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Canonical Transient Receptor Potential Channels as Novel Targets for Antiepileptic Drugs

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Abstract: Canonical transient receptor potential channels (TRPC) are a family of calcium-permeable cation channels that have emerged as novel molecular targets for epilepsy and other human diseases in recent years. Cryogenic electron microscopic structures for the majority of TRPC have been resolved and these structures have provided new insights regarding the gating mechanisms of TRPC and aided the developments of small molecule modulators of these channels. Small molecule modulators target several TRPC and show promise as anti-seizure drugs. However, the pharmacokinetics need improvement, and better understanding of native TRPC will facilitate future drug development.

Keywords: cryo-EM structure; epileptiform discharges; small molecule modulators; transient receptor potential channels; TRPC

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INTRODUCTION

Most current anti-seizure drugs target either voltage-gated ion channels or ligand-gated ion channels (1–4). These drugs are effective in reducing either focal or generalized seizures. However, a third of epilepsy patients have refractory seizures which are resistant to current drug treatment (5). Therefore, there is an urgent need to identify novel molecular targets to develop new therapeutics for epilepsy.

Canonical transient receptor potential channels (TRPC) , which are a family of distinct calcium permeable cation channels (6–8), are the focus of this chapter. There are seven members in the mammalian TRPC family, TRPC1, 2, 3, 4, 5, 6, and 7, and based on sequence homology, they can be divided into three subgroups: TRPC1, 4, 5; TRPC3, 6, 7; and TRPC2. Structurally, they are highly similar to voltage-gated cation channels with six transmembrane domains and a pore loop but lack voltage sensors. However, they are gated by G-protein coupled receptors via the phospholipase C signaling pathway. All TRPC family members are capable to form functional homo-tetrameric channels in artificial expression system. They can also form heterotetramers with other TRPC family members or members of the broader transient receptor potential (*TRP)* superfamily. The exact subunit composition of native TRPC in various cells or tissues remains hotly debated.

The functional roles of TRPC have also been subjects to controversy (6, 9). The initial lack of good pharmacological tools has limited the study of the functional roles of TRPC, and genetic knockout mouse lines became indispensable for revealing the specific roles of each TRPC family member. Initial reports suggested that TRPC1 and TPRC4 may be involved in store-operated calcium (SOC) influx (10–14). Another ion channel, Orai, was later cloned and identified to be the core component of SOC (15, 16). However, the debate about the precise role of TRPC in SOC is still ongoing (17). An emerging consensus is that TPRC are polymodal, and their roles include receptor-operated calcium influx (ROC) (18), sensors for stretch in vasculatures (19, 20), and oxidative stress (21). Altogether, TRPC knockout mouse lines have produced over 30 proposed roles of TRPC in native tissues (17, 19)

The fact that such a wide variety of potential functional roles have linked to TRPC (17) showed that these channels potentially are promising molecular targets for drug developments. In the last decade, a new generation of small molecule modulators for TRPC3, 4, 5, 6 has been developed and some of these compounds have progressed into early clinical trials for a host of diseases (8, 22–24). The recent cryogenic electron microscopic (cryo-EM) studies of TRPC3, 4, 5, and 6 have revealed new insights regarding the structure and gating of these channels, and identified new modulatory sites that can be exploited for the developments of a next generation of small molecule modulators (25–35). The pace of the development is anticipated to further accelerate and brings a degree of optimism about the therapeutic potentials of TRPC. At the same time, the rapid pace has also generated some concerns about unresolved controversy regarding the functional roles of various types of TRPC.

The goal of this chapter is to review the current literature and discuss why and how TRPC3, 4, 5, and 6 could be targeted for the development of new antiepileptic drugs. Although TRPC7 are involved in seizure generation (36), the lack of recent progress on small molecule modulators for TRPC7 has diminished the need for further review.

TRPC: SUBUNIT COMPOSITION, STRUCTURE, AND GATING

TRPC are the first group of cloned mammalian homologues of drosophila TRPC, and are part of the TRP superfamily of calcium permeable cation channels (37–39). TRPC are activated by a wide range of stimuli including intra- and extracellular messengers, chemical, mechanical, and osmotic stress (40, 41). TRPC are calcium permeable cation channels but with complex rectifications in their I-V relationship. All homomeric TRPC show a double rectification in most studies in artificial expression systems. TRPC exhibit enhanced activity up to approximately -50mV holding potential and drastically reduced activity between 0-40 mV positive holding potentials. Heteromeric channels formed by TRPC1, and other TRPC family members showed a simpler I-V relationship. The rectification at the positive potential is lost whereas the rectification at the negative holding potential becomes more pronounced. This I-V relationship closely resembles the calcium-activated non-selective cationic current in hippocampal pyramidal neurons and other neurons (42, 43), which has been postulated to be involved in epileptiform discharges (44–46).

The subunit composition of native TRPC in various tissues and cell types is an issue that is critical for the understanding of TRPC functions but remains unsettled. The tissue expression pattern of each TRPC family member is unique. TRPC1 is ubiquitously expressed in all cell types and tissues (47–51). TRPC2 is a pseudogene in humans but critically involved in the olfactory function in rodents (52). For the rest of TRPC family members, there are broad overlapping low to moderate expressions in many tissues and unique high expression in certain cell types. In the central nervous system, TRPC3 is highly expressed in cerebellar Purkinje cells (49, 50, 53). TRPC4 is highly expressed in the lateral septal neurons and CA1 pyramidal neurons (54–56). TRPC5 is highly expressed in CA3 pyramidal neurons and amygdala neurons (57–60). TRPC6 is highly expressed in dentate granule cells (61, 62). TRPC7 is moderately expressed in cerebellum and hippocampus (63). The distinct patterns of expression for each TRPC argue for the existence of functional homomeric receptors in at least some cell types in the brain. Since mRNAs for several TRPCs can often be detected in a single cell type, it is likely that heteromeric TRPC receptors exist *in vivo*. However, it is difficult to distinguish heteromeric TRPC from homomeric TRPC in native tissues and assign functional roles to them. The first reason is the uncertainty about all possible permutations of functional heteromeric TRPC. Although it is generally believed that TRPC1 forms heteromeric channels with closely related TRPC4 and TRPC5, Storch and colleagues reported that TRPC1 formed functional heteromeric channels with all other members of the TRPC family (64). Another case of heteromeric TRPC formed by members from different subfamily is the TRPC3/4 heteromeric channels in porcine aortic endothelial cells (21). The second reason is the technical limitations of the current approaches used to demonstrate the existence of heteromeric receptors in native cells or tissues (65). There is an urgent need for innovative tools that can be used in native tissues.

Structurally, all TRPC resemble voltage-gated ion channels. They are all tetrameric, i.e., each functional channel is composed of four subunits. Each subunit has six transmembrane domains and one pore loop, flanked by an intracellular N-terminal domain and an intracellular C-terminal domain (Figure 1). Using cryo-EM approach, David Julius' group resolved the structure

of TRPV1 (66, 67). This technical breakthrough opened a flood gate, and the same approach have been used to resolve structures for many ion channels, including homomeric TRPC3, 4, 5 and 6 (25–35). The overall structures of these TRPC are very similar, showing a series of conserved domains. Embedded in the membrane is the core of the ion channel which includes the pore domain (i.e., the ion conducting pathway) and a voltage sensing-like domain (VSLD). The pore domain is formed by the re-entrant pore loop and TM5 and TM6 from each subunit. The VSLD is formed by TM1-TM4 and interacts with the pore domain. An elbow-like structural component is embedded in the lipid bilayer and makes hydrophobic contacts with the intracellular half of TM1. The ion conducting pathway consists of a selectivity filter formed by pore loop helixes near the extracellular side and a gate formed by distal TM6 near the intracellular side. All TRPC also have a large cytosolic domain, which is assembled through interactions between the ankyrin repeat domain at the N-terminus and the rib helix and coiled-coil at the C-terminus. Adjacent to TM6, the highly conserved TRP domain is a α-helix running parallel to the rib helix, and both are considered to be involved in the gating of TRPC.

These structures have provided some insights into the gating of TRPC. Three conserved binding sites for small molecule modulators or endogenous ligands have been identified (27, 33–35). The first site is the *lipid binding site* in the pore domain, formed by the re-entrant loop and TM5 of one subunit with the TM6 of the adjacent subunit (red star in Figure 1). It is accessible from extracellular side. Diacylglycerol (DAG), an endogenous agonist of TRPC, binds to this site. Small molecule modulators of TRPC4/5 (HC-070, pico145), and a small molecule

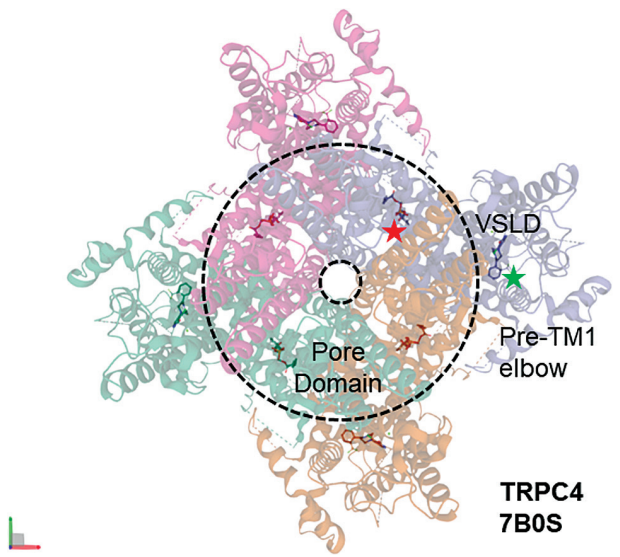

Figure 1. Cryo-EM Structure of TRPC4 (PDB: 7B0S). A top view is shown. Note the lipid binding site (red star) in the pore domain between each subunit, and the modulatory site (green star) in the VSLD domain occupied by GFB-8438

agonist of TRPC6 (AM-0883), also bind to this site. The second modulatory site is located in the VSLD of each subunit (green star in Figure1) and is accessible from the intracellular side. Small molecule modulators of TRPC4/5 (clemizole, GFB8438, GFB8749, and GFB9289) and a small molecule inhibitor of TRPC6 (AM1473) bind to this site. The third site is located between the pore domain and the VSLD, and is formed by TM3, TM4, TM4-TM5 linker of one subunit and TM5 and TM6 of the adjacent subunit. In human TRPC6, this site is either occupied by BTDM or a phospholipid (33). Although no small molecule modulators are known to occupy this site for other TRPC, point mutations of the TM4-TM5 linker in TRPC4/5 result in constitutively active channels (68), indicating a critical role of this region in gating. In addition to these small molecule modulator sites, there are two conserved cation binding sites (one in the VSLD for calcium and another one in the cytoplasmic domain for zinc), and the calmodulin/IP3-receptor binding (CIRB) site in the cytoplasmic domain. The calcium binding site is formed by 4 negatively charged or polar residues in the TM2 and TM3, and the zinc binding site is formed by 4 histidine and cysteine residues adjacent to the LH1 helix. The CIRB site is located at the proximal end of the rib helix and adjacent linker (27). The exact roles of these sites in gating need to be further investigated.

TRPC4 and TPRC5

TRPC4 and TRPC5 belong to the TRPC1/4/5 subgroup, and are thought to be activated by G-protein coupled receptors via phospholipase C signaling pathway (69). In artificial expression systems, TRPC4 and TRPC5 can form homomeric receptors and the channel properties are remarkably similar (68, 70–72). TRPC1 cannot form functional channel alone in artificial expression systems, and behaves more like a modulator when it forms heteromeric channels with TRPC4 or TRPC5 (64, 73–75). One notable property of the heteromeric TRPC1/4 or TRPC1/5 is the lack of double rectification normally seen for homomeric TRPC (57, 68, 74). However, the I-V relationship of recombinant heteromeric TRPC1/4 or TRPC1/5 appear to be somewhat variable. Some laboratories observed a very renowned negative slope region between -80 to -40 mV membrane potential (57, 76), whereas others showed only a marginal non-linearity (74, 77).

The subunit composition of native TRPC comprised by TRPC1/4/5 subgroup have been investigated with a panel of TRPC1, 4, 5 single knockout, TRPC1/4, TRPC1/5 double knockout and TRPC1/4/5 triple knockout mice. The evidence for the existence of native TRPC1/4 heteromeric channels is clear and convincing (54, 78, 79). In lateral septal neurons where the TRPC4 expression level is very high, activation of group I mGluRs elicits a prolonged epileptiform burst firing with an underlying plateau potential (80–82). This plateau potential was thought to be mediated by a calcium-activated non-selective conductance and has been confirmed later as largely mediated by heteromeric TRPC1/4. This mGluR agonist-induced response can be abolished by either knockout TRPC1 in mice (54) or TRPC4 in mice (79) and rat (54). This is in clear contrast to the comparison of TRPC1 and TRPC5 KO in the hippocampus (78), where Schafer-collateral-CA1 LTP is reduced by genetic ablation of TRPC5, but not reduced by genetic ablation of TRPC1. Thus, TRPC involved in CA1 LTP is likely homomeric TRPC5, not heteromeric TRPC1/5. The I/V relationship of heteromeric TRPC1/4 in lateral septal neurons shows a pronounced negative slope region (54, 83, 84), similar to

heteromeric TRPC1/4 or TRPC1/5 in artificial expression systems. If one infers from the existence of a negative slope region in mGluR1/5-induced current, heteromeric TRPC1/5 could be abundant in CA3 pyramidal neurons. Heteromeric channels comprised of all three members of the TRPC1/4/5 subgroup may also exist in some neurons (85). There are also evidence for the existence of homomeric TRPC4 or TRPC5 (78). The unique C-terminal PDZ domain in TRPC4 or TRPC5 suggests that homomeric TRPC4 or TRPC5 may be localized into synapses and modulate synaptic plasticity.

Since the initial report of the activation of TRPC1 by metabotropic glutamate receptor 1 (mGluR1) (86), TRPC1/4/5 subgroup has always been linked with mGluR signaling and often assigned a role in the generation of epileptiform discharges (42, 43, 54, 78). These studies suggest that selective blockers of TRPC1/4/5 may have high therapeutic potentials as antiepileptic drugs (87, 88). ML204 emerged as the first selective blocker of TRPC4/5 (89). However, it is a poor candidate for antiepileptic drug because it failed to effectively block the plateau potential mediated by TRPC1/4 in lateral septal neurons (79). Its therapeutic potential has also been hampered by poor pharmacokinetics. A new generation of TRPC1/4/5 small molecule modulators began to emerge in 2015 when (-)-Englerin A was identified as a TRPC4/5 agonist (90, 91). A few years later, Pico-145 was identified as a highly potent inhibitor of TRPC1/4/5 (77). More importantly, pico-145 is effective against heteromeric TRPC1/4 and TRPC1/5. AM-237, which activates homomeric TRPC5 but inhibit homomeric TRPC4 and heteromeric TRPC1/4 and TRPC1/5 (92), is another intriguing compound for in vivo testing. These new tools (23, 92) provided a golden opportunity to evaluate the therapeutic potential of small molecule modulators of TRPC1/4/5 as antiepileptic drugs.

A future challenge is to find small molecule modulators that can differentiate TRPC4 and TRPC5. Despite the initial claims (93), all current TRPC4/5 inhibitors blocks both TRPC4 and TRPC5 with similar potency (Personal communication, R.Bon). The lipid binding site in the pore domain could be further exploited as the presence of gadolinium cation Gd^{3+} could turn pico-125 from an inhibitor to activator of TRPC4 (77). The zinc binding site and CIRB site in the more variable cytosolic domain may also be promising for developing drugs that can differentiate TRPC4 and TRPC5.

Another challenge is to determine whether homomeric TRPC4 and TRPC5 are pharmacological and functionally distinct from the heteromeric TRPC1/4 and TRPC1/5. This is a critical question with implications for future development of antiepileptic drugs. The poor efficacy of ML204 for TRPC1/4 suggest that homomeric TRPC4 and heteromeric TRPC1/4 are pharmacologically distinct. Assuming they are also functionally distinct, a selective inhibitor for TRPC1/4 may be a better antiepileptic drug than pico-145, which blocks both homomeric TRPC4 and heteromeric TRPC1/4.

TRPC3

TRPC3 is the most prominent member of the TRPC3/6/7 subgroup and has been implicated in CNS (94–96) and cardiovascular diseases (97). TRPC3 is expressed widely at moderate levels in the brain and is a downstream effector of brain-derived neurotrophic factor (BDNF) signaling pathway (98–100). Since BDNF signaling is

critical for epileptogenesis (101–103), the involvement in BDNF signaling makes TRCP3 a promising target for the development of antiepileptic drugs.

Pyr3 is the first identified TRPC3-prefering inhibitor (104). Using Pyr3 and TRPC3 global knockout mice, it has been shown that TRPC3 are directly involved in the generation and propagation of pilocarpine-induced *status epilepticus* (SE) (105). The seizure severity was reduced both by genetic ablation of TRPC3 and by intraperitoneal administration of Pyr3. This reduction is due to a specific reduction of the theta activity induced by pilocarpine. However, SE induced neuronal cell death is not significantly reduced either by genetic ablation of TRPC3 or by Pyr3. Pyr3 has been reported to reduce SE-induced neuronal cell death in rats (106). The reason for the different effects of Pyr3 on neuronal cell death in rodents remains unclear.

TRPC3 expressed in vasculatures are also involved in epilepsy. SE upregulate TRPC3 expression in cerebrovascular endothelial cells and intraventricular infusion of Pyr3 reduces SE-induced edema and neuronal cell death (107). A follow-up study from the same group showed the involvement of ETB receptors and PI-3K in these pathological processes (108). TRPC3 expressed in smooth muscle cells also contribute to the pilocarpine-induced SE (109). SMC-specific and inducible TRPC3 knockout shortened the duration of pilocarpine-induced SE, due to the elimination of a secondary phase caused by SE-induced inverse hemodynamic response (109). This surprise finding suggests that targeting vascular TRPC3 may be a viable novel strategy to develop antiepileptic drugs.

Although Pyr3 is relatively selective for TRPC3, it suffers from instability and cellular toxicity in vivo (104, 110). A better TRPC3 inhibitor with reduced toxicity and improved stability has been developed (111). This compound needs to be tested to determine whether TRPC3 is a viable molecular target for future developments of antiepileptic drugs.

TRPC6

In the brain, TRPC6 is highly expressed in dentate granule cells in the hippocampus. Dentate granule cells (DGCs) receive excitatory input from entorhinal cortex via the perforant pathway and they send out mossy fibers that innervate CA3 pyramidal cells (112). Mossy fibers also innervate excitatory mossy cells, which in turn innervate GABAergic 'basket' interneurons in the hilar region to reduce granule cell excitability (113–117). One of the early signs of temporal lobe epilepsy is the loss of normal paired-pulse inhibition and granule cell hyper-excitability, which is caused by the loss of mossy cells (116, 118). The unique high expression pattern of TRPC6 in dentate granule cells naturally prompted heightened interests in investigating whether TRPC6 played a role in epileptogenesis.

An initial report described a decrease of TRPC6 in DGCs after pilocarpine-induced SE in rats (106). Intraventricular infusion of a TRPC6 agonist, hyperforin (119), prevented the down regulation of TRPC6 expression and reduced SE-induced neuronal cell death in the hilar, CA3 and CA1 regions (106). Subsequent study from the same group showed that knockdown of TRPC6 using siRNA increased seizure susceptibility (120). A more notable finding was that TRPC6 knockdown made the normally resistant DGCs susceptible to SE-induced excitotoxic cell death, but reduced SE-induced cell death in downstream CA3 and CA1 region (120). So,

both activation and inhibition of TRPC6 activity in rats reduced the SE-induced hippocampal neuronal cell death, which appear to be contradictory. Brain samples from temporal lobe epilepsy (TLE) patients and pilocarpine-treated mice showed opposite results, and the TRPC6 expression in both human cortex and mouse hippocampus were increased (95). TRPC6 KO mice showed no detectable changes either in seizure susceptibility or SE-induced neuronal cell death in any region of the hippocampus (Unpublished data. F. Zheng). Thus, the precise roles of TRPC6 played in epileptogenesis remain uncertain.

Despite these somewhat inconsistent results, the recent advances in small molecule moderators have provided an opportunity to revisit the role of TRPC6 in epilepsy. There are two pressing questions that need to be answered: (i) does a selective TRPC6 inhibitor reduce SE-induced neuronal cell death in the hilar, CA3 and CA1 region? and (ii) Does a selective activator of TRPC6 reduce or exacerbate seizure susceptibility? TRPC6 belong to the subgroup of TRPC3/6/7 which are directly activated by DAG and highly permeable to calcium ion (62, 121). The previous TRPC6 knockdown data appears to be more consistent with what are known about the TRPC6 function than the previous results with hyperforin. It is likely a highly selective TRPC6 inhibitor will be protective against SE-induced neuronal cell death and will have therapeutic potential for epilepsy. On the other hand, a selective activator of TRPC6 may increase excitability of DGCs. The hyper-excitability of DGCs will likely propagate along the tri-synaptic pathway and lead to increased susceptibility to seizures.

CONCLUSION

Overall, there are good reasons to be optimistic regarding the prospect of new therapeutic agents emerging from small molecule modulators of TRPC, and epilepsy should be among the primary diseases targeted for drug development. Current literature suggests that heteromeric TRPC1/4 and TRPC1/5 may be highly promising targets for developing new antiepileptic drugs. A more provocative idea is to target TRPC3 in cerebral vasculature as a treatment option for epilepsy. The detailed understanding of the structure of these TRPC will help to accelerate the development of small molecule modulators for them. A major obstacle for targeting TRPC to develop novel therapy for epilepsy is the limited understanding of subunit composition and function of native TRPC. Current approaches are not adequate and new tools are needed.

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