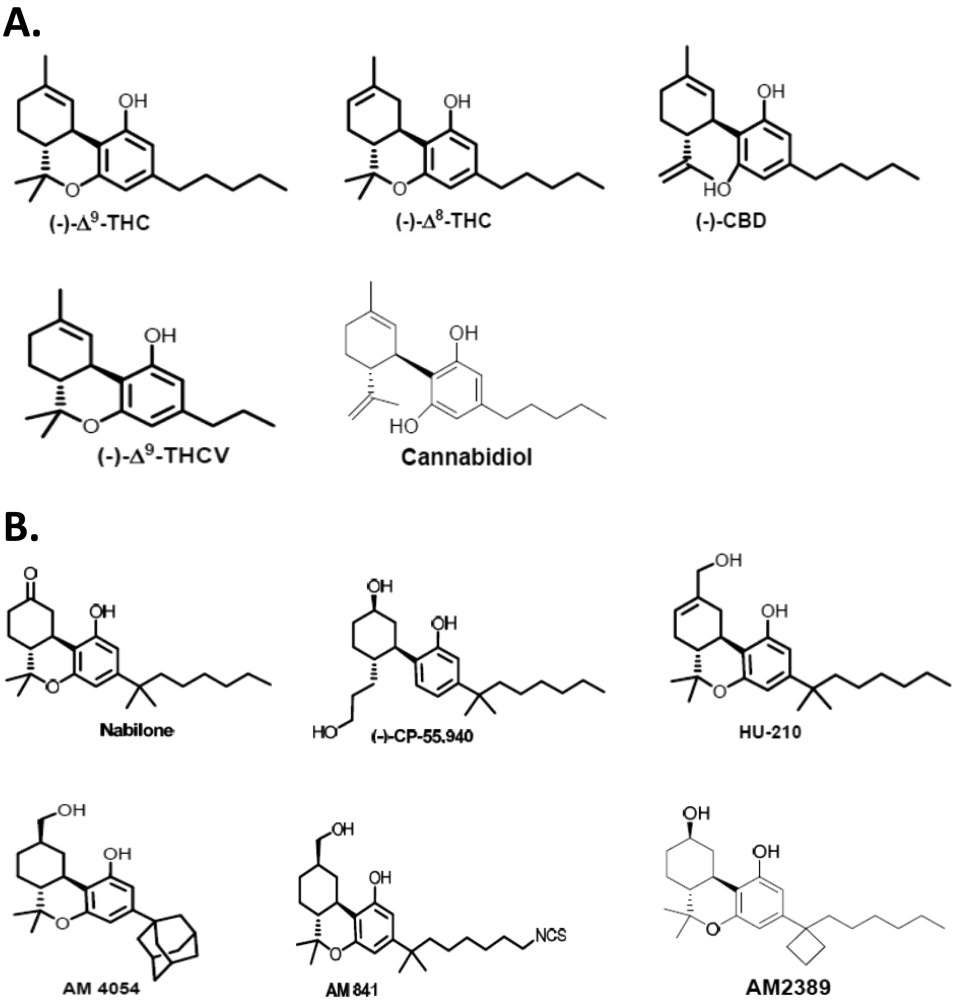

Figure 1. Chemical structures of select plant-derived terpenoid cannabinoids (phytocannabinoids) (A) and select synthetic terpenoid cannabinoids (B) discussed in the text.

derived from diacylglycerol and *N*-acyl-phosphatidycholine, respectively (Figure 2A). They originate from membrane phospholipids by distinct enzymatic pathways and possess specific functional and pharmacological properties.[4] In the central nervous system (CNS), the presynaptic serine hydrolase, monoacylglyceorol lipase (MGL), is primarily responsible for 2-AG inactivation in vivo along with the α,β-hydrolase domain-containing proteins 6 and 12 (ABHD6 and ABHD12), whereas AEA is inactivated by fatty acid amide hydrolase (FAAH) postsynaptically.[5] Aside from its canonical role in the CNS as a key retrograde modulator of neurotransmitter release,[6] the endocananibinoid system, either alone or in concert with other neuromodulatory signaling systems, is involved in a number of fundamental (patho)physiological processes, including energy balance, emotional processing, reward and motivation, immune function, and pain sensing.[7−10]

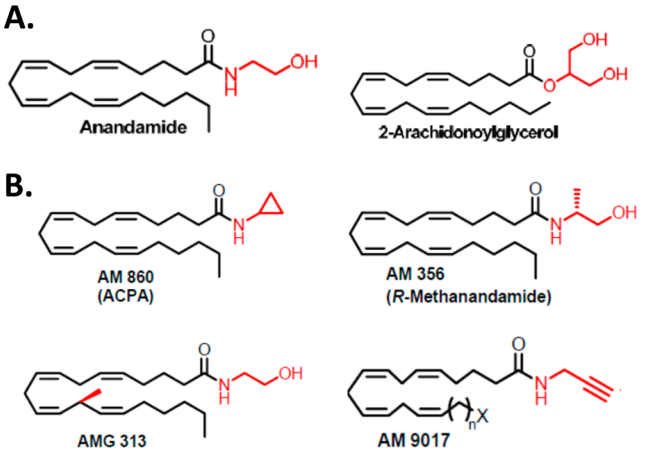

Figure 2. Chemical structures of select lipid endocannabinoids (A) and structurally related synthetic cannabinergic agents (B) discussed in the text.

Across animal phyla, TRP channels constitute a superfamily of over 50 nonselective cation-channel membrane proteins that function as cellular sensors whose activity in response to external stimuli ultimately elicits a change in cell-membrane potential.[11] All known TRP channels evidence six transmembrane segments (TMS1−TMS6) and a short, hydrophobic, cation-permeable pore domain between TMS5 and TMS6. TRP channels are polymodal: their ion permeability can be modulated by diverse mechanisms including G-protein coupled signaling, membrane depolarization, and direct ligand binding. The 28 distinct mammalian TRP channels identified have been classified on the basis of sequence homology into six subfamilies, each subfamily characterized by distinct gating mechanisms and cation selectivities.[12] Of these subfamilies, the

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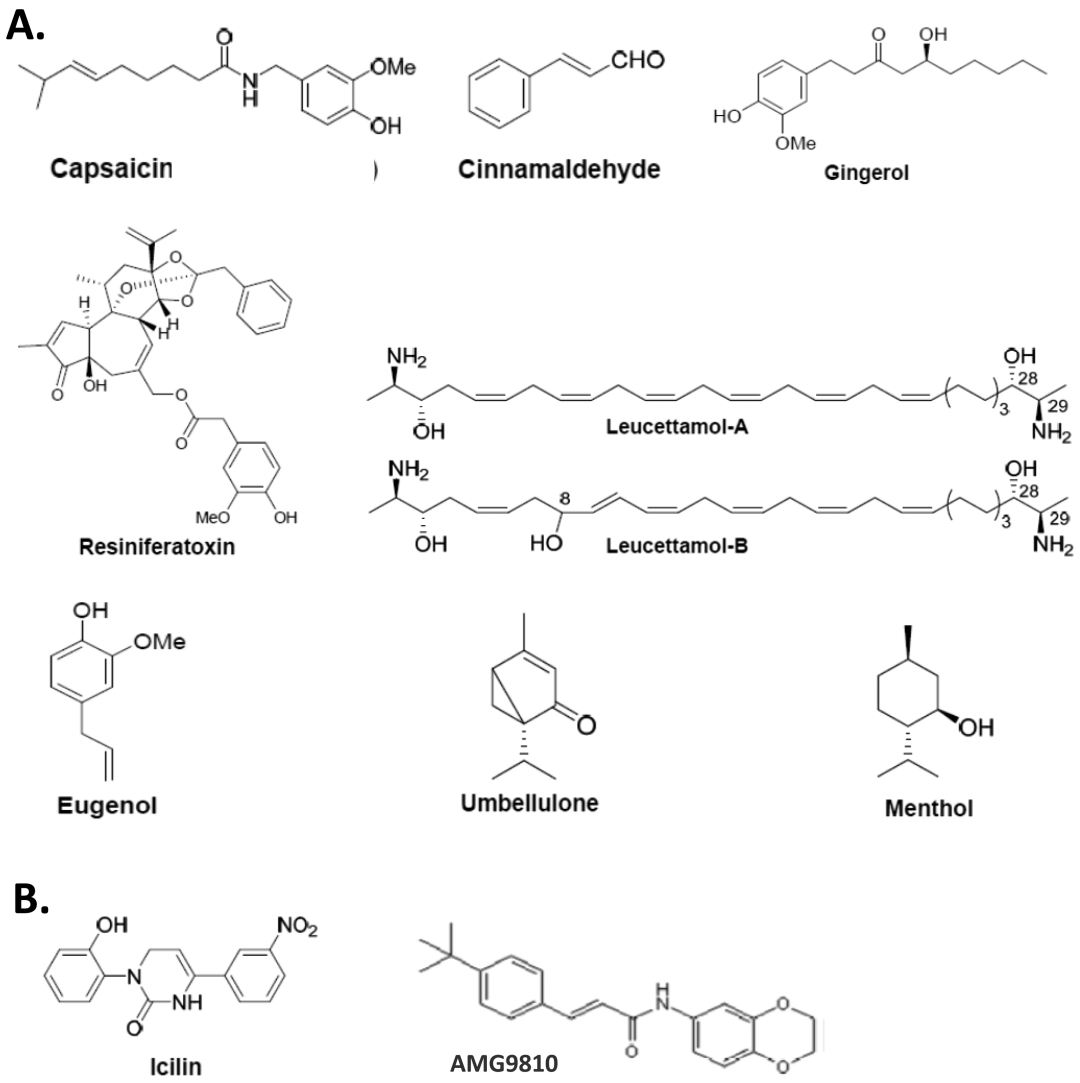

Figure 3. Chemical structures of select plant-derived terpenoid TRP-channel ligands (A) and synthetic TRP-channel ligands (B) discussed in the text.

six vanilloid or "thermo" TRP channels (TRPV1−6) have garnered the most attention, with TRPV1 being the best-characterized and first-cloned TRPV due to its physiological role in nervous tissue as a molecular integrator of diverse noxious chemical and thermal stimuli, notably its extreme responsiveness to thermal (heat) activation from the pungent vanilloid capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) (Figure 3A), an irritant found in hot chili peppers, as well as to other phytochemical toxins and acid.[13] Reminiscent of the endocananbinoid system, TRP-channel signaling is involved in many (patho)physiological processes, for example, cell proliferation/differentiation, neurotransmitter release, chemical sensing, cell death, and inflammation.[11,14,15] Indeed, both endocanabinoid-system proteins[8−10] and TRP channels[15−18] are aggressively being pursued as drug targets for indications including diabetes, pain, cancer, neurodegeneration, and substance-abuse disorders.

The goal of this Review is to summarize and discuss select concepts related to the most important ligands associated with the (in)activation of the CB and TRP-channel signaling systems. A particular focus will be on ligands belonging to the terpene or lipid chemical classes that interact with both systems.

COMMONALITIES BETWEEN CANNABINERGIC AND TRP BIOSIGNALING SYSTEMS

Aside from their basic physiological role as routes of cellular communication and focuses of contemporary drug discovery, CB-receptor- and TRP-channel-dependent signaling share several fundamental properties. Cannabinergic and TRP-signaling systems are both pleiotropic. Their pleiotropic, or "opportunistic", nature is manifested in the ability of CB1, CB2, and TRPV1 to interact with and engage structurally diverse ligands belonging to a wide variety of chemical classes, some of which may also interact with other signaling systems. Most relevant to the present discussion, the endocannabinoid and TRP systems overlap in their ligand-recognition properties with respect to select naturally occurring ligands.[19] The shared endogenous ligands are found in plants and animals and generally belong to the lipid and terpene chemical classes. The seminal discovery in this regard, demonstration in 1999 that the endocannabinoid AEA can activate TRPV1 channels,[20] also established physiological connectivity between endocananbinoid-system and TRP-channel-mediated cellular signaling, a relationship particularly relevant in the CNS where CB1 and TRPV1 activation provides a framework for Δ^9-THC's

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psychobehavioral manifestations and the transmission and modulation of thermal and pain effects. The spectrum of natural cannabinergic and TRP-channel ligands has been greatly expanded by medicinal chemistry efforts that have produced designer synthetic ligands that interact as xenobiotics with CB receptors and/or TRP channels.[9,21,22]

PHYTOCANNABINOIDS AND LIGANDS BASED UPON A TERPENOID CHEMOTYPE

Among its approximately 500 endogenous phytochemicals,[23] the cannabis plant contains some 70 unique cannabinoids ("phytocannabinoids"), of which the most well-studied are shown in Figure 1A. Δ^9-THC is the archtypical "classical CB", encompassing a fused-ring tricyclic terpenoid derivative incorporating a polar benzopyran ring with a terminal, hydrophobic alkyl (*n*-pentyl) side-chain, a characteristic lipophilic domain, and hydrogen-bonding phenolic group.[24] Δ^9-THC can engage and activate both CB1 and CB2 receptors with low nanomolar affinity, although the action of Δ^9-THC as a partial agonist at presynaptic CB1 receptors in the CNS is thought to account for its psychotropic activity as the main psychoactive cannabis phytocannabinoid. Δ^9-THC and its much less prominent natural isomer, (−)-Δ^9-tetrahydrocannabinol (Δ^8-THC), are virtually equivalent as to CB-receptor affinity and pharmacological activity, although Δ^8-THC is the more chemically stable isomer.[25] As compared to Δ^9-THC, the phytocannabinoid (−)-cannabidiol (CBD) has significantly less affinity for CB receptors, modest CB2 selectivity, and negligible psychotropic activity.[26,27] Another classical terpenoid phytocannabinoid, (−)-Δ^9-tetrahydrocannabivarin (Δ^9-THCV), is a shorter side-chain Δ^9-THC homologue with a similar CB-receptor affinity and selectivity profile. As a "neutral" CB1 antagonist in some systems, Δ^9-THCV at low doses can antagonize the effects of Δ^9-THC in a manner distinct from that of typical CB1 antagonists/inverse agonists and may also have CB receptor-independent pharmacological activities.[27,28]

The classic terpenoid phytocannabinoids THC, CBD, and Δ^9-THCV have inspired the synthesis of several structurally related cannabinergic compounds that display varying degrees of selectivity as CB1/CB2 agonists and, generally, improved CB-receptor affinity versus Δ^9-THC. Many of the synthetic CB agonists based on classic phytocannabinoids have been designed with therapeutic application in mind and, consequently, have been profiled preclinically for both their molecular pharmacology in vitro and potential salutary effects in disease models in vivo. Most prominent of these xenocannabinoids include nabilone, the first CB drug to be synthesized and used to treat chemotherapy-associated nausea, and CP-55,940, the first tritiated CB that, as a radiolabeled ligand, played a key role in the discovery of CB1.[2,7,8] Other related xenocannabinoids include HU-210,[29] AM4054,[30] AM841,[31] and AM2389[32] (Figure 1B). Of note, the isothiocyanate AM841 has been identified as an exceptionally potent "megagonist" at CB2 whose molecular mechanism of action involves covalent modification of a critical cysteine residue in the receptor's transmembrane helix 6.[33] Similarly, the analgesic potency of the novel, high-efficacy, CB1-selective agonist AM2389 is 1000-fold greater than that of morphine in the standard rat tail-flick model of pain.[34]

ENDOCANNABINOIDS AND RELATED LIPID LIGANDS

Endocannabinoid lipid mediators that activate CB1 and CB2 are exemplified by AEA and 2-AG (Figure 2A). AEA is a partial CB1 activator with modest affinity and a relatively weak CB2 ligand with low overall efficacy, whereas 2-AG is a full agonist at CB1 and CB2, albeit with lower affinity and greater efficacy relative to AEA.[3,4] As is the case for synthetic phytocannabinoid analogues, several lipid cananbinergic ligands structurally related to AEA/2-AG have been synthesized by medicinal chemists for potential therapeutic application. These include arachidonoylcyclopropylamide (AM860, ACPA), a potent, selective CB1 agonist with anxiolytic and vasorelaxant properties in vivo;[35] *R*-methanandamide (AM356), the first metabolically stable, chiral AEA analogue with partial CB1 efficacy and higher potency as compared to AEA itself that exerts therapeutic neuroprotective, antinociceptive, vasorelaxant, and anti-inflammatory effects;[36] AMG313, the first AEA analogue with a chiral methyl arachidonoyl side chain;[37] and AM9017, the first AEA analogue with high CB2 affinity (Whitten and Makriyannis, 2014, unpublished results) (Figure 2B).

PHYTO-TRPs AND RELATED TERPENOID LIGANDS

The prototypic, plant-derived TRPV1 agonist and homovanillic ester, capsaicin, is one of the five principal capsaicinoids present in Cayenne chili pepper (*Capsicum annuum* L.)[38,39] (Figure 3A). Several other structurally diverse phytochemicals have been identified as naturally occurring TRP-channel modulators of various TRP channel subfamilies. The diterpene capsaicin analogue resiniferatoxin is an extremely potent TRPV1 agonist,[40] and the phytocannabinoid cannabidiol is both a CB1/CB2 agonist as well as an activator of TRPV1, TRPV2, and TRPV3[41,42] (Figure 3A). Other phytochemical TRP-channel activators include the four transient potential receptor channel ankyrin 1 (TRPA1) agonists cinnamaldehyde (found in cinnamon),[43] eugenol (found in cloves),[44] gingerol (found in ginger),[45] and umbellulone (found in California bay laurel, the "headache tree")[46] and the two marine sphingoids leucettamol-A and leucettamol-B, which activate TRPA1 and inhibit transient receptor potential channel melastatin 8 (TRPM8)[47] (Figure 3A). Some plant-derived TRP-channel agonists have served as templates for medicinal chemistry efforts aimed at producing TRP-channel modulators with improved pharmacological profiles as potential drugs, for example, gingerol analogues.[48]

ENDOGENOUS TRP-CHANNEL AND RELATED LIPID LIGANDS

Several naturally occurring lipids act on TRP channels to modify cation flux through them.[49−51] The endocannabinoid AEA modulates CB1/CB2 and also acts as a TRPV1 agonist[20] (Figure 2A), while oleoylethanolamide (OEA) is a TRPV1 agonist that also binds to peroxisome proliferator-activated receptor alpha (PPAR-α) and the GPR119 CB-like receptor[52] (Figure 4A). Other endogenous *N*-acyl-amide lipids structurally related to AEA include the FAAH inhibitor and TRPV1 antagonist *N*-arachidonoylserotonin[53] and the CB1 and TRPV1 agonist *N*-arachidonoyldopamine (NADA).[54] NADA was the first endogenous compound ("endovanilloid") identified in mammalian nervous tissue with potency comparable to the phytochemical capsaicin at TRPV1 and is a long-chain fatty-

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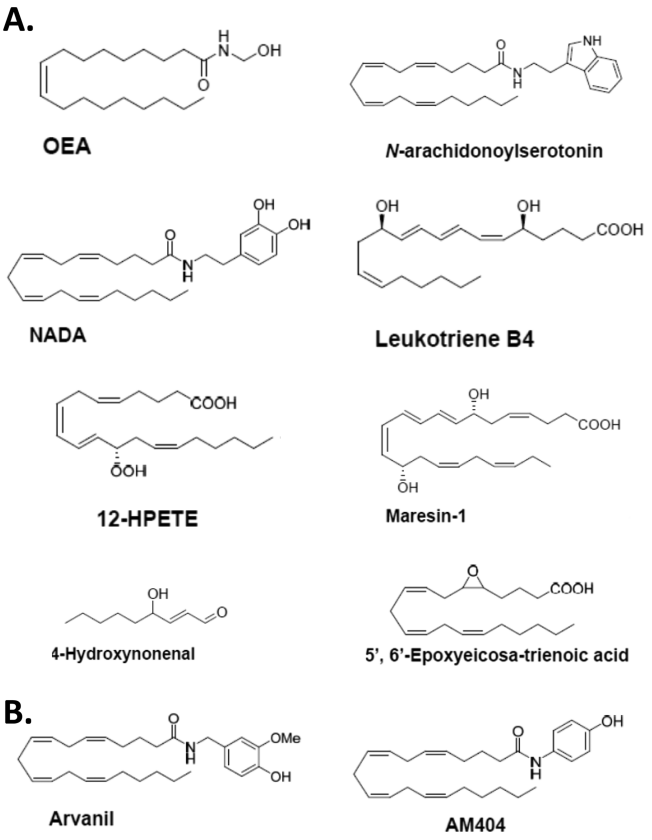

Figure 4. Chemical structures of select endogenous (A) and synthetic (B) lipid TRP-channel ligands discussed in the text.

acid amide, as are AEA and capsaicin.[55] *N*-Acyl-amide lipids that act at TRP channels have inspired synthetic analogues including *N*-vanillylarachidonamide ("arvanil"), a TRPV1 agonist and CB1 partial agonist.[56] Similarly, *N*-arachidonoylaminophenol (AM404), the first potent lipid-amide inhibitor of cellular AEA uptake, was subsequently shown to be a potent TRPV1 activator and cyclooxygenase-1/2 inhibitor as well[57−59] (Figure 4B).

Lipids produced by the lipoxygenase-mediated oxygenation of polyunsaturated 20-carbon fatty acids (especially arachidonic acid), including the eicosanoids leukotriene B4 (LTB_4) and 12-hydroperoxyeicosatetraenoic acid (12-HPETE), are potent, endogenous TRPV1 activators[60,61] (Figure 4A). Formed by macrophages in vivo, an endogenous lipid mediator involved in resolving inflammation, maresin-1 (4*Z*,7*R*,8*E*,10-*E*,12*Z*,14*S*,16*Z*,19*Z*)-7,14-dihydroxy-4,8,10,12,16,19-docosahexaenoic acid, is synthesized from docosahexaenoic acid lipoxygenation and acts as a TRPV1 antagonist[62] (Figure 4A). Other endogenous lipid-derived mediators have been identified as modulators of TRP channels from nonvanilloid subfamilies or TRP channels in the vanilloid subfamily other than TRPV1; for example, 4-hydroxynonenal produced from polyunsaturated fatty acid peroxidation activates TRPA1,[63] and epoxytrienoic acids (EETs), including 5′,6′-epoxyeicosatrienoic acid (5′,6′-EET) produced from epoxygenation of 20-carbon polyunsaturated fatty acids by cytochrome P450, activate TRPV1and TRPV4[64,65] (Figure 4A).

THERAPEUTICALLY RELEVANT FUNCTIONAL INTERPLAY BETWEEN CANNABINERGIC AND TRP-CHANNEL-MEDIATED SIGNALING

The ability of the synthetic aminoalkylindole cannabinoids *R*-(+)-WIN55,212-2 and AM1241 (Figure 5) to elicit peripherally

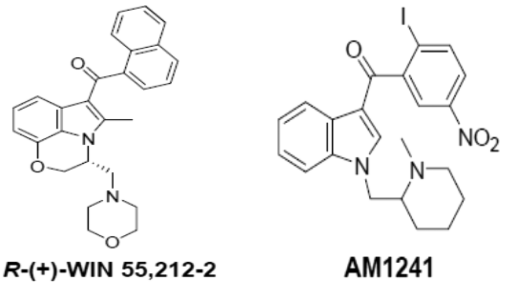

Figure 5. Chemical structures of synthetic aminoalkylindole cannabinoids discussed in the text.

mediated antinocieption and antihyperalgesia in acute pain models[66] and alleviate capsaicin-induced hyperalgesia/allodynia[67,68] prompted investigation of their mechanism of action. Particularly intriguing was the notion that both *R*-(+)-WIN55,212-2 and AM1241 can inhibit nociceptive sensory neurons while differing in their activation profiles at CB receptors: *R*-(+)-WIN55,212-2 is a full CB1 agonist,[69] whereas AM1241 is a CB2-selective agonist.[70] Cellular and in vivo animal data demonstrate that these CB agonists exert peripheral antinocifensive actions against the phytochemicals capsaicin and mustard oil by desensitizing TRPA1 and TRPV1 channels on sensory neurons.[71] Thus, these cannabinergic compounds first act to activate TRPA1 and TRPV1, which is then followed by desensitization of these TRP channels.

Another level of interaction between endocananbinoid-system and TRP-channel signaling is illustrated by the metabolic cascade responsible for TRPV4 activation by the lipids AEA (Figure 2A) and 5′,6′-EET (Figure 4A). As elucidated by Watanabe et al.,[72] enzymatic hydrolysis of the endocananbinoid AEA by FAAH produces arachidonic acid. This FAAH-dependent AEA hydrolysis is a metabolic conversion that is obligatory for AEA to activate TRPV4, since the arachidonic acid so produced serves as substrate for EET production through the cytochrome-P450 epoxygenase pathway. A resulting lipid epoxide product, 5′,6′-EET, is able to activate and open TRPV4, leading to calcium influx into the target cell, a phenomenon important to the physiological modulation of vascular tone and AEA's vasorelaxant property.

A further example of the functional crosstalk between the endocananibnoid system and TRP channel-mediated information transduction has emerged from a series of laboratory studies in rodents on the mechanism of action of acetaminophen (*N*-acetyl-*p*-aminophenol), a widely used over-the-counter analgesic and antipyretic drug.[59,73,74] Spanning a decade, these studies by Zygmunt and colleagues demonstrated that the antinociceptive effect of acetaminophen is dependent upon brain TRPV1 and that acetaminophen is biotransformed to the synthetic lipid AM404 through the action of the endocananbinoid-system enzyme, FAAH, in rat and mouse brain. The mechanism of acetaminophen's TRPV1-mediated antinociception was demonstrated to reflect acetaminophen hepatic metabolism to *p*-aminophenol, which is subsequently conjugated with arachidonic acid in FAAH-

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containing neurons expressing TRPV1, leading to the formation of the TRPV1 activator AM404, which directly interacts with this TRP channel to elicit a therapeutic effect (analgesia, reduce fever). Notably, neither acetaminophen nor *p*-aminophenol interacts with TRPV1. Prior to this work, AM404 was shown to inhibit cellular AEA uptake and cyclooxygenase-1/2 and activate TRPV1.[57,59] Thus, AM404's potent analgesic activity in vivo may reflect its pleiotropic activity profile and effects on multiple endocananbinoid-system and TRP-channel targets.

INVOLVEMENT OF CANNABIBERGIC AND TRP-CHANNEL SIGNALING IN DRUG ABUSE

Potentiation of cannabinergic and TRP-channel signaling by phytochemicals has been linked to substance-abuse-related disorders, with great implications for human health. Stimulation of CB1 in the CNS by the phytocannabinoid Δ^9-THC is generally accepted to be the basis for the negative cognitive effects of marijuana and its abuse liability,[75] inviting novel medicinal chemistry approaches (e.g., CB1 agonists with limited CNS penetration[76]) for modulating CB1 activity without inviting adverse psychobehavioral events. Observations that changes in cannabinergic activity and/or endocannabinoid tone have been associated with a variety of physiological challenges and disease states involving the nervous system and most every peripheral organ suggest that the endocananbinoid system contributes to normal physiological conditions by responding to injurious or disease-provoking insults in order to attenuate or delay their potentially damaging consequences and help maintain homeostatic balance.[77,78] Thus, modulation of endocannabinoid-system activity has been of great therapeutic interest with respect to two general modalities: (a) regulating endocananbinoid-system activity with an agent whose dosing regimen/molecular pharmacology does not itself invite adverse events; (b) enhancing cyto- and tissue-protective endocannabinoid-system activation in a time-, event-, and tissue/organ-specific manner so as to reduce the potential for adverse responses. Examples of the former modality are the successful introduction into the clinic in certain markets of Sativex, a mixture of Δ^9-THC and the nonpsychoactive phytocannabinoid CBD (Figure 1A), for relief of neuropathic pain associated with multiple sclerosis, as an adjunctive pain reliever for advanced cancer, and for treating spasticity due to multiple sclerosis[79] and CB1 (periphero-)neutral antagonists for cardiometabolic disease.[80] The latter modality would include FAAH inhibitors that enhance the CNS endocannabinoid elevation observed after brain injury to therapeutic levels.[10]

The well-known cooling sensation of menthol (Figure 3A), a constituent of the wild mint plant (*Mentha arvensis*), reflects this phytochemical's ability to trigger chemically the cold-sensitive TRPM8 receptors in cold-sensitive sensory neurons. Menthol also has complex olefactory- and somatosensory-stimulating properties and interacts with TRPA1, an irritant-sensing TRP channel expressed by nociceptors in the lung and respiratory tract.[81] In humans, a common haplotype of the gene encoding for TRPA1 provides a functional TRPA1 channel associated with a preference for mentholated cigarettes among heavy smokers.[82] This genetic and biological profile along with the ubiquitous presence of menthol as an additive in most commercial cigarettes, the preference for menthol-containing cigarettes during smoking initiation, and the lower smoking-cessation rates for menthol smokers have prompted investigation as to menthol's potential role in promoting smoking behavior/nicotine addiction and its contribution to the incidence of tobacco-related diseases.[83] Data in mice demonstrate that menthol, through TRPM8 activation, acts as a potent respiratory counterirritant to suppress the respiratory irritation caused by a wide variety of irritants in tobacco smoke.[84] In this manner, menthol's biological activity at TRPM8 may facilitate smoke inhalation and promote tobacco smoking/nicotine addiction, an enormous health problem as the leading cause of preventable death and illness underserved by current pharmacotherapeutic strategies.[85] In the clinic, the CB1 antagonist/inverse agonist rimonabant has been shown to increase the likelihood that smokers will quit,[86] and inhaled CBD reduces cigarette consumption, perhaps by modulating the craving-related salience of smoking cues.[87] These aggregate in vivo and clinical data regarding menthol pharmacology support the proposition that TRP-channel and endocannabinoid-system signaling are involved in sustaining tobacco smoking and may be leveraged for therapeutic gain against nicotine addiction.

Perhaps instigated by menthol's biological properties as related to tobacco smoking, the very potent synthetic TRPM8 agonist, icilin (Figure 3B), has been studied by the tobacco industry as a flavor enhancer for cigarettes.[88] It is noteworthy, however, that icilin, but not menthol, requires calcium as a coagonist to attain maximal levels of TRPM8 activation, suggesting that discrete structural requirements must be fulfilled for ligand-induced TRP channel activation and degree of thermosensitivity.[89−91] This proposition was indeed supported by mutagenesis experiments demonstrating that specific residues in the cytoplasmic loop interconnecting TMS2 and TMS3 (i.e., N799, D802, and G805) are critical for TRPM8's icilin sensitivity, just as residues in analogous positions (i.e., Y511 and S512) are critical for activation of TRPV1 by capsaicin.[91] Further evidence for ligand-sensitive functional domains in TRP channels comes from demonstration that many noxious TRPA1-activating compounds are electrophiles whose covalent modification of select reactive cysteine residues in this TRP channel is critical for the rapid signaling of potential tissue damage through the neural pain pathway.[92] Despite their noxious and abuse-related properties, then, some phytochemicals have proven their value for interrogating the molecular mechanisms by which TRP channels are activated.

CONCLUSIONS

Both naturally occurring and synthetic terpenes and lipids stimulate cannabinergic or TRP channel-mediated signaling in mammals. Some of these signaling molecules are co-opted by both information systems and are able to act at both discrete CB and TRP-channel protein targets. Interaction of phytochemcials and synthetic ligands with both CB receptors and TRP channels and the significant degree to which CB1 and TRPV1 are coexpressed in several brain regions (including the hypothalamus, striatum, hippocampus and substantia nigra)[93] carry implications for human health and disease treatment. For instance, demonstration that the competitive TRPV1 antagonist AMG9810 (Figure 3B) further reduces the inflammatory activation of human endothelial cells elicited by the synthetic CB *R*-(+)-WIN55,212-2 or the naturally occurring CB1 and TRPV1 agonist NADA, whereas TRPV1 inhibition with AMG9810 alone potentiated the inflammation suggests that cannabinergic and TRP-mediated signaling work in concert to regulate endothelial inflammatory sensitivity/homeostasis.[94]

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The anticonvulsant effect of dual FAAH and TRPV1 blockade with *N*-arachidonoyl-serotonin depends upon potentiation of CB1 activity as a result of the increased AEA levels consequent to FAAH inhibition with a component of TRPV1 blockade against the neuroexcitatory effect of TRPV1 activation by AEA.[95] Such findings suggest that discrete functional and pharmacological interactions between TRP channels and endocannabinoid-system proteins offer opportunities to develop novel, dual-acting ligands both as both probes for interrogation of their independent and integrative functionality and as drugs that modulate these two biosignaling systems for therapeutic gain.

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Author Contributions

Both authors contributed to the writing of the manuscript.

Notes

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ABBREVIATIONS

CB, cannabinoid; TRP, transient receptor potential; CB1, cannabinoid 1 receptor; (−)-Δ^9-THC, (−)-Δ^9-tetrahydrocannabinol; CB2, cannabinoid 2 receptor; GPCR, G-protein coupled receptor; 2-AG, 2-arachidonoylglycerol; AEA, anandamide; CNS, central nervous system; MGL, monoacylglycerol lipase; ABHD6, α,β-hydrolase domain-containing protein 6; ABHD12, α,β-hydrolase domain-containing protein 12; FAAH, fatty acid amide hydrolase; TMS, transmembrane segment; TRPV, transient receptor potential vanilloid; (−)-Δ^8-THC, (−)-Δ^8-tetrahydrocannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; ACPA, arachidonoylcyclopropylamide; TRPA1, transient potential receptor channel ankyrin 1; TRPM8, transient receptor potential channel melastatin 8; OEA, oleoylethanolamide; PPAR-α, peroxisome proliferator-activated receptor alpha; NADA, *N*-arachidonoyl dopamine; LTB_4, leukotriene B_4; 12-HPETE, 12-hydroperoxyeicosatrienoic acid; EET, epoxytrienoic acid; 5′,6′-EET, 5′,6′- epoxytrienoic acid

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