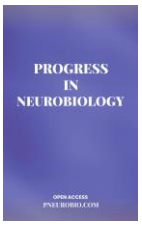


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**Review Article**

# Targeting AKAP79/150 in Human Disorders: An Emerging Opportunity for Future Therapies?

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ABSTRACT

A-kinase anchoring protein 79/150 (AKAP79/150) is an important scaffolding protein, which anchors various important proteins to locate in appropriate synaptic domains to regulate excitatory synaptic intensity. With sweeping advances in the biology of AKAP79/150 and its critical role in the pathophysiology of various human disorders, more and more evidence is breeding new opportunities for potential therapeutic intervention in an attempt to improve the clinical outcomes of those patients. Herein, we review the basic structure and main functions of AKAP79/150, focusing on the pathophysiological mechanisms of AKAP79/150 in different human disorders, with a particular emphasis on the inflammatory pain, epilepsy, and depression, to discuss their potential therapeutic intervention value in patients with those diseases.



## 1. Introduction

AKAP79 is a prototypic A-kinase-anchoring protein (AKAP), with three orthologs (comprising human AKAP79, rodent AKAP150, and bovine AKAP75, gene name *AKAP5*), which fulfills key physiological roles. As signal-organizing molecules, AKAPs tether those noncatalytic regulatory proteins, which profoundly influence the action of protein kinases and phosphatases, in subcellular environments to control the phosphorylation state of neighboring substrates [1].

AKAP79/150 directs its cohort of anchored enzymes toward selected transmembrane proteins to facilitate their efficient regulation [1]. For example, AKAP79/150 connects with N-methyl-D-aspartate receptors (NMDARs) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) through two membrane-associated guanylate kinase (MAGUK) family proteins synapse-associated protein 97 (SAP97) and post synaptic density protein 95 (PSD-95), and also recruits protein kinase A (PKA), protein kinase C (PKC), and calcineurin (CaN) in appropriate synaptic domains to regulate excitatory synaptic strength [2-9].

AKAP79/150 also coordinates signal transduction at different subcellular locations and participate in regulating normal physiological functions of cells [10]. AKAP79/150 organizes $Ca^{2+}$/calmodulin-dependent protein phosphatase (PP2B, also known as CaN), calmodulin, cAMP-dependent PKA, PKC, and the transcription factor nuclear factor of activated T cells (NFAT) into a membrane-delimited signalosome at the plasma membrane [11-13]. Upon $Ca^{2+}$ store depletion, the stromal-interactingmolecule-1 protein on the plasma membrane targets Orai1 to AKAP79 signaling complex, which interacts with the AKAR on the N-terminus of the Orai1 $Ca^{2+}$ channel [14-16]. The $Ca^{2+}$ spikes can transmit signals from the distal dendrite to the nucleus by stimulating CaN to dephosphorylation and activating NFAT [12, 17-23]. The neuronal activity regulated by M current induces NFAT-mediated transcriptional up-regulation of KCNQ channels and inhibits neuronal excitability. This

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signal pathway limits neuronal hyperexcitation through negative-feedback, which is the basis of myriad diseases such as chronic pains, epilepsy and cardiovascular dysfunction [24].

Accumulating evidence suggests that aberrant expression of AKAP79/150 contributes to the pathophysiological mechanisms of various human disorders. Both chronic restraint stress and unpredictable chronic mild stress can increase the expression level of AKAP150 protein in the basolateral amygdala of depressive mice and induce its redistribution into the synapses. Moreover, studies have also shown that the expression of AKAP150 in dorsal root ganglia neurons of inflammatory pain mice is significantly increased, and the pain response is reduced in *Akap5* knockout mice [25]. In addition, the palmitoylation of AKAP150 is significantly increased in the hippocampus of epileptic mice [26], and inhibition of palmitoylation of AKAP79/150 is helpful to the anticonvulsive effect of valproic acid, a seizure treatment drug [27].

In this review, we present an overview on the physiological roles of AKAP79/150 in the brain and deregulations of AKAP79/150 expression and its substrates in various disorders, like inflammatory pain, epilepsy, and depression, providing a new entry point for the diagnosis and treatment intervention for these disorders.

## 2. Biological Characteristics of AKAP79/150

### 2.1. Overview of AKAPs

AKAPs belong to a family of scaffolding proteins, which anchor PKA and other important proteins, including protein kinase, protein phosphatase, phosphodiesterase, G protein coupled receptors (GPCRs) [10, 28]. AKAPs are also a group of functionally related regulatory proteins with different structures, which play an important role in ensuring the accuracy of intracellular PKA-dependent signaling pathways and coordinating the precision of signal transduction at different subcellular [29]. Therefore, AKAPs are not only widely involved in the regulation of normal physiological functions of cells, but also play a vital role in various human diseases [10].

Indeed, more than 70 different AKAPs have been isolated and identified so far [10]. AKAPs can form multi-protein complexes in different subcellular regions that integrate the cyclic adenosine monophosphate (cAMP) signaling with pathways. Evidence suggests that AKAP can recognize and specifically anchor activated GPCR. Subsequently, other proteins anchored to AKAP are sequentially activated to generate, utilize, degrade, and regulate the synthesis of cAMP [30]. In addition, cAMP activation of PKA anchoring to AKAPs is crucial for regulating human dendritic cells lipid rafts antigen presentation [31, 32]. AKAPs signaling complexes have been identified as crucial regulators of a variety of glutamate receptors and ion channels [8, 33, 34]. In the past decades, as a member of the AKAPs, many studies have focused on the distribution and function of AKAP79/150 in the brain [8, 35, 36].

### 2.2. Structure of AKAP79/150

AKAP79/150 is a prominent synapse-targeted AKAP, which is mainly expressed in the central nervous system and play an important role in signal transmission and synaptic plasticity [37]. AKAP150 is anchored by binding the hydrophobic surface of an amphiphilic helical molecule in its molecule to the N-terminal of the PKA regulatory subunit dimer (RII) [38]. Furthermore, in addition to targeting PKA, AKAP150 also has binding sites with other signal molecules, such as PKC, PP2B, some membrane receptors, and ion channels, so that different signal pathways can interact with each other, which is conducive to the integration and transmission of specific information in cells [39, 40].

AKAP79/150 contains a unique targeting sequence near the N-terminal, also known as the targeting domain. In this domain, AKAP79/150 has three different basic targeting sub-domains (A, B, and C domains) (Figure 1). Three membrane-bound basic regions can bind with phosphatidylinositol 4,5-bisphosphate (PIP2) and target specific subcellular regions, making PKA very close to its specific substrate molecules, and the catalytic reaction can be carried out efficiently [40, 41]. AKAP79/150 binds to PKC through the A sub-domain of the basic N-terminal targeting domain [42], but binds to a variety of adenylyl cyclases (ACs) isomers through the B sub-domain of the targeted domain [43, 44].

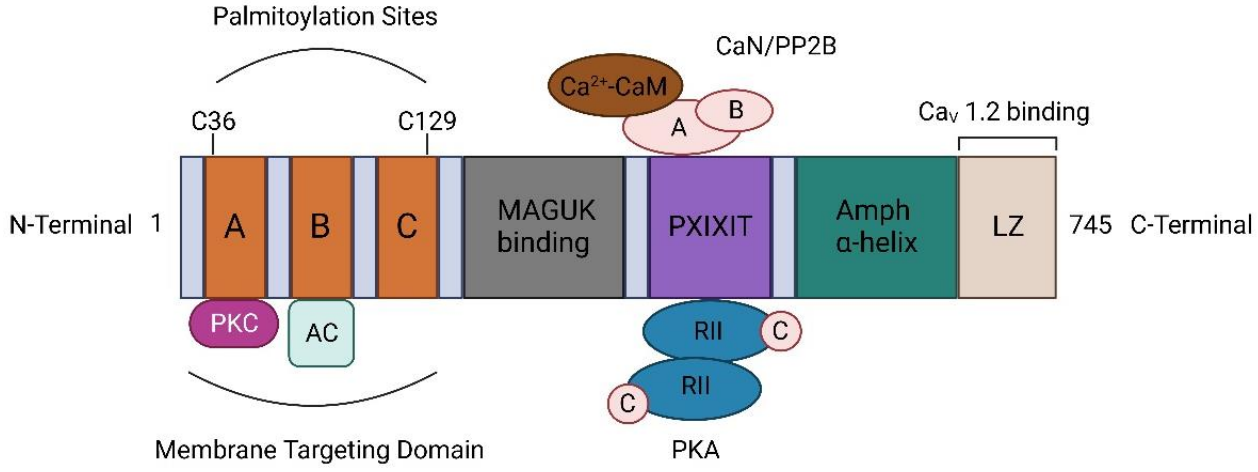


**FIGURE 1:** Domain organization of the AKAP79/150 Scaffolding protein. Amino acid numbering is given for rodent AKAP150 from 1 at the N-terminal to 745 at the C-terminal. The locations of the diverse binding sites and the indicated binding partners are shown. See the text for more details.

AKAP79 anchors CaN through the 'PxIxIT' type docking motif near the C-terminal [41, 45, 46]. Between the targeting domain and the CaN anchoring domain, AKAP150 has an internal structure that binds to MAGUK. In addition, through the PDZ (an initialism combining the first letters of the first three proteins discovered to share the domain-PSD-95, Drosophila disc large tumor suppressor (DLG1), and Zonula occludens-1 protein (ZO-1)) domains in MAGUKs, AKAP150 is connected to the NMDARs and the C-terminal of AMPARs [47-50].

### 2.3. Function of AKAP79/150

AKAP79/150 can combine with GPCR superfamily members β2-adrenergic receptor [51, 52], orchestrating the interaction of F-actin [53], PIP2 [41], MAGUKs [48], cadherin cell adhesion molecule [54, 55], ACs [43, 56, 57], protein kinase [1], and protein phosphatase [58], and regulating active-dependent synaptic transmission by connecting with AMPA receptors [48], heat-activated transient receptor potential family V type 1 (TRPV1, also known as the capsaicin receptor) channels [59], L-type calcium ($Ca_V$) channels [60], M-type potassium (KCNQ, Kv7) channels [61], and acid sensing ion channels [62] in PSD. PSD scaffolding proteins are an important structural basis of synaptic transmission and play an important supporting role in the integration of multiple receptors and signal molecules [63]. A variety of protein kinases and protein phosphatases, including PKA, PKC, and CaN, are integrated into the PSD region via AKAP150 and play an important regulatory role in the dendritic spine stability [49].

cAMP-dependent PKA is a tetrameric molecule consisting of a tetramer that contains a regulatory (R) subunit dimer, which include four different phenotypes of RIα, RIβ, RIIα and RIIβ [64-68], and two catalytic (C) subunits [69]. When the body is stimulated by the outside world, it will trigger a signal cascade reaction and activate the cAMP signaling pathway. The activated cAMP is combined with the R subunit of PKA, causing the C subunit to be released from PKA and activated. The activated catalytic subunit plays a role in signal transduction. PKA-mediated signaling pathways play an important role in the function of many neurons and the formation of learning and memory, and are also involved in various forms of synaptic plasticity [2, 70].

The PKC family of phospholipid-dependent serine/threonine kinase consists of different isozymes (PKC$\alpha$, PKC$\beta I$, PKC$\beta II$, PKC$\gamma$, PKC$\delta$, PKC$\varepsilon$, PKC$\eta$, PKC$\theta$, PKC$\zeta$, and PKC$\iota/\lambda$) [71, 72], all of which have a R domain that can bind to PKC activators and a C domain, and variable regions [72]. The function of PKC is to phosphorylate other proteins by interacting with them to participate in synaptic plasticity [73, 74]. PKC also modulates the targeting of the NR1 subunit of NMDAR to the postsynaptic membrane [75]. The serine/threonine phosphatase CaN holoenzyme is a heterodimeric protein, consisting of a C subunit A and a R subunit B [76, 77]. CaN is not only important for cardiac development, pathophysiology, and nervous system development [78], but also as a structural protein to control synaptic function and behavioral learning [79]. Interestingly, a recent study discover that CaN can directly suppress the activity of PKA when removing phosphate from substrates initiated by PKA, thereby avoiding the costly and persistent ineffective cycle of phosphorylation and dephosphorylation of PKA and CaN at these sites [80].

AKAP79/150 can regulate the phosphorylation and dephosphorylation of various ionotropic receptors by anchoring PKA, PKC, and CaN in the postsynaptic membrane [24, 39, 43, 81, 82], thereby affecting the activity and transport of ion channels. In the basal state, AKAP79/150 bound to a pool of largely inactive CaN in synapses. During NMDAR-dependent long-term depression (LTD), AKAP79/150 binds to PSD-95, causing the release of CaN, which helps to NMDAR-triggered an enhancement of synaptic AMPAR endocytosis [83, 84]. In addition, AKAP79/150-anchored PKA and CaN can control the recruitment or removal of $Ca^{2+}$-permeable AMPA-type glutamate receptors at hippocampus synapses by regulating GluA1 serine845 (S845) phosphorylation during long-term potentiation (LTP) / LTD, playing key antagonistic roles [83, 85-89].

Indeed, L-type $Ca^{2+}$ channels and AMPA/kainate receptors are modulated by KA [35, 90, 91], while NMDARs are phosphorylated by PKC [92, 93] and dephosphorylated by CaN [94-96]. PKA-mediated phosphorylation of GluA1 serine 845 (S845) has been shown to promote GluA1 cell-surface targeting and synaptic retention, increase channel open-probability, and facilitate the induction of LTP through AKAP5 [97-103], while dephosphorylation of GluA1 S845 is associated with endocytosis and LTD [98, 100, 102, 104-107]. CaMKII/PKC-mediated phosphorylation of GluA1 serine 831 (S831) increases channel conductance and regulates LTP [100, 104, 108-111]. Finally, PKC-mediated phosphorylation of GluA2 serine 880 (S880) disrupts the interaction between GluA2 and GRIP, allowing for AMPAR endocytosis and LTD [47, 112, 113].

### 2.4. Distribution of AKAP79/150

AKAP79/150 is widely distributed in the nervous system. In the peripheral nervous system, AKAP150 is mainly expressed in sensory neurons of dorsal root ganglion (DRG) [25, 114], and locates in the plasma membrane of the soma, axon initiation segment, and small fibers. Most of these neurons are nociceptive afferent C fibers and a small portion is Aδ-fibers [115]. In the central nervous system, AKAP5 is detected in an increasing number of tissues and cells. AKAP5 is widely distributed in the brain [116-122], heart [123], arterial smooth muscle [124, 125], pancreas [122], liver [116, 122], skeletal muscle [122], uterus [126], stomach [127], parotid [128, 129], diploid fibroblasts [130], amnion fibroblasts [131], T cells [132], red nucleus [133], Purkinje cells, olfactory bulb neurons, basal ganglia, and cortical actin cells [134]. Intriguingly, studies have found striking differences in AKAP150 between brain regions in mouse [135]. Among them, striatum and cerebral cortex had the highest expression levels, followed by hippocampus and olfactory bulb, while cerebellum, hypothalamus, and brain stem had low expression levels [135].

### 2.5. Post-Translational Modification of AKAP79/150

Before proteins become biologically active, they undergo a series of complex modification processes such as phosphorylation, glycosylation, ubiquitination, and lipidation. Protein palmitoylation is the most common and only reversible post-translational lipid modification, usually refers to the covalent binding of 16-carbon palmitic acid to the side chain of protein specific cysteine residues (Cys) via a labile thioester

bond, which is of great significance for protein trafficking, localization in cells and function [136-138].

Protein palmitoylation is achieved by palmitoyl transfer mediated by protein acyltransferase, and its activity is mainly mediated by the structure of DHHC (Asp-His-His-Cys) [139, 140]. These enzymes are distributed in different tissues, mainly located in Golgi apparatus, endoplasmic reticulum or plasma membrane [141]. Currently, 23 DHHC enzymes have been reported, which play an important role in neuronal development and synaptic plasticity [142].

Of note, ZDHHC2 is a member of the important DHHC family in neuroendocrine cells [143], which can mediate palmitoylation of PSD-95 and AKAP79/150, impacting synaptic targeting of AMPARs [144, 145]. Studies have shown that ZDHHC2 can catalyze the S-palmitoylation of two conserved cysteine residues (Cys36 and Cys129) within the A and C basic regions of AKAP79/150 [146]. Although this modification is not important for the localization of AKAP79/150 in the plasma membrane and the connection with F-actin, it is required for the localization of AKAP79/150 to the recycling endosomes, and is closely associated with its localization to cholesterol rich, anti-detergents lipid rafts [141, 147, 148]. Additionally, it is worth noting that PSD is an important structure for anti-detergents and therefore palmitoylation of many PSD proteins is closely related to their synaptic localization [50].

One recent study showed that the palmitoylation of AKAP79/150 modulates its postsynaptic nanoscale organization, trafficking, and mobility in hippocampal neurons [149]. In cultured hippocampal neurons, researchers have observed that the palmitoylation of AKAP79/150 is bidirectionally regulated by synaptic activity, thereby coordinating receptor exocytosis, synaptic spine morphological changes, GluA1 membrane surface expression and AMPAR synaptic activity closely related to LTP and LTD [50, 149]. The literature reported that CP-AMPARs containing GluA1 and lacking GluA2 play an important role in the formation of LTP. Palmitoylation of AKAP79/150 not only regulates synaptic transmission of CP-AMPARs under normal conditions, but also is critical for $Ca^{2+}$-permeable AMPA-type glutamate receptors -dependent LTP [26, 50, 150].

On the other hand, protein depalmitoylation is the process by which palmitic acid is removed from modified proteins and contributes. Similarly, protein depalmitoylation also serves as particularly crucial regulators of protein function in neurons. The research shows that CaMKII-mediated autonomous phosphorylation and depalmitoylation are required for the synaptic removal of AKAP79/150 accompanied by the shrinkage of the volume of dendritic spines after the induction of LTD [151, 152]. In addition, synaptic removal of AKAP79/150 can prevent PKA-mediated re-phosphorylation of AMPAR, promoting endocytosis of AMPAR, which weakens the strength of the synapse [151]. Of note, the fully phosphorylated AKAP79 mutant showed a significant decrease in palmitoylation levels compared with the partially phosphorylated mutations [151].

## 3. Potential Role of Akap79/150 in Human Disorders

So far, many studies have shown that the dysfunction of AKAP79/150 expression plays an important regulatory role in a variety of neural physiological activities, especially in some major neuropsychiatric diseases.

### 3.1. Inflammatory Pain

#### 3.1.1. Inflammatory Pain Overview

Inflammatory pain is a severe chronic pain that is caused by inflammation caused by trauma, bacterial and viral infections, and surgical procedures. Allodynia, hyperalgesia and sensitization are its main clinical manifestations [153]. Injury or inflammation leads to the release of inflammatory mediators such as bradykinin, prostaglandin $E_2$ ($PGE_2$), $_L$-glutamate and nerve growth factor (NGF), which activate "pain-" sensing neurons, increase nociceptor responsiveness and lower the threshold for pain [154-157].

Inflammatory pain not only severely affects the quality of life, but also increases the incidence of mental diseases [158]. Therefore, it is of great significance to further study its pathogenesis and develop corresponding analgesic drugs in clinical treatment. Of note, some important discoveries in this field in recent years are closely related to the AKAP79/150.

#### 3.1.2. Potential Mechanism of AKAP79/150 in Inflammatory Pain

The nociceptive transduction molecule TRPV1 is the best-studied TRP channel, which plays a crucial role in hyperalgesia [159]. Activation of PKA or PKCε by inflammatory mediators phosphorylates TRPV1 and increases the sensitivity of channel gating, depending not only on the ability of the associated these kinases to bind AKAP79/150, but also on the ability of AKAP79/150 to bind TRPV1 [59, 160].

Previous studies have demonstrated that AKAP150-anchored PKA and PKC control the phosphorylation and functional status of TRPV1 [161, 162], but the scaffolding protein is not involved in PP2B-driven channel desensitization [76]. Although both AKAP150 and the PKA regulatory subunit PKA RIIα are associated with TRPV1, the association between PKA and TRPV1 is mediated by AKAP150. Disruption of PKA binding to AKAP150 strongly attenuated the reduction of TRPV1 desensitization and hyperalgesia induced by $PGE_2$ [163].

Blocking binding or removing AKAP79/150 inhibits the sensitization of TRPV1 [59]. The siRNA against AKAP150 effectively blocked the NMDA-induced phosphorylation of S800 of TRPV1 in trigeminal ganglia [164]. In addition, phosphorylation of the S502 site on TRPV1 as the main mechanism by which AKAP79 mediates translocation of TRPV1 to the membrane [59]. A 14 aa domain, corresponding to residues 736–749 mediating AKAP79 binding was found in the C-terminal domain of TRPV1 [59]. In fact, critical residues within this binding site, namely D738, R740, C742, and V745 have been identified [165]. If binding is blocked, the sensitization effect was abrogated. 736–745-TAT (a membrane-permeable decoy peptide) attenuated the thermal hyperalgesia induced by Formalin was attenuated, as well as the mechanical hyperalgesia induced by Group I metabotropic glutamate receptors (mGluR1/5) agonist (DHPG) [165, 166]. In turn, amino acids 326–336 on AKAP79 responsible for its interaction with TRPV1. the

binding site of TRPV1 on AKAP79 a sequence of 11 aa, 326–336 in the C-terminal. The sensitization of TRPV1 by PKC and PKA in vitro and inflammatory hyperalgesia in vivo were reduced by using a peptide mimicking the 326–336 site on AKAP79 [167]. Thus, antagonizing the interaction between AKAP79 and TRPV1 may offer a promising analgesic strategy.

As mentioned earlier, $_{L}$-glutamate mediate hyperalgesia. mGlu1/5 couple activation of phospholipase C (PLC), resulting in release of AKAP150 from cell membrane of the $PIP_2$-rich region can associate with target substrate proteins, including TRPV1 [168]. There was a twofold increase in AKAP association with TRPV1 following DHPG treatment [169]. AKAP5 KO mice with inflammation did not facilitate DHPG-induced pain behavior and the proportion of S800-phosphorylated TRPV1 was significantly reduced in DRG neurons from AKAP5 KO mice after NGF treatment [25]. Moreover, a functional transcriptional link has been observed between serum response factor (SRF) and AKAP150. DHPG-stimulated upregulation of AKAP150 was blocked pretreated with SRF siRNA ([170].

AKAP150 trafficking and synaptic localization is modulated by palmitoylation [26]. A recent study showed that AKAP150 translocated from cytoplasmic to synaptic site after intraplantar injection of complete freund's adjuvant (CFA). The palmitoylation levels of AKAP150 were significantly increased, and mediated the accumulation and phosphorylation of GluA1. Inhibition of AKAP150 palmitoylation through intrathecal injection palmitoylation-deficient AKAP150 mutant vectors, AKAP150 (C36, 123S) or ZDHHC 2-siRNA or 2-bromopalmitate (2-BP) could relieved inflammatory pain [171].

Noxious thermal, mechanical, or chemical stimuli lead to depolarization of nociceptive sensory neurons, triggering a series of events such as calcium influx, $Ca^{2+}$/CaM–dependent activation of ACs, and intracellular cAMP production [172-174]. AKAP79/150-anchored AC is vital for the sensitization of TRPV1 to cAMP/PKA-dependent regulation [175]. Furthermore, AC5/6 interaction with AKAP150 is necessary for persistent nociceptor spontaneous activity [114]. Genetic deletion of AC1 prevented the translocation of AKAP79/150 and PKA, as well as upregulation of synaptic GluA1-containing AMPARs in the insular cortex after nerve injury [176].

AKAP79/150 anchoring of kinases and phosphatase control ion channels response to activation signals [177]. There are 63.0%, 57.6%, and 11.8% of APAP150-positive neurons were co-expressed with $Ca_V1.2$, voltage gated sodium channel, and Kv1.2 in rat DRG neurons, respectively. Studies in small nociceptive DRG neurons demonstrated that AKAP150 interacts with TRPV1 and $Ca_V1.2$ in the soma and axon initial segment [115]. Depolarization of sensory neurons rapidly activates PKA type II (PKA-II) in nociceptors by $Ca^{2+}$ influx through $Ca_V1.2$ channels [178]. BAPTA-AM-driven chelation of intracellular $Ca^{2+}$ not only increased PKA-mediated sensitization of TRPV1, but also increase the association of AKAP150 with TRPV1 [179]. CaM serves as a part of a calcium-sensitive complex was able to bind to C terminus 35-aa segment of TRPV1 and effectively prohibits AKAP150 from associating with TRPV1 [179, 180]. Another low voltage-gated (T-type) $Ca^{2+}$ channels isoform, $Ca_V3.2$ was found to be able to immunoprecipitated with AKAP150. The increased phosphorylation of Ser/Thr residues in $Ca_V3.2$ induced by dibutyryl cAMP can be reversed by AKAP St-Ht31 inhibitory peptide ([181].

Like TRPV1, TRPV4 was shown an interaction with AKAP79 by co-immunoprecipitation in small nociceptive sensory neurons [59]. Previous study has demonstrated that AKAP79 plays a critical role in tethering PKA and PKC to TRPV4 to modulate its gating [182]. Modulating TRPV4 function using peptide antagonists targeting the interaction between TRPV4 and AKAP79 is considered to be an effective therapeutic strategy [183].

AKAP150 is also involved in chemotherapy-induced neuropathic pain (CINP). Knocked down AKAP150 by intrathecal injection of AKAP150 siRNA or AAV5-Cre-GFP virus significantly alleviated paclitaxel-induced hypersensitivity, and partially restored CaN phosphatase activity and IL-4 expression [184]. In addition, AKAP150 mediates the sensitization of transient receptor potential anchor protein 1 (TRPA1) regulated carboplatin-induced mechanical allodynia and cold hyperalgesia [185]. These findings indicate that AKAP150 plays an important role in the neuropathic pain (Figure 2).

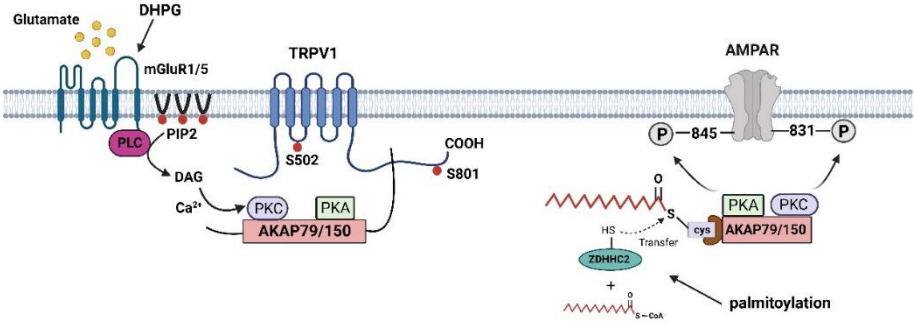


**FIGURE 2:** Schematic diagram of the role of AKAP79/150 in inflammatory pain. Under inflammatory conditions, endogenous glutamate is released, promoting the stimulation of mGluR1/5 by DHPG. TRPV1-mediated inward current via the PLC-DAG pathway to directly excite the nociceptive neurons, and PIP2 is degraded, leading to the release of AKAP79/150 from the plasma membrane anchor site and subsequent binding to TRPV1, increasing the sensitization of AKAP79/150 anchored PKA and PKC to TRPV1 and in *vivo* inflammatory hyperalgesia. On the other hand, Inflammatory pain increases the mediated palmitoylation levels of AKAP150 mediated by ZDHHC2, which maintains the synaptic location of AKAP150 and induces pain in mice. With the redistribution of AKAP150, the phosphorylation of GluA1 at serine 845 mediated by AKAP150-PKA and GluA1 at serine 831 mediated by AKAP150-PKC raises.

### 3.2. Epilepsy

#### 3.2.1. Epilepsy Overview

Epilepsy is a common chronic neurological disease characterized by epilepsy, which is caused by overexcitation and synchronous abnormal discharge of brain neurons. The formation of neuronal network is closely related to synaptic transmission. When the synaptic transmission function is abnormal, the equilibrium between excitation and inhibition of the neural network is destroyed, which induces abnormal firing of neurons and finally leads to seizures [186]. Despite more than 40 kinds of antiseizure drugs have been used in clinic in recent years, about one-third of patients are still unable to effectively control epileptic seizures [187].

The etiology of epilepsy is complex and diverse, involving structural, genetic, metabolic, infectious, or immune factors [188]. The abnormal firing of neurons is found to be closely related to dysfunction of the mitochondrion and abnormalities of neurotransmitters and ion channels [189-191]. When neurons in the brain discharge abnormally, motor, sensory, cognitive, psychic and autonomic nervous functions will be impaired [192]. Intriguingly, studies have found that AKAP79/150 may play an important role in the onset and development of epilepsy.

#### 3.2.2. Potential Mechanisms of AKAP79/150 in the Development of Epilepsy

It was previously shown that AKAP150 knockout mice show learning disabilities and are resistant to seizure after peritoneal injection of pilocarpine (300 mg/kg) [193]. In particular, kainic acid (KA)-induced seizures have been demonstrated to increase palmitoylation of AKAP150, thereby promoting movement to postsynaptic lipid rafts [26]. Hence, AKAP150 may have a significant role in the pathogenesis of epilepsy.

On the one hand, the KCNQ2/3 mutation, which leads to a mild decrease of M-channel activity, is associated with the onset of benign neonatal epilepsy. These mutations can reduce the excessive excitability responsible for epileptic seizures [194]. The palmitoylation of AKAP79/150 has been proved to be critical to its mediated regulation of KCNQ2 both *in vivo* and *in vitro* experiments, and M-current suppression is involved in the pathophysiology of seizures [27]. Seizures activate Gq-coupled receptors, and Kv7.2 subunit is phosphorylated by AKAP79/150-anchored PKC. Phosphorylated Kv7.2 subunits release calmodulin (CaM), thereby reducing the binding of PIP2 to Kv7.2 subunit. Suppressed M-current reduces channel functionality, ultimately leading to neuronal hyperexcitability [193, 195-199]. Due to the palmitoylation modification of AKAP79/150 being necessary for phosphorylation of Kv7.2 subunit by AKAP79/150-anchored PKC, the anticonvulsant effect of valproic acid is achieved by interfering with the palmitoylation of AKAP79/150 to prevent the M-current from suppressive neurotransmitters during seizures, thereby preventing the progression of seizures [27, 199].

On the other hand, AKAP79/150 regulates the transcriptional expression of KCNQ2/3 by coordinating L-type voltage-gated $Ca^{2+}$ channels to limit the overexcitation of the nervous system [24]. After induction of seizures by pilocarpine and KA, the opening of $Ca_V1.3$ channels produces an elevated local $Ca^{2+}{}_i$ signals, activating AKAP79/150-anchored CaN associated with $Ca_V1.3$ channels. NFAT is then dephosphorylated and activated by $Ca^{2+}$-CaM/CaN, causing NFAT to translocate from the cytoplasm to the nucleus, acting on the KCNQ2/3 gene regulatory elements and upregulating M-current. The increased expression of KCNQ2/3 channels serves as a negative-feedback loop to suppresses the increase in neuronal excitability [24,200].

The above findings suggest a crucial role of AKAP79/150 and its palmitoylation in the pathophysiology of epilepsy (Figure 3). However, extensive research is needed to clarify the potential molecular mechanisms of AKAP79/150 in the development of epilepsy.

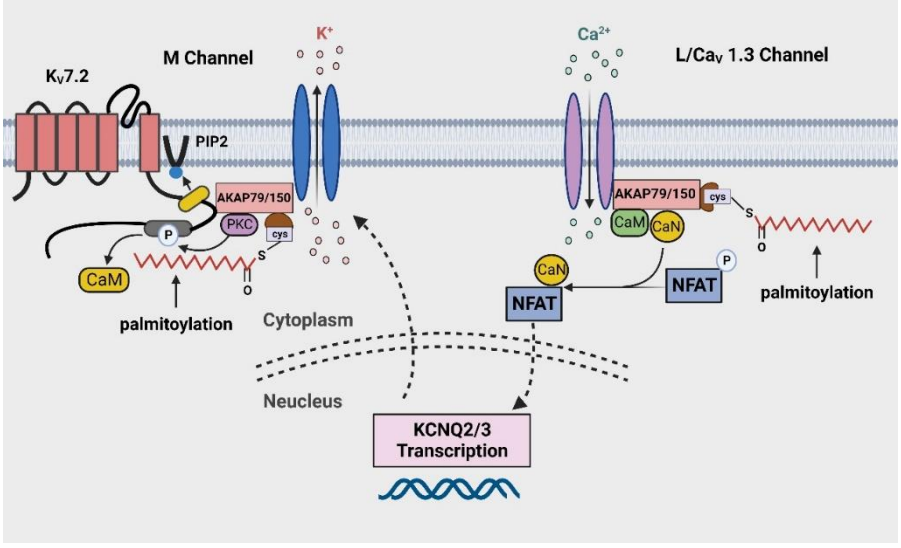


**FIGURE 3:** Potential mechanism of AKAP79/150 in epilepsy. After seizures, the opening of L/$Ca_V1.3$ channels produces an elevated local $Ca^{2+}{}_i$ signals, activating AKAP79/150-anchored CaN associated with L-type ($Ca_V1.3$) $Ca^{2+}$ channels. NFAT is then dephosphorylated and activated by $Ca^{2+}$-CaM/CaN, causing NFAT to translocate from the cytoplasm to the nucleus, acting on the KCNQ2/3 gene regulatory elements and upregulating M-current. On the other hand, seizures activate Gq-coupled receptors, and Kv7.2 subunit is phosphorylated by AKAP79/150-anchored PKC, which is mediated by palmitoylation

of AKAP79/150. Phosphorylated Kv7.2 subunits release CaM, thereby reducing the binding of PIP2 to Kv7.2 subunit. Suppressed M-current reduces channel functionality, ultimately leading to neuronal hyperexcitability.

### 3.3. Depression

#### 3.3.1. Depression Overview

Depression is a common mental disorder characterized by persistent low mood, intellectual disability, cognitive impairment, volitional decline, and impaired social function, affecting more than 300 million worldwide [201, 202]. The etiological hypotheses of depression include the monoamine neurotransmitter hypothesis, the hypothalamic pituitary adrenal axis dysfunction hypothesis, the neural plasticity and neurotrophic factor hypothesis, the inflammation and cytokine hypothesis, and the intestinal flora imbalance hypothesis [203-208]. In the past decades, however, the pathogenesis of depression still remains poorly understood, and currently there is no cure for depression. Impressively, the role of AKAP79/150 in the development of depression advances our understanding of this disease.

#### 3.3.2 Potential Mechanisms of AKAP79/150 in Depression

The synaptic dysfunction has been extensively studied in patients with depression and in animal models [209-211]. The glutamate-mediated excessive activation of extra synaptic NMDAR has been found to be closely related to animal behaviors such as decreased food intake, weight loss, loss of pleasure, cognitive impairment, and social disorder, which are also common clinical manifestations of patients with depression [212-216].

A study identified AKAP5 copy-number increases using DNA copy-number analysis from the human brain DNA samples of post-mortem bipolar disorder and schizophrenia patients [217, 218]. Of interest, the numerical density of AKAP5-expressing neurons was significantly increased in the left and right anterior cingulate cortex of patients with bipolar disorder [219]. The DNA copy variants in eight AKAP5 were also found in individuals with autism spectrum disorders [220].

Another study found that aberrant expression of *Akap5* is found in amygdala after unpredictable chronic mild stress-induced depression-like behavior in rats, and antidepressants could reverse the expression of *Akap5* [221]. Furthermore, a recent study shows that both chronic restraint stress and unpredictable chronic mild stress increase the expression of AKAP150 and induce its redistribution into the synapses in the basolateral amygdala of depressive mice [222]. As a AKAP79/150 anchoring kinase in SH-SY5Y neurons, PKA is recruited to the synaptic compartment, facilitating the phosphorylation of GluA1 Ser845 site and the insertion of GluA1-containing AMPARs into the neuronal postsynaptic membrane [49, 222, 223]. AMPAR transported to the postsynaptic membrane is located on the PSD-95 scaffold and mediated glutamatergic synaptic transmission contributes to depressive-like behaviors [222, 224]. Interestingly, studies have found that curcumin, a multitarget drug with antidepressant effect, can protect neurons from glutamate insult by reducing $Ca^{2+}$ influx induced by NMDAR and blocking the translocation of AKAP79 from cytomembrane to cytoplasm. At the same time, curcumin facilitates the phosphorylation of AMPAR and its downstream signal transmission from MEK1/2 to ERK1/2 in PKA dependent manner [223]. These findings reveal insight into the pathophysiology of depression and provide a novel target for the development of antidepressants (Figure 4).

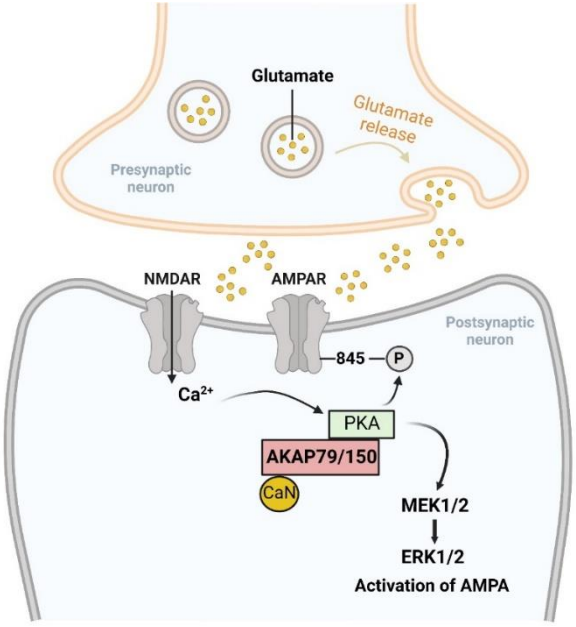


**FIGURE 4:** AKAP150-mediated synaptic dysfunction in chronic restraint stress and unpredictable chronic mild stress-induced depressive-like behaviors. Both chronic restraint stress and unpredictable chronic mild stress increase $Ca^{2+}$ influx induced by NMDAR and the translocation of AKAP79 from cytomembrane to cytoplasm, and facilitate the phosphorylation GluA1Ser845 site of AMPAR and its downstream signal transmission from MEK1/2 to ERK1/2 in PKA dependent manner, thus improving the transmission of excitatory synapse in basolateral amygdala of mice and inducing depressive behavior.

### 3.4. Diabetes

Interestingly, more recently has found that the adipocyte hormone leptin could not promote $K_{ATP}$ channel trafficking and membrane hyperpolarization in human β-cells from obese type II diabetic donors and β-cells from obese diabetic *db/db* mice lacking functional leptin receptors; however, leptin activates Src kinase, and AKAP79/150 anchors and activates PKA after Src kinase activation, initiating NMDAR-CaMKKβ-AMPK signaling cascades and reactivates the action of leptin. PKA-dependent actin remodeling promotes $K_{ATP}$ channel trafficking and increase in $K^+$ conductance, causing β-Cells hyperpolarization and inhibit glucose stimulated insulin secretion [37]. Noteworthy, studies have found that insulin secretion can be regulated by the reversible phosphorylation of *β* cell proteins through the AKAP79/150 targeting of PKA and PP2B [37, 122, 225]. In addition, studies have found that separately selective down-regulation of $K_V2.1$ and large conductance $Ca^{2+}$-activated $K^+$ channel by activating AKAP150-CaN dependent NFATc3 signaling and the β1 subunit of the large conductance $Ca^{2+}$-activated $K^+$ channel in vascular smooth muscle cells can enhance arterial tone during diabetes [226-228].

In another study of diabetic hyperglycemia, it was found that when the extracellular glucose level increased, P2Y11 receptor activated, promoting AC5 activity and local cAMP production. This cAMP microdomain can enable AKAP5 to recruit PKA that is intimately associated with L-type $Ca_V1.2$ channels to increase their phosphorylation at serine 1928 (S1928), which will potentiate channel activity [229, 230]. Intriguingly, the selective P2Y11 agonist NF546 increases cAMP levels and $Ca_V1.2$ channel activity in human and mouse vascular smooth muscle cells, thus exerting a similar effect as increasing glucose. Counterintuitively, genetic ablation of AKAP5 ($AKAP5^{-/-}$) inhibited the increase in cAMP and $Ca_V1.2$ channel activity induced by elevated glucose and the NF546. In addition, $AKAP5^{-/-}$ can completely abrogated the association of P2Y11 receptors with PKA and the $Ca_V1.2$ $\alpha_{1C}$ subunit, as well as the $Ca_V1.2$ $\alpha_{1C}$ subunit with AC5 and PKA with AC5 in vascular smooth muscle cells. Altogether, the results suggested the AKAP5/P2Y11/AC5/PKA/$Ca_V1.2$ signaling complex may be targeted for the treat diabetic vascular complications [231, 232].

### 3.5. Cardiovascular Disorders

AKAP79/150 plays an important role in heart function mainly by regulating the calcium ion changes in the heart, myocardial hypertrophy, and heart failure. On one hand, previous study found that *Akap5*-knockout mice have significant cardiac hypertrophy, and carvedilol can reverse cardiac hypertrophy and cardiac insufficiency in *Akap5* gene knockout mice by regulating the activity of CaN and CaMKII [28, 233]. It is worth noting that recent studies have found that Selective *β*1-adrenergic receptor blocker metoprolol reduces ischemic cardiac remodeling and fibrosis by improving cardiac AKAP5 expression and AKAP5-PP2B interaction [234]. Studies have shown that chronic activation of CaN is associated with cardiac hypertrophy and a secondary enhancement of intracellular $Ca^{2+}$ treatment that is tied to the hypertrophy response itself, while targeted inhibition of CaN alleviates cardiac hypertrophy *in vivo* [235-239]. In addition, AKAP79/150 regulates *β*-adrenergic receptor signaling, trafficking, and recycling by anchoring to PKA or CaN exert cardioprotective effects [240, 241]. Interestingly, a recent study suggests that *AKAP5* may anchor CaN to regulate NFATc3 remodeling in H9c2 cardiomyocytes exposed to hypoxia and reoxygenation after ischemia-reperfusion injury [242]. Furthermore, AKAP150-anchored CaN acute activation transcription factor NFATc3 mediates voltage gated $K^+$ currents downregulation in ventricular myocytes following myocardial infarction, increasing the probability of arrhythmias [243]. On the other hand, by anchoring and activating conventional PKCs, AKAP150 promotes the activation of NF-κB, and mediates the toxic cardiac effects of hyperglycemia [244, 245].

### 3.6. Alzheimer's Disease

Previous studies have shown that AKAP79 is highly expressed in cortical regions and hippocampal subregions that are susceptible to the development of neurofibrillary pathology in alzheimer's disease [42, 117, 246]. In addition, the activity of CaN, which binds and localizes with AKAP79, decreases in alzheimer's disease [42, 246]. Interestingly, dysregulation of subcellular localization of PKA-C*β*, PKA-RII*β*, and AKAP79 exist in alzheimer's disease, which may allow for the specific targeting of tau protein by activated PKA after elevations in cAMP levels. Hyper-phosphorylation of the tau protein can form neurofibrillary tangles in the brain of alzheimer's disease patients [247, 248]. It has been reported that AKAP150 may coordinates PKA and CaN regulation of CP-AMPARs to mediate disruption of hippocampal neuronal plasticity and LTP/LTD balance by Aβ oligomers in Alzheimer's disease, thus impairing learning and memory [150, 249].

### 3.7. Hypertension

Research has found that when the angiotensin II signal is elevated, activation activates Gq coupled receptors, increasing cytosolic DAG and IP3 levels. DAG activates PKC and CaN anchored by AKAP150. When PKC is activated, it can phosphorylate nearby TRPV4 and $Ca_V1.2$ channels, increasing the probability of their opening. The opening of the TRPV4 channel develop stuttering persistent $Ca^{2+}$ sparklets signals in arterial myocytes that regulate $Ca^{2+}$ influx and NFATc3-dependent gene expression in smooth muscle. This increases arterial $[Ca^{2+}]_i$ and myogenic tension, ultimately leading to hypertension [124, 125, 250-255].

### 3.8. Cancer

Recently, an analysis using chi-square and Fisher exact test found that AKAP5 expression was decreased in non-mucin producing stomach adenocarcinoma based on the cancer genome atlas data [256]. In addition, using GSEA to analyze the cancer genome atlas dataset, it was found that gene sets related to cholesterol homeostasis, glycolysis, estrogen response late, adipogenesis, estrogen response early, notch signaling, and peroxisome were differentially enriched with the low *AKAP5* expression phenotype. It suggested that these may be the key pathways regulated by *AKAP5* in non-mucin producing stomach adenocarcinoma [256].

Moreover, it was found that the nonsynonymous coding mutations of *AKAP5* was enriched in the metastatic tumor of primary breast cancers with paired metastatic lesions by exome sequencing. Interestingly, further exploration using the cancer genome atlas dataset found that

*AKAP5* was expressed at lower levels in the subtypes (basal-like and HER2-enriched) of breast cancer with highest risk of recurrence. Accordingly, low expression of *AKAP5* is more likely to recurrence and metastasis in breast cancer [257].

## 4. Conclusion

A growing body of evidence has suggested the crucial role of AKAP79/150 in the pathophysiological conditions of some human disorders. Notably, increased AKAP150 expression is closely associated with the pathogenesis of depression. Pharmacological targeting of AKAP150 expression has shown great promise for the depression treatment. In addition, alterations of AKAP150 expression also exist in patients with epilepsy or epileptic animal models, neuropathic pain, or schizophrenia. These lines of evidence highlight the important roles of AKAP79/150 in the progression of these disorders, and render AKAP79/150 as a valuable therapeutic target. Together, the contributions of the AKAP79/150 in regulating disruptions of the synaptic circuits is critical for our understanding of the pathophysiology of some diseases and attempts for development of novel treatments. We envision that the future advances into the molecular mechanisms of AKAP79/150 deregulation and its involvement in the pathogenesis of those disorders can be a key in developing new promising treatment strategies.

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## Authors' Contributions

Y.-H. H., W.-R. F., and F. C.: conceptualization. C.-C. C. and Y.-H. H.: writing-original draft preparation. C.-Y. W., L. Z., J. X., X.-P. L., and F.C.: writing-review and editing. F. C., Y.-H. H., W.-R. F., L. Z., and X.-P. L.: funding acquisition. All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

None.

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