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Potential for Therapeutic Targeting of AKAP Signaling Complexes in Nervous System Disorders

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Abstract

A common feature of neurological and neuropsychiatric disorders is a breakdown in the integrity of intracellular signal transduction pathways. Dysregulation of ion channels and receptors in the cell membrane and the enzymatic mediators that link them to intracellular effectors can lead to synaptic dysfunction and neuronal death. However, therapeutic targeting of these ubiquitous signaling elements can lead to off-target side effects due to their widespread expression in multiple systems of the body. A-kinase anchoring proteins (AKAPs) are multivalent scaffolding proteins that compartmentalize a diverse range of receptor and effector proteins to streamline signaling within nanodomain signalosomes. A number of essential neurological processes are known to critically depend on AKAP-directed signaling and an understanding of the role AKAPs play in nervous system disorders has emerged in recent years. Selective targeting of AKAP protein-protein interactions may be a means to uncouple pathologically active signaling pathways in neurological disorders with a greater degree of specificity. In this review we will discuss the role of AKAPs in both regulating normal nervous system function and dysfunction associated with disease, and the potential for therapeutic targeting of AKAP signaling complexes.

Keywords

AKAP; Calcium; cAMP; Ion channel; Nervous system; PKA

1. Introduction

Within the neuronal cytosol exists an array of enzymes and signaling molecules that compete for substrates and binding partners. These molecules must be orchestrated into temporally and spatially restricted signaling cascades in order to perform the myriad of neuronal adaptations that occur in response to environmental stimuli. Precise arrangement is critical, as many of these pathways are composed of common signaling elements, including

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11. Conflict of interest statement

The authors declare that there are no conflicts of interest.

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a number of ubiquitous second messengers and enzymes with broad substrate specificity. Unsurprisingly, numerous neurological disorders are known to arise from a breakdown in signal transduction integrity. How then are pathways organized? The answer lies in the numerous multivalent protein scaffolds that are able to sequester enzymes and their effector proteins in selective cellular compartments. A-kinase anchoring proteins (AKAPs) are a large family of structurally diverse scaffolding proteins that are particularly important for this function. They share a common ability to bind the cAMP-dependent protein kinase A (PKA), and are therefore often understood in terms of their capacity to compartmentalize cAMP-dependent processes. However, many AKAPs also concurrently bind additional interacting proteins including phosphatases, other scaffolding proteins, ion channels and receptors. The focus of this review is to discuss the major signaling complexes assembled by AKAPs in the nervous system, and to consider how dysfunction in these complexes might be therapeutically targeted to provide treatment for nervous system disorders.

2. AKAP anchoring of PKA holoenzymes

AKAPs are defined by their capability to anchor the Ser/Thr kinase PKA, which is a heterotetrameric holoenzyme composed of two catalytic (C α or C β) and two regulatory (RI α , RI β , RII α or RII β) subunits. Structural studies of these subunits have revealed interesting features related to the function of PKA (Taylor et al., 2013; Smith et al., 2013). The R subunit consists of an N-terminal docking and dimerization (D/D) domain that is joined by a flexible linker to a larger domain that cooperatively binds to two molecules of cAMP and also interacts with the C subunit, inhibiting its catalytic activity in the absence of cAMP (Vigil et al., 2004; Smith et al., 2013). The D/D domain forms both the contact point between two R subunits to assemble the RI or RII dimer, and also the binding site for the canonical amphipathic α -helix anchoring motif common to all AKAPs. An X-type four helix bundle within the R subunit D/D domain creates a hydrophobic groove that accommodates the AKAP amphipathic helix (Newlon et al., 2001; Gold et al., 2006; Kinderman et al., 2006). The PKA R subunit identity (RI or RII) in the PKA holoenzyme determines both sensitivity to cAMP (RI > RII subunits) and selectivity of AKAP interactions. In general, the majority of AKAPs (including most of those discussed in this review) anchor RII subunits with higher affinity than RI subunits; however, several AKAPs anchor RI and RII subunits with similar affinities (e.g. D-AKAP1/AKAP121) or preferentially anchor RI subunits (Herberg et al., 2000; Gold et al., 2006; Aye et al., 2009).

The presence of a flexible linker between the AKAP anchoring D/D domain and the cAMP binding/C-subunit domain allows PKA to adopt a range of conformations, throughout which it can search for substrates to phosphorylate even under basal conditions via the cAMP-independent basal kinase activity of the PKA holoenzyme (Wang et al., 1991; Smith et al., 2013) (Fig. 7A). Interestingly, it was also recently demonstrated that AKAP bound type II PKA is able to increase cellular substrate phosphorylation in the absence of measurable C and R subunit dissociation following physiological elevations in cAMP that would occupy the tandem binding sites on the RII subunits (Smith et al., 2017). These recent findings are consistent with often overlooked previous studies of PKA holoenzyme dynamics indicating that cAMP binding to R subunits does not necessarily result in R-C dissociation and can regulate PKA catalytic activity in the absence of C subunit dissociation (Yang et al., 1995;

Kopperud et al., 2002). Collectively these past and present studies overturn the dogma that C subunit dissociation from the R subunit is required for cAMP-stimulated catalytic activity in cells (Taylor et al., 2013). Furthermore, the activity of AKAP-anchored PKA may be more spatially restricted than previously anticipated, whereby substrates that are within 150–250 angstroms of the PKA-AKAP anchoring site will be most available as phosphorylation targets (Smith et al., 2013, 2017).

3. AKAP79/150

A pivotal advance in our understanding of AKAPs as multi-functional scaffold proteins came from the finding that AKAP79/150 (79 human isoform; 150 rodent isoform; 75 bovine isoform) could concomitantly anchor both PKA and the phosphatase calcineurin (Coghlan et al., 1995). Now one of the AKAPs most studied and best characterized in the nervous system, the list of AKAP79/150 binding partners has greatly expanded, and the broad spectrum of biological processes that critically depend on neuronal AKAP79/150 is being ever more clearly defined (Fig. 1A). Encoded by the *AKAP5* gene, AKAP79/150 is expressed in numerous neuronal subtypes and is responsible for the assembly of a range of signaling proteins with ion channels and receptors to form highly dynamic and complex signaling hubs. More recent discoveries have demonstrated the ability of AKAP79/150 to form nanodomain super-complexes composed of diverse but functionally coupled ion channels and receptors (Zhang et al., 2016). Below we will outline the structure of AKAP79/150, along with the latest understanding of the key signaling complexes it assembles and the essential physiological roles that these complexes perform.

AKAP79/150 Functional Domains

The canonical PKA binding amphipathic α -helix of AKAP79/150 was the first scaffolding site to be characterized and is located in the distal C-terminal domain of AKAP79/150 (Carr et al., 1992). Soon after, the Ca^{2+} -CaM-dependent phosphatase calcineurin (CaN; PP2B; PPP3) was identified as a binding partner, later shown to interact via its A subunit through a β -sheet interaction with a short, linear motif that is related to PxIxIT docking motifs found in several other CaN binding proteins. This motif is located in the C-terminal domain just N-terminal to the PKA anchoring site (Coghlan et al., 1995; Dell'Acqua et al., 2002; Oliveria et al., 2003, 2007; Li et al., 2012). Protein kinase C (PKC), which can be activated by the second messengers Ca^{2+} and diacylglycerol (DAG), was later also found to associate with AKAP79/150 through a pseudosubstrate-like sequence within the N-terminal domain (Klauck et al., 1996; Faux et al., 1999). In addition, PKC anchoring at this site competes with Ca^{2+} -CaM and is therefore regulated by changes in intracellular Ca^{2+} (Faux & Scott, 1997). Partially overlapping with the PKC anchoring site are three N-terminal polybasic membrane targeting regions, which include two Cys moieties that can be palmitoylated, allowing for dynamic shuttling of the AKAP79/150 signaling complex between the plasma membrane and endosomal membrane compartments (Delint-Ramirez et al., 2011; Keith et al., 2012; Woolfrey et al., 2015). Additional plasma membrane targeting of AKAP79/150 is achieved through direct electrostatic interactions of the three polybasic domains with the acidic lipid phosphatidylinositol 4,5-bisphosphate (PIP_2), cadherin cell adhesion molecules and cortical F-actin (Gomez et al., 2002; Dell'Acqua et al., 2002; Gorski et al., 2005).

AKAP79/150 can also bind to other scaffolding proteins, namely PSD-95 and SAP97, of the membrane-associated guanylate kinase (MAGUK) family of proteins (Colledge et al., 2000; Robertson et al., 2009). These scaffold-scaffold interactions allow for the modular assembly of more complex AKAP79/150 signaling hubs, bringing scaffolded kinases and phosphatases into close proximity with a greater number of substrates, including postsynaptic receptors and ion channels (Fig. 2). A critical function of AKAP79/150 is to couple the activation of receptors and ion channels in the cell membrane to downstream activation of effector proteins with high spatiotemporal efficiency. Below we will discuss the ion channel and receptor complexes that are assembled and regulated by AKAP79/150 to perform specific neuronal functions.

AKAP79/150 assembly of AMPAR complexes and synaptic plasticity

The capacity of neural networks to modify the strength of their synaptic connections is accepted to be the mechanism by which experiences are stored in the form of persistent memories in the brain (Citri & Malenka, 2008). This activity-dependent modulation of synaptic strength, known as synaptic plasticity, has been studied extensively in the hippocampus, one of the brain's key memory centers. A great deal of work has been invested in delineating the molecular mechanisms by which synapses strengthen and weaken in response to prior activity. The importance of postsynaptic ionotropic glutamate receptors, including *N*-methyl-D-aspartate receptors (NMDARs) and α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA), in both triggering and manifesting changes in synaptic strength has been appreciated for many years. In particular, the expression of synaptic long-term potentiation (LTP) and long-term depression (LTD) are now known to be heavily influenced by changes in the number of AMPARs within the postsynaptic density (PSD) and in their biophysical properties, which can both be altered by phosphorylation and dephosphorylation (Malenka & Bear, 2004).

AMPA receptors mediate the majority of fast excitatory neurotransmission in the nervous system and are composed of four subunits, GluA1-GluA4. The most common assemblies in hippocampal neurons are heteromeric complexes that include GluA1/GluA2 or GluA2/GluA3 subunits (Lu et al., 2009). As a result of RNA editing (Q/R), the presence of a positively charged Arg residue in the selectivity filter of GluA2 subunit channel pore renders receptors containing edited GluA2 subunits impermeable to Ca^{2+} . Therefore, AMPARs that either contain unedited GluA2 or lack GluA2 subunits entirely, such as homomeric tetramers of GluA1, form Ca^{2+} permeable AMPARs (cp-AMPA). Unedited GluA2 subunits have for the most part been only observed during early development or after ischemic insults (Peng et al., 2006; Henley & Wilkinson, 2016). However, GluA1 containing cp-AMPA are more common and have recently garnered interest owing to the unique roles they play in regulating synaptic strength. Hereafter, we will refer to cp-AMPA as those that are composed only of GluA1 subunits.

The coordinated insertion and removal of cp-AMPA into and out of the PSD is thought to underlie certain forms of LTP and LTD. For example, during LTP AMPAR GluA1 subunits are phosphorylated at multiple residues within their C-terminal tail, including Ser-831 (phosphorylated by CaMKII and PKC) and Ser-818 (phosphorylated by PKC). These

modifications promote synaptic localization and increase single channel conductance (Barria et al., 1997; Benke et al., 1998; Lee et al., 2000, 2003; Boehm et al., 2006). Additionally, Ser-845 of GluA1 is a substrate for PKA, which when phosphorylated promotes forward trafficking of GluA1 to the plasma membrane to prime synaptic insertion and enhance channel open probability (Hayashi et al., 2000; Banke et al., 2000; Esteban et al., 2003; Oh et al., 2006; He et al., 2009; Yang et al., 2010).

Recent work has defined an important role for AKAP79/150 in regulating synaptic plasticity through targeting of PKA and CaN to AMPARs, where they are able to alter the Ser-845 phosphorylation state of cp-AMPA receptors. Experiments utilizing PKA binding-deficient AKAP150 PKA and D36 knock-in mice have determined the importance of AKAP79/150-anchored PKA in regulating both LTP and LTD (Lu et al., 2007, 2008; Sanderson et al., 2016) (Fig. 2). In particular, stimulation-induced phosphorylation of Ser-845 of GluA1 and its recruitment to the synapse during both LTP and LTD is dependent on PKA that is anchored to AKAP79/150 (Fig. 2A; upper panel). Following PKA-dependent GluA1 insertion, AKAP79/150-anchored CaN can then promote the rapid removal of cp-AMPA receptors, along with other AMPAR subtypes, to consolidate depression of hippocampal synapses during LTD (Sanderson et al., 2012) (Fig. 2A; lower panel). Importantly, CaN anchoring-deficient AKAP150 PIX mice (containing an in-frame deletion of the PxIxIT-like CaN docking motif) are deficient in LTD and show impaired dephosphorylation of Ser-845 and removal of GluA1 from synapses (Sanderson et al., 2012). Homeostatic scaling is another form of synaptic plasticity that alters the complement of AMPARs in the post-synaptic membrane but has the ability to induce compensatory changes in the strength of many or all synapses on a neuron simultaneously to counter chronic alterations in neuronal firing (Turrigiano et al., 1998). Scaling allows neurons to maintain their firing rates within a suitable range in order to facilitate network stability during continued LTD and LTP (Turrigiano, 2008). Consistent with utilizing underlying mechanisms in common with LTP and LTD, homeostatic scaling-up or -down of synaptic strength in response to chronic decrease or increases in firing, respectively, can also be regulated by the respective insertion or removal of GluA1 from the plasma membrane, the former of which is controlled by Ser-845 phosphorylation by PKA anchored to AKAP79/150 in cortical neurons (Diering et al., 2014).

These studies of AKAP79/150 in both LTP/LTD and homeostatic synaptic plasticity are supported by behavioral studies that have determined a requirement for AKAP79/150-anchored PKA in reversal learning and both PKA and CaN in spatial and contextual fear learning (Tunquist et al., 2008; Weisenhaus et al., 2010; Dell'Acqua et al., unpublished). The learning and memory alterations observed in AKAP150 KO and PKA-anchoring-deficient mutant mice might be explained by the profound loss of type II PKA from the PSD and its redistribution from dendritic spines to dendrite shafts and the soma in hippocampal neurons, which indicates that other AKAPs are not able to compensate for loss of AKAP79/150-PKA postsynaptic scaffolding (Lu et al., 2007; Weisenhaus et al., 2010; Murphy et al., 2014; Sanderson et al., 2016).

Another related form of LTP that is also dependent on AKAP79/150 scaffolding involves β -adrenergic receptor (β -AR) stimulation of PKA to increase GluA1 Ser-845 phosphorylation

(Qian et al., 2012). In particular, low frequency, sub-threshold synaptic stimulation in the presence of β -adrenergic agonists induces a form of LTP that is NMDAR-independent, prevented by knock-out of AKAP150 (Zhang et al., 2013), and requires PKA phosphorylation, not only of cp-AMPA receptors, but also of $\text{Ca}_v1.2$ L-type voltage-gated Ca^{2+} channels (discussed more below) (Qian et al., 2012, 2017). A large complex is formed to facilitate this signaling that includes AMPARs, β_2 -ARs, adenylyl cyclase (AC), PSD-95, $\text{Ca}_v1.2$ and AKAP79/150 (Bauman et al., 2006; Qian et al., 2012, 2017; Zhang et al., 2013). Overall, these studies outline a clear role for AKAP79/150 centered signaling complexes in coordinating numerous forms of synaptic plasticity, which ultimately underlie learning and memory.

Dynamic regulation of AKAP79/150 subcellular targeting

Given the central role of AKAP79/150 in a myriad of neurological processes, it is vital that AKAP79/150 is trafficked appropriately to specific subcellular compartments containing its regulatory targets. As mentioned above, the N-terminal polybasic domain localizes AKAP79/150 to dendritic spine membranes through interactions with phosphoinositide lipids, cadherin adhesion molecules and F-actin (Dell'Acqua et al., 1998; Gomez et al., 2002; Gorski et al., 2005; Horne & Dell'Acqua, 2007). More recent studies have revealed highly dynamic trafficking of AKAP79/150 between the plasma membrane and intracellular endosomes that is regulated by neuronal activity. In hippocampal neurons, this is achieved by reversible palmitoylation of the N-terminal membrane targeting domain by the palmitoyl-acyl transferase DHHC2 (Keith et al., 2012; Woolfrey et al., 2015) (Fig. 2B). Two cysteine residues (Cys-36 and Cys-129) within this domain can be modified by addition of a palmitoyl moiety, promoting AKAP79/150 inclusion in dendritic recycling endosomes and plasma membrane lipid rafts that are found within the PSD (Delint-Ramirez et al., 2011; Keith et al., 2012). Importantly, the palmitoylation state and localization of AKAP79/150 can be modified in response to neuronal activity. Chemically induced LTD (cLTD) decreases AKAP79/150 localization within the PSD and recycling endosomes through a combination of de-palmitoylation, CaN-dependent F-actin reorganization and PLC-dependent PIP_2 cleavage (Gomez et al., 2002; Horne & Dell'Acqua, 2007; Keith et al., 2012). Conversely, in response to chemical LTP (cLTP), palmitoylation of AKAP79/150 is enhanced by DHHC2, promoting endosome exocytosis and delivery of both AKAP79/150 and GluA1 to the PSD (Fig. 2B) (Keith et al., 2012). Disruption of AKAP79/150 palmitoylation either by mutation of the two Cys residues to Ser (AKAP79/150CS) or knock-down of DHHC2 disrupts stimulation-driven delivery of AKAP79/150 and AMPARs from recycling endosomes to the neuronal membrane and accompanying synaptic potentiation (Keith et al., 2012; Woolfrey et al., 2015). As such, this fine-tuning of AKAP79/150 localization with dynamic lipidation represents another mechanism by which AKAP79/150 is able to regulate changes in synaptic strength.

AKAP79/150 scaffolding of L-type Ca^{2+} channels and signaling to the nucleus to regulate gene expression

Ca^{2+} is one of the most ubiquitous signaling molecules in the brain, with a well-defined role in neuronal development, plasticity, remodeling, transcriptional control and activation of neuronal survival and death signaling pathways. With this breadth of signaling capability

comes a requirement for highly compartmentalized neuronal Ca^{2+} entry and targeted coupling to Ca^{2+} sensitive effector proteins. One important and highly regulated source of Ca^{2+} entry comes from voltage-gated Ca^{2+} channels, which serve a dual function by both altering membrane potential with depolarizing inward current and increasing intracellular Ca^{2+} in a manner that is directly linked to neuronal activity. In particular, L-type Ca^{2+} channels (LTCCs) have been found to be critically involved in a range of essential neuronal functions including certain types of synaptic plasticity (as discussed above), control of neuronal excitability and activity-dependent gene transcription, also known as excitation-transcription (E-T) coupling (Grover & Teyler, 1990; Bolshakov & Siegelbaum, 1994; Marrion & Tavalin, 1998; Moosmang et al., 2005; Oliveria et al., 2007; Ch'Ng et al., 2012; Li et al., 2012; Wheeler et al., 2012; Murphy et al., 2014).

LTCCs are composed of pore-forming α_1 and auxiliary $\alpha_2\delta$ and β subunits, with the most abundant LTCC isoforms in the brain being formed of $\text{Ca}_v1.2$ (70 %) and $\text{Ca}_v1.3$ (30 %) α_1 subunits (Hell et al., 1993). Neuronal LTCCs are regulated by PKA phosphorylation at multiple Ser residues within their intracellular domains that enhance channel currents, and by Ca^{2+} -CaM binding to an isoleucine-glutamine (IQ) motif on the intracellular C-terminal, which induces conformational changes to limit channel activity through promoting calcium-dependent inactivation (CDI) (Zühlke et al., 1999, 2000; Erickson et al., 2003; Kim et al., 2004; Dittmer et al., 2014; Murphy et al., 2014; Qian et al., 2017). Importantly, AKAP79/150 scaffolding has been identified as a key regulator of channel function, in both maintaining basal channel phosphorylation by PKA and promoting CDI by CaN dephosphorylation (Oliveria et al., 2007, 2012; Li et al., 2012; Dittmer et al., 2014; Murphy et al., 2014). Additionally, AKAP79/150 is required for signaling to downstream effectors, including the transcription factor nuclear factor of activated T-cells (NFAT) (Oliveria et al., 2007; Murphy et al., 2014) (Fig. 3A).

The mechanisms of neuronal LTCC regulation by AKAP79/150 have been best described in hippocampal neurons, where disruption of PKA anchoring to AKAP79/150 results in a pronounced redistribution of the PKA-RII α and RII β subunits away from dendritic spines and reduces basal phosphorylation at Ser-1700 and Ser-1928 of $\text{Ca}_v1.2$ (Murphy et al., 2014). This uncoupling of PKA from AKAP79/150 leads to LTCC functional deficits including reduced Ca^{2+} influx and channel current density (Dittmer et al., 2014; Murphy et al., 2014). While CDI was previously thought to be solely dependent on Ca^{2+} binding to pre-associated CaM at the LTCC C-terminal, studies in hippocampal cell preparations that also express AKAP79/150 found a clear role for AKAP79/150-anchored CaN in regulating CDI through reversal of the basal enhancement of channel function mediated by anchored PKA. In these studies, deletion of the PxIxIT-like CaN docking motif in AKAP79/150 prevented CDI, enhancing overall channel current density (Oliveria et al., 2012; Dittmer et al., 2014). Recent work has shown that PKA phosphorylation of Ser-1928 in $\text{Ca}_v1.2$ is also important for β_2 -AR regulation of cp-AMPA recruitment to regulate LTP (Qian et al., 2017).

An important physiological function of LTCCs in hippocampal neurons is to direct E-T coupling, which is a critical mechanism for consolidating long lasting changes in neuronal function by initiating gene transcription (Adams & Dudek, 2005; Cohen & Greenberg, 2008; Ch'ng & Martin, 2011; Fainzilber et al., 2011; Panayotis et al., 2015; Cohen et al., 2015; Ma

et al., 2015). AKAP79/150 regulates E-T coupling through the NFAT transcription factors, which redistribute from the cytosol to the nucleus upon LTCC activation and CaN dephosphorylation of multiple residues in a Ser-Pro rich region of NFAT (Kipanyula et al., 2016). Importantly, depolarization-induced NFATc3 and NFATc4 nuclear translocation is severely impaired by disrupting AKAP79/150 anchoring of either CaN (which is required for dephosphorylation of NFAT) or PKA (which is required to maintain basal phosphorylation and sufficient Ca^{2+} influx through LTCCs to activate CaN) (Oliveria et al., 2007; Murphy et al., 2014). The affinity of the AKAP79/150 calcineurin interaction is attuned to allow both CaN activation at the mouth of the LTCC and sufficient mobility within the complex for CaN to dephosphorylate NFAT. Either enhancement or reduction of AKAP79/150-CaN affinity with site-directed mutagenesis of the AKAP79/150 PxIxIT CaN binding motif disrupts NFAT nuclear accumulation and transcriptional activity (Li et al., 2012). Interestingly, the M-type potassium channel has been identified as a physiologically relevant transcriptional target of AKAP79/150-NFAT E-T coupling in neurons (Zhang & Shapiro, 2012). The role of this M-current channel in AKAP79/150 regulation of intrinsic neuronal excitability is discussed in more detail below. In summary, AKAP79/150 has emerged as a key coordinator of LTCC signaling in the nervous system, an important function when considering the roles LTCCs play in controlling neuronal plasticity, development and gene expression, in addition to the well-established role of Ca^{2+} dyshomeostasis in neurological and neuropsychiatric disorders (Simms & Zamponi, 2014).

AKAP79/150 scaffolding of potassium channels and regulation of neuronal excitability

An individual neuron within the central nervous system can receive tens of thousands of synaptic inputs, and how these inputs are integrated is determined by the activity of ion channels that decorate the dendritic membrane. One subclass of ion channels that have a central role in the control of neuronal excitability are voltage-gated potassium (K_V) channels, whose activity dampens neuronal depolarization and limits excitability. The activity of K_V channels is highly regulated by phosphorylation and membrane trafficking. An important role for AKAP79/150-directed signaling has been described for both M-type and A-type K_V channels. M-type K^+ channels ($\text{K}_V7.1-7.5$; composed of KCNQ subunits) are expressed throughout the nervous system and can control the rate of neuronal firing and neurotransmitter release (Hernandez et al., 2008). In particular, opening of M-type K^+ channels ($\text{K}_V7.2/3$) reduces neuronal excitability in order to limit repetitive action potential firing, while suppression of M-current by G-protein coupled receptors (GPCRs) allows neurons to fire more rapidly (Delmas & Brown, 2005; Hernandez et al., 2008).

In sympathetic neurons of the superior cervical ganglia (SCG), the regulated suppression of $\text{K}_V7.2/3$ is directed by a number of signaling molecules that are intimately associated via AKAP79/150 scaffolding (Fig. 3B). This channel suppression can be achieved by activation of three second messenger pathways. Briefly, mechanisms of suppression include (i) G_q -coupled GPCR-driven phospholipase C (PLC) hydrolysis of the phospholipid PIP_2 , which is a well-established positive regulator of channel opening, (ii) Ca^{2+} -CaM inhibition by direct association with the channel C-terminus, and (iii) phosphorylation of the C-terminus by PKC which alters the affinities of the channel for CaM and PIP_2 (Hoshi et al., 2005; Bal et al., 2010; Zhang et al., 2011a; Kosenko et al., 2012). A number of these processes are

directly coordinated by AKAP79/150, which assembles signaling complexes that include muscarinic acetylcholine receptors (M₁Rs) and K_v7.2/3 channels, functionally coupling neurotransmitter receptor activation with PIP₂ depletion and K_v7.2/3 regulation down-regulation (Zhang et al., 2011a, 2016). In particular, K_v7.2/3 is phosphorylated by PKC that is localized to the channel by AKAP79/150 anchoring to reduce the affinity of the channel for CaM and PIP₂ (Hoshi et al., 2003, 2005; Zhang et al., 2011a; Kosenko et al., 2012). Finally, the AKAP79/150 regulatory complex can be disrupted by Ca²⁺-CaM binding at the K_v7.2/3 C-terminus (Zhang & Shapiro, 2016).

In hippocampal neurons, AKAP79/150 also regulates neuronal excitability by forming complexes with the A-type K_v channel, K_v4.2 (Lin et al., 2011) (Fig. 3B). These channels have a role in synaptic integration and control of action potential back-propagation in dendrites (Hoffman & Johnston, 1998; Kim & Hoffman, 2008). Furthermore, down-regulation of K_v4.2 channels following LTP-inducing stimuli leads to changes in neuronal excitability that can act as a form of plasticity (Jung & Hoffman, 2009). PKA is known to promote internalization of K_v4.2 and down-regulation of A-type current (Hoffman & Johnston, 1998; Hammond et al., 2008). Importantly, K_v4.2 directly binds to the MAGUK binding site on AKAP79/150 and anchored PKA and CaN bi-directionally regulate K_v4.2 current density. Knockdown of endogenous AKAP79/150 in hippocampal neurons increases K_v4.2 surface expression and currents, while disruption of PKA anchoring reduces neuronal excitability, demonstrating that AKAP79/150 anchoring of PKA in close proximity to K_v4.2 suppresses A-current to enhance hippocampal excitability (Lin et al., 2011). Thus, AKAP79/150 is intricately involved in regulating neuronal excitability by coupling voltage gated K⁺ channels with the activity of GPCRs, CaN, PKA and PKC. Furthermore, this type of regulation may have implications for long-term changes in neuronal function that occur under conditions such as LTP.

AKAP79/150 scaffolding of TRPV1 and nociceptive signaling

The ability of animals to sense and avoid potentially damaging extremes of temperature and noxious chemicals owing to the sensation of pain has evolved as an important mechanism of survival. The experience of pain originates when noxious stimuli are detected by receptors in primary nociceptive sensory neurons, which then relay signals from the periphery to the central nervous system (Fischer & McNaughton, 2014). The transient receptor potential vanilloid 1 (TRPV1) ion channel is one such molecular integrator of nociceptive stimuli that is predominantly expressed in sensory neurons, where it responds to a variety of chemical and physical stimuli. TRPV1 receptors are activated by elevated temperature, acidic pH, pro-inflammatory mediators, endogenous lipid agonists and exogenous small organic agonists such as capsaicin (Cesare & McNaughton, 1996; Caterina et al., 1997, 2000; Caterina & Julius, 2001; Ramsey et al., 2006). The TRPV1 receptor is a non-selective cation channel that is highly permeable to Ca²⁺, and as such, the activation of TRPV1 by multiple concurrent stimuli leads to both neuronal depolarization and downstream Ca²⁺-dependent signal amplification (Ramsey et al., 2006).

AKAP79/150 has an essential role in maintaining TRPV1 activity by both targeting a number of effector proteins to the receptor that alter receptor sensitivity and forming

macromolecular complexes that facilitate crosstalk between TRPV1 and other membrane bound ion channels (Fig. 3C). In sensory neurons of the dorsal root ganglia (DRG), AKAP79/150 is expressed in a sub-population of neurons composed predominantly of nociceptive C fibers (Brandao et al., 2012). In these neurons, AKAP79/150 coordinates TRPV1 regulation by the inflammatory mediator prostaglandin E2 (PGE2), by scaffolding PKA that in turn phosphorylates TRPV1 to enhance its sensitivity (Rathee et al., 2002; Schnitzler et al., 2008a). AKAP79/150 also anchors AC5 to the TRPV1-AKAP79-PKA complex, which is another essential component for TRPV1 sensitization by PGE2 in DRG neurons (Efendiev et al., 2013). Studies of sensory trigeminal ganglia neurons found that PKC and PKA phosphorylation both sensitize TRPV1 and depend on AKAP79/150 anchoring for their targeting to the channel (Zhang et al., 2008; Jeske et al., 2008, 2009). Finally, TRPV1 channels undergo a form of desensitization following activation by capsaicin, which may depend on AKAP79/150-anchored CaN (Mohapatra & Nau, 2005; Zhang et al., 2008). Taken together, these findings highlight a central role for AKAP79/150 in coordinating signaling complexes that are essential for TRPV1 regulation and nociception.

AKAP79/150 assembled multi-channel supercomplexes

While AKAP79/150 is known to assemble complexes that associate ion channels with their intracellular effector proteins, accumulating evidence supports the notion that it can also assemble super-complexes with diverse receptors and ion channels that are then functionally coupled. Early studies in DRG neurons revealed functional coupling between TRPV1 and a number of voltage gated Ca^{2+} channels, whereby activation of TRPV1 with capsaicin leads to profound inhibition of P/Q-, L-, N- and R-type Ca^{2+} channel current density (Wu et al., 2005). Accordingly, co-localization of LTCCs and TRPV1 in a subset of DRG neurons has been observed (Brandao et al., 2012). More recently, a study by Zhang et al. using super-resolution STORM microscopy provided direct evidence of an intimate association between TRPV1, $\text{Ca}_v1.2$ and AKAP79/150 within nanodomain clusters in nodose ganglia sensory neurons (Fig. 3D). These imaging observations were supported by data demonstrating functional crosstalk between the two channels, as Ca^{2+} influx through $\text{Ca}_v1.2$ promoted TRPV1 desensitization. Importantly, both the physical and functional coupling were abolished in AKAP150 KO mice (Zhang et al., 2016). Similarly, functional coupling between TRPV1 and M-type K^+ channels has also been described, whereby activation of TRPV1 substantially reduces M-current in HEK293 cells expressing TRPV1 and $\text{K}_v7.2/3$ (Zhang et al., 2011b). Again, this interaction was recently supported by super-resolution imaging studies that revealed an AKAP79/150-dependent co-clustering of TRPV1 with $\text{K}_v7.2/3$ (Zhang et al., 2016) (Fig. 3D). The proposed mechanism that links Ca^{2+} influx through TRPV1 to M-current suppression is likely via Ca^{2+} -CaM binding to $\text{K}_v7.2/3$, as well as activation of Ca^{2+} -dependent PLC δ signaling that depletes PIP_2 and activates PKC. Together, these events lead to suppression of M-current and enhancement of neuronal excitability, as described above. This may serve to amplify otherwise subthreshold TRPV1-driven membrane depolarization and enhance nociceptor sensitivity. Accordingly, suppression of M-current by TRPV1 activation was absent in sensory neurons from AKAP150 KO mice (Zhang et al., 2016).

While AKAP79/150 is the best characterized of the neuronal AKAPs, there are many others that are known to coordinate important neuronal functions and are potential therapeutic targets in nervous system disorders. In the next section we will outline the signaling complexes formed by these other AKAPs and their roles in neuronal physiology.

4. Gravin/AKAP250 (AKAP12)

Gravin is a large (~300 kDa) AKAP encoded by the *AKAP12* gene and is also known as AKAP250 and Src-suppressed C kinase substrate (SSECKS; rodent isoform) (Fig. 1B). There are three isoforms of gravin originating from the *AKAP12* gene (α , β and γ), that have differing tissue-specific distributions throughout the body (Camus et al., 2001; Streb et al., 2004). These isoforms are divergent in their N-termini and are generated from distinct mRNA transcripts under the control of different promoters (Streb et al., 2004). Gravin- α is the most abundant isoform in the brain and is highly expressed throughout the forebrain and hippocampus (Streb et al., 2004; Havekes et al., 2012). Early studies revealed the central role that Gravin plays in regulating β_2 -AR receptor desensitization and resensitization (Shih et al., 1999; Fan et al., 2001; Lin & Gelman, 2002). Activation of β_2 -ARs promotes direct phosphorylation of Gravin by PKA, a modification that recruits Gravin to the cell membrane, resulting in an enhanced coupling between β_2 -ARs and PKA (Shih et al., 1999; Lin et al., 2000; Tao et al., 2003).

Trafficking of Gravin and PKA is also dynamically regulated by mechanisms that can direct PKA away from the cell membrane. These mechanisms include the rapid redistribution of Gravin-PKA to intracellular membrane compartments following stimulation of PKC (Lin et al., 1996; Wassler et al., 2001; Yan et al., 2009; Schott & Grove, 2013) or in response to increases in intracellular Ca^{2+} that activate Ca^{2+} -CaM. The interaction between Ca^{2+} -CaM and gravin occurs at the CB4 putative CaM binding site and is thought to play a key role in Ca^{2+} -CaM-dependent redistribution (Schott & Grove, 2013; Schott et al., 2016). Mechanisms such as these that direct the signaling complex to intracellular compartments may serve to limit PKA activity at the cell membrane.

An important physiological consequence of gravin regulation of β_2 -ARs has been described in the hippocampus, where Gravin-mediated scaffolding of PKA and the β_2 -AR plays a role in synaptic plasticity. This study by Havekes et al. found that mice selectively lacking Gravin- α have marked deficits in late-phase LTP, β_2 -AR-mediated plasticity and impairments in behavioral long-term memory tests (Havekes et al., 2012). Interestingly, loss of Gravin- α led to an impairment in ERK1/2 signaling, which is required for long-lasting forms of LTP and is stimulated by PKA phosphorylation of β_2 -ARs (Daaka et al., 1997; Impey et al., 1998; Baillie et al., 2003) (Fig. 4A). This study highlighted an important role for Gravin- α in both PKA- and β_2 -AR-dependent forms of synaptic plasticity and in driving processes that result in long-term memory storage, further establishing the importance of AKAP-directed signaling complexes in fine-tuning spatial and temporal control of kinase signaling following synaptic stimulation. As mentioned above, AKAP79/150 is also involved in β_2 -AR regulation of LTP (Zhang et al., 2013), indicating that these two different postsynaptic AKAPs may work together to coordinately regulate synaptic plasticity mechanisms in the hippocampus and learning and memory.

5. Yotiao (*AKAP9*)

Yotiao is a short variant generated from alternative splicing of the *AKAP9* gene (Fig. 1C). Other splice variants include the larger product AKAP350/450 and the PKA binding-deficient GISP (Kantamneni et al., 2007; Collado-Hilly & Coquil, 2009). Yotiao is known to regulate $K_V7.1$ in the heart (Marx et al., 2002), while in the nervous system, yotiao has an important role as a PKA scaffold that binds directly to the NMDAR (Lin et al., 1998; Westphal et al., 1999). Immunostaining has revealed expression of yotiao in brain regions that include the cerebral cortex, hippocampus and cerebellum, and in the peripheral nervous system at the neuromuscular junction (Lin et al., 1998). Yotiao directly interacts with NMDARs via with the C1 cassette of the GluN1 subunit, anchoring PKA and protein phosphatase-1 (PP1) to the NMDAR for bi-directional modulation of NMDAR currents (Fig. 4B). PKA-dependent enhancement of NMDAR currents is more pronounced in cells that express yotiao, while yotiao scaffolding of PP1 to the NMDA receptor complex is responsible for a tonic NMDAR inhibition (Westphal et al., 1999) (Fig. 4B). Another study found that yotiao anchoring of both PKA and PP1 is important for dopamine D4 receptor modulation of GABA_A currents in the pre-frontal cortex (Wang et al., 2002) (Fig. 4B). IP₃ receptors (IP₃Rs) are subject to PKA-dependent regulation, and yotiao has been found to interact with type 1 IP₃Rs that are highly expressed in the brain (Fig. 4B). This interaction occurs between leucine/isoleucine zipper (LIZ) motifs found in both proteins, promoting association of IP₃R1 with the GluN1 subunit of the NMDA and directing phosphoregulation of IP₃R1s by PKA and PP1 (Tu et al., 2004). AC can also be incorporated into yotiao signaling complexes, expanding its function as part of the cAMP signaling machinery. In particular, yotiao can interact with AC isoforms 1, 2, 3 and 9, while AC2 association of yotiao reduces AC2 activity (Piggott et al., 2008).

Alternate splice variants of the *AKAP9* gene have also been implicated in receptor regulation. AKAP450 targets PKA to IP₃Rs in the golgi apparatus of cerebellar granule cells (Collado-Hilly & Coquil, 2009), and a short C-terminal splice variant that lacks PKA binding ability known as GISP can enhance cell surface expression of GABA_B receptors (Kantamneni et al., 2007). Knockout of the *AKAP9* gene disrupts signaling by Traf2 and NcK interacting kinase (TNiK), a protein that is expressed in the nervous system and has been implicated in postsynaptic signaling and regulation of glutamate receptors (Camargo et al., 2007; Coba et al., 2009; Hussain et al., 2010). TNiK is associated with NMDARs via the binding of an *AKAP9* gene product to the GluN1 subunit C-terminal, and this interaction is disrupted in *AKAP9* knockout mice (Coba et al., 2012). Taken together, a clear role has emerged for *AKAP9* splice variants, and in particular yotiao, in regulation of a variety of receptors that have important roles in neuronal physiology.

6. AKAP15/18 (*AKAP7*)

The *AKAP7* gene encodes four AKAP15/18 isoforms derived via alternative splicing that are either short (α and β) or long (γ and δ). All isoforms share an amino acid sequence that includes a core PKA binding domain and a modified LZ motif, but otherwise differ in their N-termini (Fraser et al., 1998; Gray et al., 1998; Trotter et al., 1999; Henn et al., 2004). Short isoforms include an N-terminal α cassette that targets AKAP15/18 to the membrane

by myristoylation and palmitoylation, while longer AKAP7 isoforms lack this region and are predominantly cytosolic (Fraser et al., 1998; Gray et al., 1998). The γ and δ isoforms are expressed throughout the body, while α isoforms are predominantly expressed in the brain, in key regions that include the hippocampus, cerebellum, cortex, thalamus and striatum (Jones et al., 2012, 2016). Importantly, the α isoform is involved in a number of neuronal physiological processes, and will be the focus of further discussion (Fig. 1D).

In neurons and muscle cells, AKAP15 α can form a complex that contains Ca ν 1.2 LTCCs, PKA and β_2 ARs (Gray et al., 1998; Hulme et al., 2003; Marshall et al., 2011). AKAP15 α binds directly to the Ca ν 1.2 distal C-terminal domain via a modified LZ interaction. Disruption of the formation of this complex *in vivo* by deletion of the distal Ca ν 1.2 C-terminal via a knock-in approach reduced L-type Ca $^{2+}$ currents and disrupted phosphorylation of CREB, which is an important downstream Ca ν 1.2 signaling event involved in E-T coupling (Marshall et al., 2011). However, a complication of this study is that deletion of Ca ν 1.2 distal C-terminus will additionally disrupt association with AKAP79/150, which also interacts with the Ca ν 1.2 C-terminus via a modified LZ interaction (Oliveria et al., 2007; Murphy et al., 2014). Thus decreased LTCC currents and impaired E-T coupling in these Ca ν 1.2 C-terminal truncation knock-in mice may reflect loss of not only AKAP15 but also AKAP79/150 from neuronal LTCC signaling complexes. AKAP15/18 α also forms complexes with brain Na $^{+}$ channels (Tibbs et al., 1998) and promotes phospho-regulation of Na $^{+}$ channels via PKA anchoring (Cantrell et al., 1999) (Fig. 4C). In particular, PKA-mediated phosphorylation of the Na ν 1.2 α subunit downregulates Na $^{+}$ channel activity following activation of dopamine D1 receptors in hippocampal neurons (Cantrell et al., 1999, 2002).

Recently an interesting study found a unique role for AKAP15 α in presynaptic type II PKA anchoring in the hippocampal mossy fiber (MF) projection (Jones et al., 2016). This output projection from the dentate gyrus to the CA3 region is involved in modulation of spatial and contextual pattern separation, an important feature of memory encoding (Aimone et al., 2011; Myers & Scharfman, 2011). Importantly, the MF-CA3 synapse is known to express several forms of pre-synaptic LTP that are dependent on pre-synaptic Ca $^{2+}$ influx and AC-cAMP-PKA signaling (Weisskopf et al., 1994; Wang et al., 2003) (Fig. 4C). In their study, Jones et al. determined that knockout of the mouse *AKAP7* gene results in redistribution of PKA-RII β out of MF axons and terminals, loss of cAMP-induced MF-LTP and specific deficits in behavior including non-cued spatial and contextual pattern recognition (Jones et al., 2016). These findings are particularly interesting as this is the first functional report of a role for pre-synaptic PKA scaffolding by an AKAP.

7. D-AKAP1/AKAP121 (AKAP1)

D-AKAP1 primarily localizes to the outer mitochondrial membrane (OMM), where it scaffolds kinases, phosphatases and other signaling molecules that regulate mitochondrial physiology and health. Multiple splice variants of D-AKAP1 expressed from the *AKAP1* gene exist, with expression in a broad range of tissues including the brain, heart, liver, kidney and skeletal muscle (Merrill & Strack, 2014). All splice variants include a core N-terminal region encoding the PKA binding amphipathic α -helix and a mitochondrial

targeting sequence. The most commonly occurring and best characterized isoform is the full-length D-AKAP1 (AKAP121 mouse; AKAP149 human), which additionally includes a C-terminal RNA binding K homology and Tudor (KH-T) domain (Huang et al., 1999; Taskén & Aandahl, 2004; Merrill & Strack, 2014) (Fig. 1E). A notable function of D-AKAP1 in hippocampal neurons is to anchor PKA to the OMM to coordinate mitochondrial fusion/fission events. These events are essential for regulation of mitochondrial function and can alter a range of processes including mitochondrial transport, ATP generation, Ca^{2+} buffering, and free radical production (Aggarwal-Howarth & Scott, 2017). Mechanistically, D-AKAP1 anchors PKA in close proximity to its substrate, dynamin-related protein 1 (Drp1), which is a dynamin-like GTPase with an integral role in driving mitochondrial fission (Lin et al., 1995; Hoppins et al., 2007; Carlucci et al., 2008). The activity of Drp1 is inhibited by PKA phosphorylation and as such, elevations in cAMP that activate PKA promote mitochondrial elongation, owing to inhibition of fission in the presence of unopposed fusion (Fig. 4D). Mitochondrial elongation can also be promoted by overexpression of D-AKAP1 (Cribbs & Strack, 2007; Dickey & Strack, 2011; Merrill et al., 2011). In contrast, fission is driven by PP2A or CaN, which dephosphorylate Drp1, allowing for the assembly of the mitochondrial fission machinery (Abrenica et al., 2009; Dickey & Strack, 2011). These events are also regulators of mitochondrial membrane potential (ψ_m), with D-AKAP1-PKA-Drp1-driven elongation leading to increased ψ_m (Dickey & Strack, 2011). D-AKAP1-PKA signaling is particularly important during neuronal development, where dendritic outgrowth is coordinated by D-AKAP1-PKA. Overexpression of D-AKAP1 during development leads to enhanced dendritic complexity, without accompanying increases in synapse number (Dickey & Strack, 2011). Thus coordination of cAMP-PKA signaling at the OMM by D-AKAP1 is critical for neuronal health, development, metabolism and physiology.

8. AKAPs in nervous system disorders

Pharmacological interventions that target the selective uncoupling of AKAP-directed signaling pathways could be a way to regulate disrupted signaling with a high degree of specificity. In the following sections, we will discuss the roles that AKAPs are thought to play in neurological disorders and the potential modifications to AKAP signaling complexes that have promise as future drug targets.

Seizures

Epileptic seizures are a result of abnormal neuronal activity, whereby hyperexcitability in a small group of neurons rapidly spreads across large interconnected neuronal networks (Steinlein, 2004). Genetic studies over the last 20 years have revealed that several epileptic phenotypes are a result of voltage gated potassium (K_v) channel dysfunction (Villa & Combi, 2016). For example, mutations in *KCNQ2* and *KCNQ3* genes can give rise to benign familial neonatal epilepsy (Maljevic & Lerche, 2014). As described above, activation of K_v channels dampens neuronal excitability, whereas suppression of K_v current through a number of AKAP79/150-dependent mechanisms leads to enhanced excitability (Fig. 3B). Therefore, disruption of AKAP79/150 signaling may be a mechanism for suppressing pathological increases in neuronal excitability. A key study supporting this notion found that AKAP150 knockout mice were more resistant to seizures induced by peritoneal injection of

the muscarinic agonist pilocarpine (Tunquist et al., 2008). The same study used electrophysiological recordings of SCG neurons from AKAP150 knockout mice to show that this resistance may be due to a partial loss of M-current suppression, most likely due to a disruption of AKAP-PKC inhibition of K_V7 channels (Tunquist et al., 2008).

In order to regulate ion channel function, AKAP79/150 must first be targeted to cell membranes. As described above in Figure 2B, dynamic membrane targeting is achieved by palmitoylation of AKAP79/150, which promotes association with membrane lipid rafts and facilitates AKAP79/150 trafficking through recycling endosomes (Keith et al., 2012).

Interestingly, seizures induced by hippocampal injection of kainate can increase AKAP79/150 palmitoylation (Keith et al., 2012), while the anti-seizure medication valproic acid inhibits palmitoylation of several proteins including AKAP79/150 and also reduces AKAP79/150-dependent K_V7 channel suppression (Kay et al., 2015). These findings indicate that AKAP79/150 targeting may be altered in response to seizures, and disrupting this targeting may contribute to the therapeutic actions of anti-seizure medications such as valproic acid.

Dampening of excitability can also be achieved by increasing the number of K_V7 channels expressed at the plasma membrane by transcriptional regulation. In particular, a study by Zhang & Shapiro found that up-regulation of K_V7.2/3 in SCG neurons is activity-dependent and was achieved through activation of the LTCC-CaN-NFAT pathway described above Figure 3A. Upregulation of these channels in isolated hippocampi was observed following seizure induced by intrapleural injections of either kainate or pilocarpine, suggesting this pathway may constitute a negative feedback mechanism to dampen neuronal excitability following excessive activity. AKAP79/150 was required for signaling through the LTCC-CaN-NFAT pathway and for the upregulation of K_V7.2/3 following induced seizures (Zhang & Shapiro, 2012). These results suggest that complete removal of AKAP79/150 and the transcriptional feedback pathway may be detrimental and may enhance the likelihood of seizure reoccurrence. As such, therapeutic interventions that selectively target AKAP79/150 anchoring of enzymes that suppress M-current (for example PKC; Fig. 3B), while leaving LTCC-AKAP79/150-CaN-NFAT signaling (Fig. 3A) intact may be more effective.

Addiction

Drug addiction is defined as a compulsive drive toward drug-seeking and use, despite serious harmful consequences (Volkow & Li, 2004). A common feature of all addictive drugs is their ability to hijack the mesocorticolimbic dopamine system, the primary brain circuit involved in reward-motivated learning. This circuit is composed of the dopamine-releasing neurons of the ventral tegmental area (VTA) that send projections to the nucleus accumbens (NAc) and the pre-frontal cortex (PFC) (Fig. 5A). The most notable action of all drugs of abuse is to increase release of dopamine from VTA neurons in each of these brain regions. Enhanced dopamine release attenuates synaptic transmission, leading to plastic changes that promote the formation of emotional memories related to drug craving. This drug-evoked synaptic plasticity has many features in common with the hippocampal synaptic plasticity described previously, including phosphorylation-driven alterations in the complement of postsynaptic AMPARs. Furthermore, PKA signaling pathways have been repeatedly

identified as contributors to cocaine-induced neuronal adaptations (Reissner, 2013). It is therefore likely that AKAP signaling complexes may play a role during drug-evoked plasticity in the mesocorticolimbic system. Early indications of AKAP79/150-coordinated alterations in specific forms of VTA and NAc plasticity support this notion. First, AKAP anchoring of PKA (likely mediated by AKAP79/150) has been found to mediate a form of plasticity involving LTD at GABAergic inhibitory synapses within the VTA. Like their glutamatergic counterparts, GABAergic synapses are highly plastic and can undergo LTP (LTP_{GABA}) and LTD (LTD_{GABA}) (Nugent et al., 2007; Dacher et al., 2013). Both processes are suppressed by opioids, indicating that inhibitory synaptic plasticity in the VTA may be an important regulatory mechanism that is disrupted during drug addiction. AKAP79/150 is expressed in VTA dopamine neurons and has been suggested to be localized to GABAergic synapses. Anchoring of PKA by AKAP79/150 is implicated in maintaining basal $GABA_A$ receptor activity and directing LTD_{GABA} that is mediated by dopamine D_2R inhibition of AC and activation of CaN (Dacher et al., 2013) (Fig. 5B). In particular, Dacher et al. found that pharmacologic inhibition of AKAP-PKA anchoring with Ht31 peptide (see below; Fig. 7B) leads to a CaN-mediated depression of $GABA_A$ receptor activity that mimicked and occluded LTD_{GABA} . However, as these mechanisms of GABAR regulation are likely complex and are not yet fully delineated, more work needs to be done before selective targeting of AKAP79/150 to enhance $GABA_A$ receptor activity at these synapses is feasible. Second, AKAP79/150 is also expressed at excitatory synapses on GABAergic medium spiny projection neurons (MSNs) of the NAc, where it has been implicated in the relapse of cocaine-seeking behavior, which is an important feature of addictive pathology following withdrawal (Conrad et al., 2008). To identify synaptic proteins that are altered during cocaine withdrawal, Reissner et al. employed an unbiased proteomic screen of synaptic proteins that are differentially regulated following two weeks of cocaine self-administration and two weeks of extinction training. AKAP79/150 expression was significantly increased in the postsynaptic fraction of NAc neurons, while pharmacologic inhibition of AKAP-PKA anchoring with a cell-permeable stearylated version of the Ht31 peptide (St-Ht31, see below) reduced surface expression of GluA1 cp-AMPA receptors and impaired reinstatement of cocaine-seeking (Reissner et al., 2011) (Fig. 5C). These findings indicate that enhanced AKAP79/150 expression following withdrawal may be linked to increases in synaptic GluA1 and the promotion of cue-induced cocaine-seeking. Disruption of the synaptic localization of AKAP79/150 or PKA anchoring may provide ways to suppress this behavior and reduce the risk of relapse. In summary, plasticity mechanisms at VTA inhibitory synapses and NAc excitatory synapses that are altered by addictive drugs may be augmented by AKAP79/150 scaffolding complexes.

Pain

While nociception and acute pain are important for protecting against harmful environmental stimuli, pathological activation of nociceptive pathways can lead to the development of maladaptive and chronic pain. Triggers for such activation can include infection, inflammation, neuronal injury, chronic diseases, and trauma (Kuner & Flor, 2016). A characteristic of the manifestation of chronic pain is the long-term neuronal sensitization by intrinsic amplification of pain pathways, which can lead to hyperalgesia (increased pain sensitivity) and neuropathic pain (pain resulting from neuronal damage or dysfunction). A

number of ion channels are involved in this sensitization, many of which are regulated by AKAP79/150 signaling complexes. As described above, TRPV1 plays a key role in pain sensation, and as such has garnered attention as a drug target for hyperalgesia. AKAP79/150 assembled complexes can enhance the sensitivity of TRPV1 channels, so disrupting AKAP79/150 signaling may be of therapeutic benefit. A key study found that a cell-permeable peptide that disrupts the interaction between AKAP79/150 and TRPV1 alleviated hyperalgesia in three mouse models (Fischer et al., 2013). Another study found that pain-related behavior following capsaicin injection was substantially reduced in AKAP79/150 knock-out animals (Por et al., 2010). As mentioned above, AKAP-anchored PKA is involved in TRPV1 sensitization in response to inflammatory mediators (Fig. 3C), therefore it may be beneficial to also target the AKAP79/150-PKA interaction for treatment of hyperalgesia (Rathee et al., 2002). In particular, Schnizler et al. showed that either genetic deletion of AKAP150-PKA anchoring in D36 mice or injection St-Ht31 in WT mice could prevent PGE2-mediated thermal hyperalgesia (Schnizler et al., 2008b).

Other AKAP79/150-regulated ion channels that are involved in pain sensitization include β_2 -adrenergic receptors (β_2 -ARs) and $\text{Ca}_v1.2$ calcium channels. AKAP79/150 recruitment of PKA and PKC to β_2 -ARs regulates receptor phosphorylation following agonist stimulation and downstream signaling through the MAP kinase pathway (Fraser et al., 2000). There are early indications that β_2 -ARs may be a target for analgesia, as chronic application of β_2 -AR agonists can alleviate the excessive sensitization of pain pathways that are a feature of neuropathic pain (Yalcin et al., 2010). $\text{Ca}_v1.2$ is upregulated in the spinal dorsal horn during development of neuropathic pain and inhibiting $\text{Ca}_v1.2$ expression with micro-RNAs can relieve pain in neuropathic animal models (Favereaux et al., 2011). While direct evidence for $\text{Ca}_v1.2$ -AKAP79/150 signaling in pain is still lacking, the central role that AKAP79/150 plays in regulating $\text{Ca}_v1.2$ in hippocampal neurons described in Figure 3A further makes targeting AKAP79/150-PKA anchoring in sensory neurons an interesting prospect.

Neurodegenerative Diseases

Over the course of the last century, advances in modern medicine, nutrition and public health have greatly extended the average human lifespan. This has led to a concurrent increase in the incidence of age-related neurodegenerative diseases, which present a substantial societal and economic burden. Many of these diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), share common features, most notably a progressive loss of certain neuronal populations, leading to cognitive decline, disability, and eventual death. Prior to neurodegeneration, both diseases manifest characteristic deficits in synaptic function within the affected brain regions. To date, surprisingly few studies have directly investigated a role for disrupted AKAP signaling in AD- and PD-related synaptic dysfunction. Here we will discuss several AKAP-dependent signaling pathways that are known to be altered in neurodegenerative diseases and highlight the need for future studies to determine if AKAP targeting will be beneficial in these disorders.

Alzheimer's Disease—AD is the most common age-related neurodegenerative disorder, currently affecting around 50 million people globally (Prince et al., 2016). Patients with AD

present clinically with deficits in memory and cognition, while post-mortem examination of AD brains reveals two hallmark neurological lesions; neurofibrillary tangles and amyloid plaques (Sisodia & St George-Hyslop, 2002; Ittner & Götz, 2011). Neurofibrillary tangles are a result of hyperphosphorylation of the microtubule-associated protein tau, while amyloid plaques are composed of aggregates of a toxic peptide that is proteolytically cleaved from the amyloid precursor protein (APP) by γ - and β -secretase. The overproduction of this APP cleavage product, known as A β 1–42 (A β), leads to the formation of highly toxic, soluble A β oligomers, prior to the appearance of amyloid plaques. In the early stages of AD, the toxic effects of A β are thought to be manifested at the synapse, whereby acute exposure to A β oligomers can strongly suppress synaptic function while more prolonged exposure leads to eventual synapse elimination. These events take place in the hippocampus and cortex, giving rise to many of the memory deficits that characterize the disease.

Animal models of AD show both profound alterations in LTP and LTD at hippocampal synapses (Chapman et al., 1999; Oddo et al., 2003; Hsieh et al., 2006; Shankar et al., 2007, 2008; Knobloch & Mansuy, 2008; Chakroborty et al., 2012) and substantial deficits in hippocampal learning and memory tasks (Chapman et al., 1999; Oddo et al., 2003). A large number of neuronal receptors and intracellular effectors have been proposed to mediate the toxic effects of A β , including several known AKAP-regulated proteins. Notably, accumulating evidence suggests that enhanced NMDAR-dependent activation of CaN may lead to imbalance in a number of pathways that regulate synaptic function. For example, CaN is known to drive the dephosphorylation and synaptic removal of cp-AMPA receptors during LTD (Sanderson et al., 2012, 2016). Interestingly, brief incubations in A β can also promote CaN-dependent GluA1 internalization while inhibitors of CaN can prevent spine morphological changes, GluA1 internalization and effectively improve memory function in transgenic AD mouse models (Dineley et al., 2007; Wu et al., 2012). As discussed above, these actions of CaN on cp-AMPA receptors during LTD are known to be coordinated by AKAP79/150 (Sanderson et al., 2012, 2016) (Fig. 2A). Studies are now needed to determine if disruption of AKAP79/150-CaN signaling can restore synaptic function after exposure to A β .

The CaN-NFAT pathway has also been implicated in synaptic dysfunction in AD, whereby A β -induced spine loss can be mimicked by constitutively active NFATc4 and inhibited by peptide inhibitors of CaN that are known to disrupt the CaN-NFAT interaction (Wu et al., 2010, 2012; Hudry et al., 2012). Thus, there is a potential link between A β -driven NFAT-dependent gene transcription and synapse elimination. While the upstream activators of CaN that lead to enhanced NFAT signaling following A β toxicity have not yet been identified, it is possible that CaN scaffolded within AKAP79/150 signaling complexes may play a role. As described in Figure 3A, depolarization-driven activation of the LTCC-CaN-NFAT pathway critically depends on AKAP79/150 scaffolding of CaN to the LTCC. While global CaN antagonists such as Cyclosporin A and FK506 can provide symptomatic improvement in AD models, they also have widespread side effects including cardiovascular complications, chronic pain, renal toxicity and impaired blood glucose regulation (Tedesco & Haragsim, 2012). Future studies are warranted to determine if the AKAP79/150-CaN interaction is a viable target for therapeutic intervention in AD to more selectively limit both NFAT-driven spine loss and dysfunctional regulation of cp-AMPA receptors.

Disruption of PKA signaling has also been implicated in AD synaptic dysfunction. Several studies have found that enhancement of cAMP/PKA signaling with either the phosphodiesterase inhibitor rolipram or β_2 AR stimulation can prevent A β -induced deficits in LTP and improve synaptic and cognitive functions in AD rodent models (Vitolo et al., 2002; Gong et al., 2004; Wang et al., 2009). Furthermore, an enriched environment has been shown to protect against hippocampal impairment induced by A β oligomers by stimulating β_2 AR activity and enhancing phosphorylation of GluA1 at Ser-845 (Li et al., 2013*b*). However, the effects of A β on GluA1 containing AMPARs are complex, as another study found that Ser-845 phosphorylation and synaptic insertion of cp-AMPA receptors were enhanced following intracellular application of A β , which together might act as catalyst for the onset of pathological synaptic changes (Whitcomb et al., 2015). The role that AKAP79/150 plays in coordinating PKA-dependent insertion of GluA1 during LTD is now well characterized (Fig. 2A) and if enhanced insertion of GluA1 occurs during A β pathology, targeted uncoupling of PKA from AKAP79/150 may instead be beneficial (Sanderson et al., 2016). More selective therapies directed at the AKAP79/150 signaling complex will likely have fewer side effects than global modulators of cAMP-PKA signaling, which have pronounced effects in the cardiovascular system (Rockman et al., 2002; Bender & Beavo, 2006). In summary, while direct evidence is not yet available for AKAP79/150 involvement in AD pathology, it is well established that signaling through numerous AKAP79/150 scaffolded receptors and effectors is altered in the disease, highlighting a clear need for progress in determining if there is a role for AKAP-coordinated pathways in AD.

Parkinson's Disease—PD is an age-related, neurodegenerative disorder that most notably affects a motor circuit within the brain known as the basal ganglia (Redgrave et al., 2010). One of the defining features of PD is the degeneration of midbrain dopamine neurons within the substantia nigra pars compacta (SNc) that innervate the dorsal striatum, leading to a profound disruption in the balance of striatal outputs through the basal ganglia direct and indirect pathways. Dysfunctional activity of striatal MSN projection neurons (SPNs) as a result of a reduction in striatal dopamine release underlies many of the motor symptoms that are highly debilitating for patients with PD (Obeso et al., 2008). Dopamine release at SNc-SPN synapses can activate dopamine D₁ receptors (D₁Rs) to modulate striatal output, in part by activating PKA signaling pathways that modulate SPN excitability, NMDAR phosphorylation and the postsynaptic targeting of AMPARs (Snyder et al., 1998; Parisiadou et al., 2014; Nagai et al., 2016). The importance of PKA in signaling at these synapses raises the possibility that AKAPs may be involved in PD-related synaptic dysfunction.

A recent study by Parisiadou et al. found that leucine-rich repeat kinase 2 (LRRK2), which is encoded by the *PARK8* gene that is commonly mutated in genetic forms of PD, is enriched in a subset of SPNs and has PKA-RII β subunit-binding AKAP-like properties (Cookson, 2010; Parisiadou et al., 2014) (Fig. 1F). LRRK2 was found to confine PKA to dendritic shafts of SPNs in a manner comparable to the shaft-localized AKAP activity of MAP2 in hippocampal and cortical neurons, which is in contrast to the spine-enriched anchoring activity of AKAP79/150 (Smith et al., 2006; Zhong et al., 2009; Murphy et al., 2014). Shaft retention of PKA by LRRK2 in SPNs limits phosphorylation of GluA1 and the actin-disassembling enzyme cofilin, which are both elevated by knockout of LRRK2 (Fig.

6A). Knockout of LRRK2 also led to impaired synaptogenesis and altered synaptic transmission in developing SPNs, and enhanced GluA1 phosphorylation following activation of dopamine D₁Rs in older mice. Importantly, a known PD mutation (R1441C) within the PKA binding region of LRRK2 disrupted RII β binding and produced a similar phenotype to that seen in knockout animals, indicating that a loss of LRRK2-AKAP activity and subcellular targeting of PKA may underlie synaptic dysfunction associated with this mutation (Parisiadou et al., 2014). It is possible that any PKA that translocates from shaft to spine when LRRK2 anchoring is disrupted may associate with spine localized AKAPs such as AKAP79/150. This association could in turn facilitate pathological elevations in GluA1 and cofilin phosphorylation.

Autism Spectrum Disorders

Autism Spectrum Disorders (ASDs) are a group of early onset neurodevelopmental disorders with a broad spectrum of clinical presentations including sustained impairments in social interaction, repetitive patterns of behavior, and deficits in language and development (Kanner, 1968; Bourgeron, 2015). There is an interest in synaptic dysfunction in ASDs owing to the number of ASD genetic factors that are involved in activity-dependent signaling to regulate synaptic plasticity and development (Ebert & Greenberg, 2013). For example, a number of ion channels, receptors and synaptic adhesion molecules are encoded by ASD risk genes, such as LTCC (Ca_v1.2; *CACNA1C* gene), NMDAR (GluN2B; *GRIN2B* gene), GABAR (α 3; *GABRA1* gene and β 3; *GABRB3* gene) subunits, and neuroligins and neuroligins (Bourgeron, 2015). A well-studied mutation in Ca_v1.2 (G406R) gives rise to Timothy Syndrome (TS), an ASD that is also associated with severe cardiac symptoms including action potential prolongation and life-threatening arrhythmia (Splawski et al., 2004). Many studies in heterologous cells and cardiomyocytes have found that G406R leads to LTCC gain-of-function due to impaired calcium- and voltage-dependent inactivation (Barrett & Tsien, 2008; Dick et al., 2016; Li et al., 2016). At present, it is not clear how the G406R mutation might alter synaptic development and function in the nervous system. As described above, neuronal LTCCs are engaged during a number processes that are essential for synaptic function, and their activity is tightly regulated by AKAP79/150-coordinated phosphorylation events (Fig. 3A). However, AKAP79/150 regulation of G406R-LTCCs in the brain has not yet been investigated. Interestingly, knockout of AKAP150 in ventricular myocytes of G406R-LTCC mice prevented a number of TS dysfunctional phenotypes, including increased activation and reduced inactivation of Ca²⁺ current and abnormalities in cardiac AP waveform and rhythm (Cheng et al., 2011; Dixon et al., 2012). These findings highlight the need for investigation of the effects of neuronal TS-LTCC gain-of-function mutations on synaptic properties and E-T coupling, and the role that AKAP79/150 may play in coordinating these processes.

Also among the risk genes that have been linked to ASD is the multi-domain scaffolding AKAP neurobeachin (Nbea; *NBEA* gene) (Fig. 1G) (Smith et al., 2002; Castermans et al., 2003). Nbea knockout animals do not survive post-birth due to lethal paralysis caused by a failure of presynaptic-evoked release at the neuromuscular junction (Su et al., 2004). Loss of a single copy of the gene leads to an ASD phenotype. As mentioned earlier, ASD is thought to be associated with defects in synaptic development and function (Ebert & Greenberg,

2013; Won et al., 2013; Bourgeron, 2015). Nbea primarily localizes to endomembranes associated with the trans-golgi network, where it can modify synaptic architecture by coordinating the trafficking of essential postsynaptic cargos such as actin and synaptopodin (Wang et al., 2000; Niesmann et al., 2011; Nair et al., 2013). Additionally, Nbea regulates synaptic trafficking of neurotransmitter receptors including NMDA, kainate and GABA receptors (Nair et al., 2013). The function of PKA anchoring by Nbea is not yet fully understood, however it has been found that a loss of PKA anchoring (Nbea^{-/-} PKA) is associated with reduced surface expression of GABARs (Farzana et al., 2016). Furthermore, in non-neuronal cells, phosphorylation of PKA plasticity-related substrates including CREB and Calpain-2 is enhanced in the absence of Nbea (Nuytens et al., 2013a, 2013b). Future studies may reveal the substrates targeted by Nbea-anchored PKA within the endomembrane compartments and delineate their potential role in synaptic dysfunction related to ASD.

Mitochondrial dysfunction and cell death

Mitochondria are essential for energy production, generating large amounts of ATP via oxidative phosphorylation, without which cells cannot function or survive. They also perform critical functions such as Ca²⁺ buffering and free radical metabolism, which maintain cellular health. Mitochondrial dysfunction has been identified as a pathogenic process in many of the most prevalent neurodegenerative and neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease and schizophrenia (Knott et al., 2008; Manji et al., 2012). Mitochondria are highly dynamic, and can translocate in axons and dendrites to regions of high metabolic demand. Furthermore, damaged mitochondria can be repaired by undergoing fusion or fission to introduce the contents of healthy mitochondria or remove irreparably damaged mitochondrial components, respectively (Sheng & Cai, 2012). Mutations in a number of the proteins that coordinate fission and fusion, including protein phosphatase 2 (PP2A), lead to neurological disorders (Holmes et al., 1999; Delettre et al., 2000; Züchner et al., 2004; Waterham et al., 2007). As described above, mitochondrial fission/fusion events in hippocampal neurons are coordinated by D-AKAP1-PKA and PP2A/CaN bidirectional regulation of Ser-656 phosphorylation of Drp1 (Fig. 4D). Several studies have demonstrated that disruption of D-AKAP1-PKA signaling can lead to cell death. Knock down of D-AKAP1 in hippocampal neurons promotes mitochondrial fragmentation and apoptosis while overexpression of D-AKAP1, but not a PKA binding deficient D-AKAP1 (D-AKAP1^{-PKA}), protects neurons against cell death (Dickey & Strack, 2011; Merrill et al., 2011). Furthermore, conditional D-AKAP1 expression in neuronal PC12 cells can stimulate PKA-dependent inhibitory phosphorylation of pro-apoptotic protein BAD at Ser-155, preventing apoptosis by inhibiting cytochrome c release from the mitochondria (Affaitati et al., 2003). D-AKAP1 also binds to the Na⁺/Ca²⁺ exchanger NCX3 in the OMM where it facilitates efflux of mitochondrial Ca²⁺ in a PKA-dependent manner, improving cell survival under hypoxic conditions (Scorziello et al., 2013).

A number of Parkinson's disease risk factor genes regulate mitochondrial fission/fusion dynamics, including PTEN-induced kinase 1 (PINK1), which is a mitochondria localized serine/threonine kinase (Poole et al., 2008; Yang et al., 2008). In a Parkinson's disease cellular model that has reduced expression of endogenous PINK1, overexpression of D-

AKAP1 was able to prevent mitochondrial dysfunction associated with loss of PINK1, including mitochondrial fragmentation, induction of macroautophagy, increased superoxide production and low level ongoing cell death (Dagda et al., 2011). Furthermore, a recent study found that in dendrites of PINK1-deficient cortical neurons, expression of D-AKAP1 was able to compensate for deficits in mitochondrial trafficking, content and morphology that are a result of an absence of PINK1 (Das Banerjee et al., 2017). These studies highlight the neuroprotective role of D-AKAP1-PKA signaling in models of cell death and neurodegenerative disease.

Axonal degeneration in the Retina

Axons within the adult central nervous system (CNS) are unable to regenerate following traumatic or ischemic injury, leading to long-term disability with limited treatment options. Unlike their CNS counterparts, neurons within the peripheral nervous system (PNS) have the capacity for regeneration (Bradke et al., 2012). Multiple disabilities can arise from CNS degeneration and the development of effective treatments depends upon an understanding of the molecular mechanisms that underpin neuronal regeneration. It has been long understood that a lack of adequate trophic signaling contributes to the failure of CNS neuronal regeneration (Goldberg & Barres, 2000; Keefe et al., 2017). Blindness is one such disability that can occur as a result of degeneration of retinal ganglion cells (RGCs) that project axons from the retina through the optic nerve. Interestingly, RGC death can be delayed by application of neurotrophic factors including brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF) and fibroblast growth factor (FGF) (Unoki & LaVail, 1994; Mo et al., 2002; Wang et al., 2013). Furthermore, electrical activity and elevations in cAMP can potentiate trophic signaling, providing further neuroprotection (Goldberg et al., 2002; Corredor et al., 2012). These protective effects are lost following inhibition of PKA, opening the possibility that AKAP scaffolding may be involved (Goldberg et al., 2002). Indeed, a study has found that muscle AKAP (mAKAP; *AKAP6* gene; Fig. 1H) is involved in the coordination of stress-specific signaling and axon growth in RGCs (Wang et al., 2015a). mAKAP contains three spectrin repeats, the third of which directs localization to the outer nuclear membrane (ONM) through an interaction with ONM protein nesprin-1 α (Pare et al., 2005b). Two splice variants of mAKAP exist (α and β) that are expressed in a tissue specific manner (Kapiloff et al., 1999; Carlisle Michel et al., 2005; Pare et al., 2005b). In cardiomyocytes, mAKAP β assembles signaling complexes through direct binding of PKA, p90 ribosomal S6 kinase 3 (RSK3), and phosphodiesterase 4D3 (PDE4D3), while Epac and ERK5 are anchored to AKAP indirectly through binding to PDE4D3 (Dodge-Kafka et al., 2005; Li et al., 2013a). The larger splice variant mAKAP α is preferentially expressed in the brain and contains an additional anchoring site for 3-phosphoinositide-dependent kinase-1 (PDK1) (Fig. 1H) (Carlisle Michel et al., 2005).

Importantly, a recent study by Wang et al. found that mAKAP α is expressed in RGCs and is required for transduction of pro-survival signaling induced by cAMP, BDNF and CNTF. The report found that following knockout of mAKAP α , trophic signaling was unable to promote survival after optic nerve injury (Wang et al., 2015a). While the precise mechanisms for mAKAP α -directed neuroprotective signaling are not yet clear, it is likely that the scaffold

facilitates crosstalk between cAMP and MAPK pathways (Goldberg et al., 2002). mAKAP α -anchored PKA and PP2A enhance and inhibit PDE4D3 activity respectively (Carlisle Michel et al., 2004; Dodge-Kafka et al., 2010). As such, mAKAP can control the local concentration of cAMP at the ONM. Furthermore, ERK5 binds to mAKAP α indirectly through association with PDE4D3 (Fig. 6B) (Dodge-Kafka et al., 2005). While further studies are required to determine the precise mechanisms of cross-talk between these pathways, it is clear that mAKAP α signaling is central to the protective effects of neurotrophins following RGC damage. An enhanced understanding of these processes may pave the way for development of neuroprotective interventions following neuronal injury and degeneration.

9. Potential for therapeutic targeting of AKAP signaling complexes

In this review we have discussed the emerging role of AKAP signaling complexes in a number of nervous system disorders, many of which may result from aberrant activity of PKA and/or CaN. Disrupting AKAP79/150 anchoring of PKA may hold potential for treating disorders including AD associated with AMPAR regulation (Fig. 2A), Timothy Syndrome associated with LTCC regulation (Fig. 3A), and hyperalgesia associated with TRPV1 regulation (Fig. 3C). Conversely, enhancing AKAP-PKA signaling through D-AKAP1 mitochondrial signaling pathways may be neuroprotective (Fig. 4D). Targeted disruption of AKAP79/150-anchored CaN may be beneficial in AD pathology to correct disrupted AMPAR regulation (Fig. 2A) and NFAT signaling (Fig. 3A), while enhancing AKAP79/150-CaN-NFAT signaling to increase K_v7 channel expression following seizures might reduce the risk of seizure reoccurrence (Fig. 3A). Given the promiscuous nature of protein kinases and phosphatases and their abundance in numerous systems within the body, pharmacological targeting of these enzymes often leads to side effects that outweigh therapeutic gain.

Targeting the localization of these enzymes by disrupting AKAP signaling complexes holds great promise as a means to modify pathological signaling. In particular, uncoupling of AKAP signaling components may be advantageous as it allows for disruption within spatially restricted nanodomains. It is estimated that each cell-type contains around 15 different AKAPs, with differing subcellular loci and function (Kennedy & Scott, 2015). Therefore, a major goal of future research is to develop agents that selectively target protein-protein interactions (PPIs) between specific AKAP isoforms and their binding partners. There are three classes of molecules that are currently utilized to disrupt AKAP-PPIs: peptides, peptidomimetics and small molecule inhibitors. At present, the majority of available agents non-discriminately target common binding motifs to disrupt the PPI between AKAPs and kinases or phosphatases, while agents that can enhance AKAP PPIs are lacking. Below we will discuss the current availability of these modulators and their potential to therapeutically modify AKAP signalosomes.

Targeting the AKAP-PKA interface

The defining feature of an AKAP is its ability to anchor PKA (Fig. 7A). As such, the interface between the AKAP amphipathic α -helix and the R subunit four helix bundle is the

best studied AKAP PPI and the foremost target for development of compounds designed to disrupt AKAP signaling.

PKA targeted peptides—Short peptide sequences are well suited for disruption of PPIs. They have an extended surface area that can bind to large, geometrically diverse interaction sites that are characteristic of PPIs. Furthermore, methods for peptide design, evaluation and optimization are well established. The first tool developed to disrupt RII-AKAP binding was a 24 amino acid peptide known as Ht31, derived from the PKA binding domain of AKAP-Lbc (Carr et al., 1992a) (Fig. 7B). Ht31 binds to all R subunit isoforms of PKA albeit with higher affinity for RII, and has been employed as a non-selective blocker of all AKAP-PKA interactions. Lipid modification by addition of a stearic acid group to Ht31 (St-Ht31) increases membrane permeability and has improved the utility of this peptide. As such, it has been used in research for many years to elucidate the importance of AKAPs in a range of biological processes. Subsequent developments have led to the generation of more selective peptides with higher affinity for either RI and RII subunits. In particular, RIAD has a 1000-fold higher affinity for RI, whereas superAKAP-*IS* has a >10,000 fold higher affinity for RII (Gold et al., 2006; Carlson et al., 2006) (Fig. 7B). Although peptides that disrupt AKAP-PKA interactions have been a useful tool to study AKAP function in the nervous system, their lack of stability within the cell and the potential for membrane retention of steared peptides (e.g. St-Ht31) limit their therapeutic utility (Kennedy & Scott, 2015).

PKA targeted peptidomimetics—Efforts have been made to enhance peptide stability and permeability, leading to the development of peptidomimetics. These are a novel class of inhibitors that are chemically modified by hydrocarbon ‘staples’ along the peptide backbone, formed by introduction of non-natural amino acids into the peptide sequence which are then chemically cross-linked (Wang et al., 2014). The result is a peptide with a conformationally constrained α -helical structure known as a Stapled Anchoring Disruptor (STAD) (Fig. 7B). Importantly, these peptidomimetics have greatly improved membrane permeability and intracellular stability (Verdine & Hilinski, 2012; Kennedy & Scott, 2015; Hanold et al., 2017). Isoform selective STADs have been successfully developed to target the AKAP binding pocket on both the RI- and RII-subunit D/D domain (Wang et al., 2014, 2015b).

AKAP targeted peptides—The ultimate goal for disrupting AKAP-PKA complexes is to create stable inhibitors that are able to selectively distinguish the amphipathic helix of different AKAPs. To achieve this, inhibitors must be able to differentiate the unique structural features of each AKAP helix (Nygren & Scott, 2015). The AKAP helix consists of a series of conserved hydrophobic residues that act as critical anchor points involved in the recognition of PKA R-subunits (Gold et al., 2006; Kinderman et al., 2006; Götz et al., 2016). The helix also includes a number of non-conserved residues, which introduce a degree of variation to each AKAP helix that can be exploited when developing inhibitors. One study produced a series of RII-D/D domain derived proteins, with substitutions in the RII residues that are known to interact with the AKAP amphipathic α -helix. The result of this engineering was the generation of several selective R-subunit (R_{select}) proteins that showed preference for different AKAPs (Gold et al., 2013) (Fig. 7C). While the utility of these

proteins is currently limited, this approach is likely to help guide future design of AKAP targeted compounds.

Small molecule inhibitors—Therapeutically, the use of small molecule inhibitors has many advantages over larger peptide molecules. These include a higher oral bioavailability, enhanced intracellular stability and a low cost of synthesis. However, additional challenges must be considered when designing small molecules targeted to PPIs, which generally have a large, discontinuous surface area with interactions occurring at multiple key residues (Calejo & Taskén, 2015). The first small molecule inhibitor of PKA to be introduced was FMP-API-1, which binds to a site outside of the D/D domain, allosterically inhibiting the AKAP-PKA interaction (Christian et al., 2011) (Fig. 7B). The molecule was derived from high-throughput screening and was found to disrupt binding of both RI or RII to AKAP188, although the mechanism has yet to be fully described. The allosteric effects also promoted activation of PKA, perhaps through an interaction with the auto-inhibitory domain. Therefore, further optimization of the compound will be beneficial (Christian et al., 2011; Tröger et al., 2012). For a more comprehensive list of AKAP-PKA interface targeted molecules see (Tröger et al., 2012).

Targeting the AKAP-CaN interface

CaN is a heterodimeric Ca^{2+} -dependent Ser/Thr phosphatase assembled from a catalytic (CaNA) and regulatory (CaNB) subunit (Klee et al., 1979; Stewart et al., 1982). Activation of CaN follows direct binding of Ca^{2+} ions to the CaNB subunit and subsequent binding of Ca^{2+} -CaM to the CaNA subunit. The result is a displacement of the CaNA auto-inhibitory region from the catalytic domain (Yang & Klee, 2000; Shen et al., 2008; Li et al., 2011). Two consensus motifs (LxVP and PxIxIT) have been identified in a number of CaNA interacting proteins. Of particular relevance to this review is the PxIxIT motif, which is found in AKAP79/150 (PIAIIIT; AKAP79) and constitutes the primary anchoring domain that binds CaN (Li et al., 2012). Structurally, the PxIxIT motif forms a β -strand that is added to the edge of a β -sheet in the CaNA subunit (Li et al., 2007) (Fig. 7D). The affinity of this interaction allows for dynamic anchoring and release of CaN that is necessary for its function. Mutations in PIAIIIT of AKAP79/150 that either reduce or enhance CaN binding affinity can disrupt downstream signaling through effectors, including the transcription factor NFAT (Li et al., 2012).

CaN targeted peptides—The first peptide to be developed to target CaNA-PxIxIT interaction was the high affinity PVIVIT peptide derived from CaNA docking motifs on NFAT (Fig. 7E). PVIVIT binds within the PxIxIT binding pocket of CaNA without affecting phosphatase activity (Aramburu et al., 1999). The peptide has been used extensively to disrupt CaN-dependent NFAT nuclear signaling, but is also known to disrupt AKAP79/150 anchoring of CaN and presumably interactions with all proteins that bind CaN through a PxIxIT motif (Oliveria et al., 2007; Schwartz et al., 2009; Hudry et al., 2012). Thus these peptides face the same limitations as those that target the PKA R-subunit D/D domain, in both their lack of specificity and cellular stability.

CaN targeted small molecules—Small molecule inhibitors have been developed that interact with Cys-266 of CaNA at a site around 15 Å from the PxIxIT binding pocket and disrupt interactions with PVIVIT and NFAT via an allosteric mechanism (Fig. 7E). These molecules are known as inhibitors of NFAT-calcineurin association (INCAs) and are able to effectively disrupt NFAT signaling in cells (Kang et al., 2005). However, it is not clear if INCAs also disrupt CaN interactions with AKAP79/150. More recently, a large small molecule screen identified four compounds that act as inhibitors of the CaN-PxIxIT interaction. These compounds mimicked the PxIxIT motif and competed with CaN for NFAT binding (Fig. 7E). Additionally, they prevented NFAT-dependent gene expression in cells and did not inhibit CaN catalytic activity (Matsoukas et al., 2015). The aim of the development of these drugs was to disrupt NFAT signaling in the immune system, with potential for use as an immunosuppressive treatment. However, it remains to be seen if these compounds are able to disrupt AKAP79/150-CaN interactions, particularly in neurons. More significant advances will be made when compounds or peptides are developed to target specific PxIxIT motifs within different CaN interacting proteins such as AKAP79/150, perhaps by also targeting the interactions non-conserved flanking residues with CaNA that modulate the overall affinity, rather than only targeting the conserved core PxIxIT docking interaction.

Targeting the AKAP-PP1 interface

PP1 is a Ser/Thr phosphatase composed of a catalytic subunit encoded by three different genes and two splice variants (PP1 α ; PP1 β / δ ; PP1 γ_1 and PP1 γ_2) (Peti et al., 2013). PP1 is under the control of over 200 interacting proteins with varying tissue-specific distribution and influence on PP1 activity (Cohen, 2002). Primarily, interacting proteins are known to inhibit PP1 catalytic activity or direct its subcellular targeting (Roy & Cyert, 2009). Most of these interacting proteins contain a version of the consensus motif (K/R)(V/I)x(F/W), commonly abbreviated as RVxF. This motif forms a β -strand that is added to a β -sheet within a hydrophobic pocket of PP1, in a region distinct from the active site (Fig. 7F) (Morishita et al., 2001; Peti et al., 2013). The mechanism of PP1 anchoring via the RVxF motif (Fig. 7F) is structurally analogous to CaN anchoring to the evolutionarily related PxIxIT motif (Fig. 7D). RxVF motifs (or related basic residue containing motifs) are present in both of the PP1-anchoring AKAPs discussed in this review (D-AKAP1 and yotiao), and provide potential target sites for disruption of AKAP-PP1 anchoring and subcellular targeting (Westphal et al., 1999; Piggott et al., 2008; Rogne et al., 2009). A variety of peptides have been developed from the RVxF sequences of a number of PP1 interacting proteins. For example, the association between yotiao and PP1 was disrupted by an RVxF peptide derived from the glycogen-binding subunit of PP1 from striated muscle (G_M, sequence GRRVSEADNFGFN), although an identified RVxF motif within yotiao itself was found to be non-essential for PP1 binding (Johnson et al., 1996; Westphal et al., 1999).

Interestingly, the crystal structure of PP1 bound to G_M peptide demonstrated little change in PP1 conformation, suggesting that RVxF primarily functions as an anchoring motif (Egloff et al., 1997), as was also later shown in structure of PxIxIT docking to CaN/PP2B (Li et al., 2007; Li et al., 2012). RVxF motifs have been identified in D-AKAP1 in both the N-terminal and the KH domain, the latter of which is thought to be the primary site of PP1 interaction

(Fig. 1E) (Küntziger et al., 2006; Rogne et al., 2009). Peptides have been derived from the N-terminal sequence of D-AKAP1 (PLECPLSSPKGVLFSSKSAEVC) and bind to PP1 in a manner that is disrupted by phosphorylation of serine residues adjacent to the motif (Küntziger et al., 2006). However, studies seeking to develop peptides or peptidomimetics for the therapeutic targeting of PP1 anchoring to AKAPs are currently lacking. Furthermore, there are currently no available small molecule compounds that selectively target AKAP-PP1 interactions, although some efforts have been made to develop small molecule inhibitors of other PP1 interacting proteins as a means to disrupt PP1 activity with a higher degree of specificity (Tsytler et al., 2011).

10. Conclusions

In recent years, novel drug targets have been sought to modify pathologically active signaling pathways with subcellular precision. The goal of this approach is to develop compounds that have fewer off-target effects than those that are designed to interact with broadly expressed signaling molecules such as kinases, phosphatases, ion channels and receptors. AKAPs in the nervous system co-localize signaling factors within nanodomain compartments to coordinate a range of critical processes that are known to be perturbed in neurological and neuropsychiatric disorders. As such, an appreciation of the potential for therapeutic targeting of AKAP signaling complexes has gained momentum in recent years. We have discussed in this review the role of AKAPs in a number of neuronal functions including synaptic plasticity, excitation-transcription coupling, control of neuronal excitability, transduction of sensory information and neuroprotection. Associated with many of these functions are neurological and neuropsychiatric disorders that may be directly a result of AKAP dysfunction or have the potential to be alleviated by modification of AKAP interactions. However, more proof-of-principle studies using genetic manipulations (i.e. knockout, knock-in, RNAi approaches) to disrupt AKAP signaling functions in animal disease models are definitely needed to further validate AKAPs as viable therapeutic targets in nervous system disorders. Of the nervous system disorders discussed in the review, AD, PD, chronic pain and drug addiction most clearly warrant future research, based on progress so far implicating AKAPs and/or their binding partners in underlying signaling dysfunction.

A major goal of AKAP-centered drug discovery, and perhaps the largest hurdle to progress, will be the development of stable drugs that can target complex PPIs between individual AKAPs and their binding partners with high selectivity. While concerted efforts have been made to generate peptides and small molecules that have been used to understand the role of AKAP-anchored enzymes in neuronal physiology and disease, at present their therapeutic utility is limited. As our understanding of the role of AKAPs in nervous system disorders progresses, it is likely that so too will the development of pharmacological agents that can be used clinically to target AKAP interactions.

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constraints, we had to limit the number of citations and focus our review on specific topics and examples from the literature.

List of Abbreviation

AC	adenylyl cyclase
AD	Alzheimer's Disease
AKAP	A-kinase anchoring protein
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ASD	Autism Spectrum Disorder
β-AR	β -adrenergic receptor
CaM	calmodulin
cAMP	cyclic adenosine monophosphate
CaN	calcineurin
CNS	central nervous system
cp-AMPA	calcium-permeable AMPAR
DAG	diacylglycerol
DRG	dorsal root ganglia
Drp1	dynammin-related protein 1
E-T	excitation-transcription
GPCR	G-protein coupled receptor
IP₃R	inositol trisphosphate receptor
LTCC	L-type calcium channel
LTD	long-term depression
LTP	long-term potentiation
LZ	leucine zipper
MAGUK	membrane-associated guanylate kinase
MF	mossy fiber
NAc	nucleus accumbens
Nbea	neurobeachin
NFAT	nuclear factor of activated T-cells

NMDAR	<i>N</i> -methyl-D-aspartate receptor
PD	Parkinson's Disease
PINK1	PTEN-induced kinase 1
PIP₂	phosphatidylinositol 4,5-bisphosphate
PKA	cAMP-dependent protein kinase A
PKC	protein kinase C
PP1	protein phosphatase 1
PP2A	protein phosphatase 2
PPI	protein-protein interaction
PSD-95	postsynaptic density protein 95
SCG	superior cervical ganglia
SPN	striatal projection neurons
TRPV1	transient receptor potential vanilloid 1
VTa	ventral tegmental area;

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Figure 1. Schematic diagrams of AKAPs discussed in this review

A. AKAP79 (human isoform) anchors PKA, CaN, AC and PKC. Interactions with ion channels occur at the LZ domain and MAGUK binding domain. Membrane targeting is directed by three polybasic domains A, B and C and palmitoylation at Cys-36 and Cys-129. CaM interacts with the three polybasic domains. See main text for references. **B.** Gravin (human isoform) anchors PKA and PKC (Nauert et al., 1997) and interacts with PDE4 through an unmapped binding site (Willoughby et al., 2006). Membrane targeting is directed by three N-terminal polybasic domains (PB1, 2 and 3) and myristoylation of Gly-1 (Tao et al., 2006; Yan et al., 2009). CaM binds to PB1, 2 and 3, in addition to a fourth CaM binding site designated CB4 (Tao et al., 2006; Schott & Grove, 2013). The central portion of gravin (556–938) associates with the β 2-AR (Tao et al., 2003). **C.** Yotiao anchors PKA, PP1 (Westphal et al., 1999) and AC2 (Piggott et al., 2008). Two LZ motifs and seven leucine/isoleucine zipper (LIZ) motifs regulate interactions with ion channels and IP₃R (Tu et al., 2004). GluN1 binds between the AC2 and PP1 binding sites (970–1241) (Lin et al., 1998). **D.** AKAP15/18 (α isoform shown) binds PKA (Fraser et al., 1998) and several ion channels through an LZ motif (Cantrell et al., 1999, 2002; Hulme et al., 2002; Marshall et al., 2011). Membrane targeting is directed by myristoylation and palmitoylation of the N-terminus (Fraser et al., 1998). **E.** D-AKAP1 anchors PKA (Chen et al., 1997) and PP1 at two binding sites, with the primary PP1 binding site being located toward the C-terminus (Steen et al., 2000; Rogne et al., 2009). The extreme N-terminus contains a mitochondrial targeting domain (Huang et al., 1999). D-AKAP1 is thought to bind mRNAs encoding mitochondrial proteins via the KH and Tudor (KH-T) domains (Ginsberg et al., 2003; Rogne et al., 2006, 2009). See (Merrill & Strack, 2014) for a comprehensive list of binding partners. **F.** LRRK2 binds PKA within the Ras of complex proteins (ROC) GTPase domain (Parisiadou et al., 2014), which is also the site for microtubule association (Gandhi et al., 2008) and LRRK2

dimerization interactions (Guaitoli et al., 2016). The C-terminal of ROC (COR) domain is thought to act in concert with the ROC domain for GTPase function, while additional enzymatic activity comes from the kinase (KIN) domain. Protein-protein interaction sites include armadillo (ARM), ankyrin (ANK), leucine rich repeats (LRRs) and WD40 domains (Gilsbach & Kortholt, 2014; Cardona et al., 2014). **G.** Neurobeachin interacts with PKA (Wang et al., 2000) and the synapse-associated protein 102 (SAP102) (Lauks et al., 2012). The N-terminus contains a Concavalin Alike lectin domain (C) domain flanked by two armadillo repeats (A) (Burgess et al., 2009), while the C-terminal is made up of a domain of unknown function 1088 (D) that includes an NLS (Tuand et al., 2016), a pleckstrin homology (P), a beige and Chediak-Higashi (BEACH) and a WD40 domain (Wang et al., 2000; Jogl et al., 2002). **H.** mAKAP α anchors PKA (Kapiloff et al., 1999), PDK1 (Carlisle Michel et al., 2005), RSK3 (Li et al., 2013*a*), AC5 (Kapiloff et al., 2009), CaNA β through a non-PxIxIT motif (Pare et al., 2005*a*), PDE4D3 (Dodge et al., 2001), PP2A (Dodge-Kafka et al., 2010) and nesprin1 α (Pare et al., 2005*b*). Targeting is achieved by three spectrin repeats (Kapiloff et al., 1999). Shorter isoform mAKAP β starts at residue 245 (Passariello et al., 2015).

Figure 2. AKAP79/150 and synaptic plasticity

A. AKAP79/150 regulation of LTP and LTD. *Top:* (1) Both LTP and LTD stimuli activate NMDARs, Ca^{2+} influx increases cAMP, potentially through activation of adenylyl cyclases 1 and/or 8; (2) AKAP79/150-anchored PKA phosphorylates Ser-845 promoting exocytosis; lateral diffusion and synaptic accumulation of cp-AMPA receptors. AKAP79/150 is present in the PSD, extrasynaptic membrane and endosomes and can regulate cp-AMPA receptors in each of these locations. *Bottom:* (3) During LTD, Ca^{2+} influx through cp-AMPA receptors and NMDARs then activates AKAP79/150-anchored CaN, promoting Ser-845 dephosphorylation; (4) AMPARs are rapidly removed from the synapse along with PSD-95 and AKAP79/150; spine size decreases leading to LTD. Adapted from (Sanderson et al., 2016) **B.** Dynamic membrane trafficking of AKAP79/150 and LTP. (1) LTP stimulus activates NMDARs; (2) DHHC2 palmitoylates AKAP79/150; (3) AKAP79/150-dependent endosome exocytosis; synaptic delivery of cp-AMPA receptors and AKAP79/150; (4) spine enlargement and spine LTP.

Figure 3. AKAP79/150 regulation of ion channels and receptors

A. AKAP79/150 interacts with LTCCs through its C-terminal LZ motif (Oliveria et al., 2007). (1) AKAP79/150-anchored PKA regulates LTCC basal phosphorylation at Ser-1700 and Ser-1928, while AKAP79/150-anchored CaN regulates LTCC CDI. (2) Activation of AKAP79/150-anchored CaN by Ca^{2+} influx through LTCCs leads to dephosphorylation of multiple NFAT phosphorylation sites, uncovering an NLS and promoting NFAT nuclear translocation. NFAT associates with co-transcription factors such as fos and jun. (3) NFAT-dependent transcription increases expression of a number of gene targets including $\text{Kv}7.2/3$ channels. AKAP79/150 also associates with β_2 ARs and ACs, that enhance PKA activity and phosphorylation of LTCCs. **B. Left:** $\text{Kv}4.2$ binds to the MAGUK domain of AKAP79/150 (Lin et al., 2011), targeting PKA and CaN to the channel to bi-directionally regulate surface expression and current density. **Right:** $\text{Kv}7.2/3$ binds to the membrane targeting domains of AKAP79/150 (Hoshi et al., 2003; Bal et al., 2010). (1) Activation of M_1 Rs within the AKAP79/150 signaling complex promotes activation of PLC; (2) PLC hydrolyses $\text{Kv}7.2/3$ associated PIP_2 to IP_3 and diacylglycerol (DAG), decreasing channel current; (3) DAG activates AKAP79/150-anchored PKC, which phosphorylates $\text{Kv}7.2/3$, reducing channel affinity for CaM and PIP_2 . CaM binding to $\text{Kv}7.2/3$ disrupts the $\text{Kv}7.2/3$ -AKAP79/150 interaction. **C.** TRPV1 binds close to the CaN-binding PxIxIT motif of AKAP79/150 (Btsh

et al., 2013). *Left*: PKC phosphorylation of TRPV1 enhances channel sensitivity. *Right*: Activation of EP₄Rs by PGE₂ stimulates AKAP79/150-anchored AC and PKA, enhancing TRPV1 sensitivity. AKAP79/150-anchored CaN is engaged during TRPV1 desensitization induced by capsaicin. **D.** *Left*: AKAP79/150-TRPV1-K_v7.2/3 super-complex. Ca²⁺ influx through TRPV1 decreases K_v7.2/3 current in AKAP79/150 dependent manner, potentially through promoting PLC δ hydrolysis of PIP₂ or enhancing binding of Ca²⁺-CaM to K_v7.2/3. *Right*: AKAP79/150-TRPV1-LTCC super-complex. Ca²⁺ influx through LTCCs desensitizes TRPV1 in an AKAP79/150 dependent manner, potentially through activation of AKAP79/150-anchored CaN.

Figure 4. AKAP regulation of neuronal signalosomes

A. Gravin forms signaling complexes with β_2 ARs and PKA. (1) β_2 AR stimulation of AC and gravin-anchored PKA promotes β_2 AR phosphorylation; (2) β_2 ARs switch from G_s to G_i coupling; (3) β_2 AR G_i coupling activates ERK pathway and promotes synaptic potentiation. Adapted from (Havekes et al., 2012). **B.** Yotiao binds to the GluN1 C-terminal where it regulates NMDAR activity through PKA and PP1 phospho-regulation. Yotiao regulates GABA_ARs and IP₃R1s. AC2 activity is inhibited when anchored to yotiao. **C. Top:** AKAP15/18 α in the hippocampal mossy fiber projection anchors PKA. Pre-synaptic Ca²⁺ influx activates PKA, promoting pre-synaptic MF-LTP. **Bottom:** AKAP15/18 binds to LTCCs and Nav_v1.2, anchoring PKA to enhance and inhibit channel function respectively. **D.** D-AKAP1 anchors PKA at the outer mitochondrial membrane (OMM). The GTPase Drp1 is

inhibited by PKA phosphorylation, leading to mitochondrial elongation. This is opposed by the activity of PP2A associated with the OMM and CaN which is thought to interact with Drp1 and possibly also D-AKAP1.

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Figure 5. AKAP79/150 and drug addiction

A. Schematic of the key nuclei within the mesocorticolimbic system that are affected by drugs of abuse and regulated by AKAP signaling. **B.** AKAP coordination of LTD_{GABA} in the VTA. (1) Increased dopamine (DA) release in the VTA activates D₂Rs, inhibiting AC and reducing cAMP production; (2) PKA activity is reduced, while IP₃-dependent Ca²⁺ release from intracellular stores activates CaN; (3) enhanced dephosphorylation of GABA_ARs promotes receptor endocytosis and LTD_{GABA}. The AKAP involved has not been definitively identified but is most likely AKAP79/150. **C.** AKAP79/150 upregulation in the NAc following cocaine reinstatement. (1) In drug-naïve animals, AKAP-anchored PKA enhances surface expression of cp-AMPA receptors and increases spine content of PKA. (2) Following cocaine self-administration and two weeks of extinction training, AKAP79/150 is increased in the postsynaptic fraction. (3) Cocaine reinstatement following extinction training blocks the dopamine transporter (DAT) and increases synaptic DA, activating DA D₁Rs. D₁R activation of AKAP-anchored PKA is linked to increased cocaine-seeking behavior following reinstatement.

Figure 6. AKAPs and neuronal dysfunction

A. LRRK2 regulation of striatal MSN spine morphology. *Left:* (1) LRRK2 anchors PKA to microtubules within dendritic shafts; (2) cofilin regulates spine actin dynamics and morphology. *Right:* (3) PKA is redistributed to spines in LRRK2 ^{-/-} or R1441C animals. Responses to D₁R activation are enhanced; (4) Synaptic GluA1 phosphorylation is increased; (5) Actin dynamics are disrupted due to PKA-dependent increases in phosphorylation of cofilin, through as yet unidentified intermediate steps, increasing the number of thin spines. **B.** Model for mAKAPα coordination of RGC survival following injury. (1) mAKAPα binds to PDE4D3, anchoring ERK5-MAPK pathway signaling molecules that are responsive to neurotrophic signaling; (2) mAKAPα anchors PKA that is responsive to electrical activity; (3) integration of these pathways promotes RGC survival following neuronal injury. Adapted from (Wang et al., 2015a).

Figure 7. Disrupting AKAP signaling

A. PKA is a heterotetramer composed of two R and two C subunits. The R-subunit D/D domain is joined to the cAMP binding domain by a flexible linker, enabling multiple configurations (gray arrows). The D/D domain interacts with the amphipathic α -helix common to all AKAPs. **B.** Peptides (e.g. Ht31, superAKAP-IS, RIAD) and stapled peptides (e.g. STAD) that mimic the AKAP amphipathic α -helix and bind to the PKA D/D domain to disrupt PKA interactions with AKAPs. Small molecule inhibitor FMP-AP-1 binds to an unmapped binding site on PKA and allosterically inhibits PKA interactions with AKAPs. **C.** Peptides that mimic the D/D domain of PKA (R_{select}) are engineered to target the unique features of individual AKAP amphipathic α -helices, enabling selective inhibition of PKA interactions with a particular AKAP. **D.** CaN is a Ca^{2+} -sensitive heterodimer composed of CaNA and CaNB subunits. The AKAP PxIxIT motif forms a β -strand that is added to the edge of a β -sheet in CaNA. **E.** The PVIVIT peptide mimics the PxIxIT motif and binds to CaNA with high affinity, disrupting CaN interactions with all PxIxIT-containing proteins. Small molecule inhibitors mimic the PxIxIT motif and are also likely to disrupt all PxIxIT-

CaN interactions. Allosteric small molecule inhibitor (INCA) binds to CaNA at a site distinct from the PxIxIT binding site. **F.** The PP1 catalytic subunit (PP1c) binds to a range of interacting proteins containing an RxVF motif, which forms part of a β -strand that is incorporated into a β -sheet in PP1c. **G.** Peptides mimicking the RxVF have been derived from a number of PP1 binding partners and disrupt interactions between PP1 and RxVF-containing proteins.

Table 1

Name/Alternative names	Proteins in Complex	Cellular/subcellular localization	Associated Neurological disorders
AKAP79/150 AKAP79 (human) AKAP150 (rodent) AKAP75 (bovine) <i>AKAP5</i>	PKA (Carr et al., 1992) CaN (Coghlan et al., 1995; Dell'Acqua et al., 2002) PKC (Klauck et al., 1996) AC (Bauman et al., 2006; Efendiev et al., 2010) CaM (Carr et al., 1992; Faux & Scott, 1997) PSD-95 (Colledge et al., 2000; Robertson et al., 2009) SAP97 (Colledge et al., 2000; Robertson et al., 2009) AMPA (Colledge et al., 2000) NMDAR (Colledge et al., 2000) LTCC (Hall et al., 2007; Oliveria et al., 2007) TRPV1 (Jeske et al., 2008; Schnizler et al., 2008; Zhang et al., 2008) K _v 7.2/3 (Hoshi et al., 2003) K _v 4.2 (Lin et al., 2011) β ₂ -AR (Fraser et al., 2000)	<i>Hippocampus</i> - Excitatory post-synapse (Carr et al., 1992; Gomez et al., 2002; Lu et al., 2007; Li et al., 2012) - Endosomes (Keith et al., 2012) - Dendrites (Dell'Acqua et al., 1998) <i>Superior Cervical Ganglion</i> - (Hoshi et al., 2003; Zhang et al., 2011) <i>Dorsal Root Ganglion</i> - somatic plasma membrane (Schnizler et al., 2008; Zhang et al., 2008) <i>Nucleus Accumbens (MSN)</i> - Excitatory post-synapse (Reissner, 2013) <i>Ventral Tegmental Area (DA neuron)</i> - Inhibitory post-synapse (Dacher et al., 2013)	Seizure (Tunquist et al., 2008; Keith et al., 2012; Zhang & Shapiro, 2012; Kay et al., 2015) Pain (Schnizler et al., 2008; Por et al., 2010; Fischer et al., 2013) Addiction (Reissner et al., 2011; Reissner, 2013; Dacher et al., 2013) Alzheimer's Disease (to be determined)
Gravin AKAP250 SSeCKS (mouse) <i>AKAP12</i>	PKA, PKC (Nauert et al., 1997) PDE4 (Willoughby et al., 2006) CaM (Tao et al., 2006; Schott & Grove, 2013) β ₂ -AR (Tao et al., 2003)	<i>Hippocampus</i> - Excitatory post-synapse (Havekes et al., 2012)	To be determined
Yotiao AKAP350 AKAP450 <i>AKAP9</i>	PKA, PP1 (Westphal et al., 1999) AC2 (Piggott et al., 2008) IP ₃ R (Tu et al., 2004) GluN1 (Lin et al., 1998)	<i>Pre-frontal cortex</i> - Inhibitory post-synapse (Wang et al., 2002) <i>Whole-brain</i> - Endoplasmic reticulum (Tu et al., 2004) <i>Cerebellar granule cells</i> - Golgi (Collado-Hilly & Coquil, 2009)	To be determined
AKAP15/18 <i>AKAP7</i>	PKA (Fraser et al., 1998; Gray et al., 1998) PP1 (Rogne et al., 2009) LTCC (Fraser et al., 1998; Gray et al., 1998) Na _v (Tibbs et al., 1998; Cantrell et al., 1999)	<i>Hippocampus</i> - Mossy fiber pre-synapse (Jones et al., 2016)	To be determined
D-AKAP1 AKAP121 AKAP149 sAKAP84 <i>AKAP1</i>	PKA (Chen et al., 1997) PP1 (Steen et al., 2000; Rogne et al., 2009)	<i>Hippocampus</i> - Mitochondria (Dickey & Strack, 2011; Merrill et al., 2011)	Neuronal Death (Dickey & Strack, 2011; Merrill et al., 2011; Scorziello et al., 2013) Parkinson's Disease (Dagda et al., 2011; Das Banerjee et al., 2017)
LRRK2 <i>PARK8</i>	PKA (Parisiadou et al., 2014) Microtubules (Gandhi et al., 2008)	<i>Dorsal Striatum</i> - Dendritic shaft (Parisiadou et al., 2014)	Parkinson's Disease (Parisiadou et al., 2014)
Neurobeachin <i>NBEA</i>	PKA (Wang et al., 2000) SAP102 (Lauks et al., 2012)	<i>Hippocampus</i> - Post-synapse (Wang et al., 2000) - Endomembranes (Wang et al., 2000; Nair et al., 2013)	Autism (Smith et al., 2002; Castermans et al., 2003)
mAKAP <i>AKAP6</i>	PKA (Kapiloff et al., 1999) PDK1 (Carlisle Michel et al., 2005)	<i>Retinal Ganglion Cells</i> - Outer nuclear membrane (Pare et al., 2005b; Wang et al., 2015)	Axonal degeneration in the retina (Wang et al., 2015)

Name/Alternative names	Proteins in Complex	Cellular/subcellular localization	Associated Neurological disorders
	RSK3 (Carlisle Michel et al., 2005) AC5 (Kapiloff et al., 2009) CaNA β (Pare et al., 2005 <i>a</i>) PDE4D3 (Dodge et al., 2001) PP2A (Dodge-Kafka et al., 2010) nesprin1 α (Pare et al., 2005 <i>b</i>)		