# Chapter 8
# A Role for Phosphodiesterase 11A (PDE11A) in the Formation of Social Memories and the Stabilization of Mood

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**Abstract**  The most recently discovered 3′,5′-cyclic nucleotide phosphodiesterase family is the Phosphodiesterase 11 (PDE11) family, which is encoded by a single gene PDE11A. PDE11A is a dual-specific PDE, breaking down both cAMP and cGMP. There are four PDE11A splice variants (PDE11A1-4) with distinct tissue expression profiles and unique N-terminal regulatory regions, suggesting that each isoform could be individually targeted with a small molecule or biologic. PDE11A4 is the PDE11A isoform expressed in brain and is found in the hippocampal formation of humans and rodents. Studies in rodents show that PDE11A4 mRNA expression in brain is, in fact, restricted to the hippocampal formation (CA1, possibly CA2, subiculum, and the adjacently connected amygdalohippocampal area). Within the hippocampal formation of rodents, PDE11A4 protein is expressed in neurons but not astrocytes, with a distribution across nuclear, cytoplasmic, and membrane compartments. This subcellular localization of PDE11A4 is altered in response to social experience in mouse, and in vitro studies show the compartmentalization of PDE11A4 is controlled, at least in part, by homodimerization and N-terminal phosphorylation. PDE11A4 expression dramatically increases in the hippocampus with age in the rodent hippocampus, from early postnatal life to late aging, suggesting PDE11A4 function may evolve across the lifespan. Interestingly, PDE11A4 protein shows a three to tenfold enrichment in the rodent ventral hippocampal formation (VHIPP; a.k.a. anterior in primates) versus dorsal hippocampal formation (DHIPP). Consistent with this enrichment in VHIPP, studies in knockout mice show that PDE11A regulates the formation of social memories and the stabilization of mood and is a critical mechanism by which social experience feeds back to modify the brain and subsequent social behaviors. PDE11A4 likely controls behavior by regulating hippocampal glutamatergic, oxytocin, and cytokine signaling, as well as protein translation. Given its unique tissue distribution and relatively selective effects on behavior, PDE11A may represent a novel therapeutic target for

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neuropsychiatric, neurodevelopmental, or age-related disorders. Therapeutically targeting PDE11A4 may be a way to selectively restore aberrant cyclic nucleotide signaling in the hippocampal formation while leaving the rest of the brain and periphery untouched, thus, relieving deficits while avoiding unwanted side effects.

**Keywords** PDE11A • PDE11 • Phosphodiesterase 11 • cAMP • cGMP • Psychiatric illness • Brain • Endocrine • Immune • Hippocampus • Memory • Inflammation • Lithium • Tissue expression • Social Behavior • Oxytocin

## 8.1  Introduction

The most recently discovered phosphodiesterase (PDE) family is PDE11, which hydrolyzes cAMP and cGMP equally well (Hetman et al. 2000; Fawcett et al. 2000; Yuasa et al. 2000; Yuasa et al. 2001a; Weeks et al. 2007). The PDE11 family is comprised of a single gene, PDE11A (Hetman et al. 2000; Fawcett et al. 2000; Yuasa et al. 2000; Yuasa et al. 2001a; Yuasa et al. 2001b). As with most PDE families, the N-terminal domain of PDE11A serves a regulatory function, whereas the C-terminal domain encompasses the catalytic domain (Weeks et al. 2007). The longest isoform of mouse, rat and human PDE11A (a.k.a. PDE11A4) demonstrates ~95% protein sequence homology, suggesting results obtained in preclinical rodent models will be applicable to the human condition. As extensively reviewed elsewhere (Kelly 2015), literature findings surrounding the tissue distribution pattern for the various PDE11A isoforms are highly disparate, in part due to a number of poor quality commercially-available antibodies, but well-controlled studies consistently show select PDE11A isoforms being expressed in brain (particularly the hippocampal formation), the adrenal gland, and the prostate. Studies examining tissues from PDE11A wild-type (WT) and knockout (KO) mice find abundant PDE11A4 protein in the hippocampal formation of brain but not in any of 23 peripheral tissues assessed; whereas, PDE11A1 was found in prostate, PDE11A3 in the seminal vesicles, and PDE11A1 and PDE11A3 in spleen (Kelly 2015). Consistent with this restricted tissue distribution profile, PDE11A appears to regulate brain function, tumor physiology, and, possibly, inflammation (Kelly 2015; Fatemi et al. 2010a; Couzin 2008; Wong et al. 2006; Luo et al. 2009a; Kelly et al. 2010; Hegde et al. 2015; Pathak et al. 2016; Hegde et al. 2016b; Mertens et al. 2015 but see Laje et al. 2009; Perlis et al. 2010; Kelly 2015; Alevizaki and Stratakis 2009; Faucz et al. 2011; Greene et al. 2010; Carney et al. 2010; Almeida and Stratakis 2011; Vezzosi et al. 2012; Horvath et al. 2009; Horvath et al. 2006a; Horvath et al. 2006b; Libe et al. 2008; Libe et al. 2011 but see Bimpaki et al. 2009; Kelly 2015; Pathak et al. 2016; DeWan et al. 2010; Oki et al. 2011; Witwicka et al. 2007; Bazhin et al. 2010). Here, we review how PDE11A may regulate brain function to determine whether or not PDE11A4 holds promise as a future therapeutic target, particularly in the context of neuropsychiatric, neurodevelopmental and/or age-related disease.

## 8.2   Molecular Features of PDE11A

The PDE11A gene on chromosome 2q31.2 contains 23 exons and yields four splice variants PDE11A1-4 (Hetman et al. 2000; Fawcett et al. 2000; Yuasa et al. 2000; Yuasa et al. 2001a; Yuasa et al. 2001b), which have been recently schematically reviewed in depth (Kelly 2015). Isoform-specific promoters, coupled with alternative splicing, yield unique N-terminal domains for each PDE11A isoform (Yuasa et al. 2001b) and likely account for the differences in tissue expression that are seen with each PDE11A isoform (Kelly 2015). While the C-terminal region encompasses the catalytic domain of PDE11A, the N-terminal region encompasses various regulatory domains and sites of post-translational modification. Within the N-terminal region are 2 cGMP binding PDE, Anabaena adenylyl cyclase and *E. coli* FhlA (GAF) domains (Makhlouf et al. 2006). Perhaps not surprisingly, phylogenetic analyses suggests PDE11A is most closely related to other GAF-domain containing PDEs, particularly PDE5A and PDE6A-C as well as PDE2A and PDE10A (Yuasa et al. 2001b; Kelly 2015). As we will see below, the four PDE11A isoforms hydrolyze cAMP and cGMP, and each has a unique N-terminal region with differential representation of the GAF-A domain, which binds cGMP (Gross-Langenhoff et al. 2008; Gross-Langenhoff et al. 2006; Jager et al. 2012; Matthiesen and Nielsen 2009), and the GAF-B domain, which is required for homodimerization.

Although each of the four variants exhibits a unique N-terminal regulatory domain (c.f., Kelly 2015), the C-terminal domain is consistent across the 4 PDE11A isoforms. Exons 8–23 are included in each isoform and encode not only the C-terminal catalytic domain but also a portion of the N-terminal regulatory GAF-B domain (Makhlouf et al. 2006). In addition to exons 8–23, PDE11A1 also uniquely includes exon 7; thus, PDE11A1 includes only a truncated GAF-B domain within its N-terminus (Yuasa et al. 2001b). PDE11A2 includes exons 5 and 6, but not 7, in addition to exons 8–23; thus, PDE11A2 includes a truncated GAF-A domain and a full GAF-B domain. (Hetman et al. 2000; Makhlouf et al. 2006). The PDE11A3 transcript is encoded by exons 1, 2, 4, 5, and 6 in addition to exons 8–23; however, translation of PDE11A3 does not begin until exon 2 (Yuasa et al. 2001b). Thus, similar to PDE11A2, PDE11A3 contains a truncated GAF-A domain and a full GAF-B domain upstream of the C-terminal catalytic domain. PDE11A4 is the only isoform to include exon 3 along with the shared exons 4–6 and 8–23 (Yuasa et al. 2001b). PDE11A4, the isoform expressed in brain, is the longest isoform. Therefore, it is at times erroneously referred to as "full-length" PDE11A, despite the fact that it lacks exons 2 and 7. Importantly, exon 3 contains two validated phosphorylation sites (S117 and S162) and the beginning of the GAF-A domain (Yuasa et al. 2000); thus, PDE11A4 is the only isoform to include the GAF-A domain in its entirety. As we will review in greater detail below, these phosphorylation sites and GAF domains may be important for intramolecular signaling (Weeks et al. 2007; Gross-Langenhoff et al. 2008) and may provide a mechanism by which it will be possible to therapeutically target a single PDE11A isozyme with high selectivity (Kelly 2015). Indeed, isozyme-specific targeting of PDE11A activity has already been demonstrated as vinpocetine can inhibit PDE11A3 but not PDE11A4 (Yuasa et al. 2000).

Under physiological conditions, all PDE11A isoforms hydrolyze both cAMP and cGMP (cf. Makhlouf et al. 2006). As extensively reviewed elsewhere (Kelly 2015), PDE11A1 and PDE11A2 have higher substrate affinities relative to PDE11A3 and PDE11A4 (Yuasa et al. 2001a; Weeks et al. 2007); however, PDE11A3 and PDE11A4 have significantly higher catalytic rates relative to PDE11A1 and PDE11A2 (Yuasa et al. 2001a; Weeks et al. 2007). A comparison of rat PDE11A found similar results to those obtained using *Homo sapiens* PDE11A (Yuasa et al. 2001a). The net effect of the relative differences in substrate affinities versus turn-over rates is that the four PDE11A isoforms hydrolyze cAMP and cGMP compara-bly well (Yuasa et al. 2001a; Weeks et al. 2007). Site-directed mutagenesis shows that Q869 is required for substrate binding of the PDE11A catalytic domain (Weeks et al. 2009); however, in absence of a resolved crystal structure the full implications of these results remain to be determined. Such knowledge would benefit designing compounds capable of selectively targeting the PDE11A catalytic domain over its nearest neighbor PDE5A.

The N-terminal region of PDE11A clearly regulates catalytic function of the enzyme. For example, as the length of the N-terminus increases, the affinity of the catalytic domain for cAMP and cGMP decreases (Weeks et al. 2007). That is, PDE11A4 has the lowest substrate affinity for cAMP and cGMP and PDE11A1 and PDE11A2 have the highest substrate affinities for cAMP and cGMP (Weeks et al. 2007). Similarly, in a chimeric protein consisting of the PDE11A4 N-terminus linked to the catalytic domain of a bacterial adenylyl cyclase, deletion of the first 196 amino acids (i.e., all amino acids upstream of the GAF-A domain) increases basal catalytic activity (Gross-Langenhoff et al. 2008). Together, these studies sup-port a regulatory role for the PDE11A N-terminal region.

As mentioned above, PDE11A4 is the only PDE11A variant that includes S117 and S162, 2 serines phosphorylated by protein kinase A, protein kinase G (PKA/PKG) (Yuasa et al. 2000) and possibly other enzymes (Kelly 2015). In vitro, PKA and PKG fail to phosphorylate PDE11A3, which lacks S117 and S162, but do phos-phorylate PDE11A4 (Yuasa et al. 2000). Further, most of the PKA and PKG-induced phosphorylation of PDE11A4 is ablated by mutating S117 and S162 to phosphomu-tant alanines (Yuasa et al. 2000). The remaining PKA and PKG-induced phosphory-lation observed in the S117A/S162A PDE11A4 mutant likely reflects phosphorylation of S124, which is predicted to be phosphorylated by PKA and PKG (Kelly 2015) and is phosphorylated along with S117 and S162 in COS-1 cells (Pathak et al. 2015).

Emerging evidence suggests these N-terminal phosphorylation sites may play an important role in regulating PDE11A4 function. Gross-Langenhoff *et al.* used a chimeric protein consisting of the PDE11A4 N-terminus linked to the catalytic domain of a bacterial adenylyl cyclase to explore the functional role S117/S162 phosphorylation (Gross-Langenhoff et al. 2008). In that chimeric protein, the phosphorylation state of the N-terminal regulatory region affected intramolecular regulation of the GAF-A domain. Specifically, when both S117 and S162 were phosphorylated, or were replaced with amino acids that mimicked the phosphory-lated state, the downstream GAF-A regulatory domain had an increase in affinity for cGMP (Gross-Langenhoff et al. 2008). Interestingly, deleting the first 176 amino

acids similarly increased cGMP affinity for the GAF-A domain (Gross-Langenhoff et al. 2008), suggesting that phosphorylation of S117/S162 may produce a conformational change that exposes the cyclic nucleotide binding pocket of the GAF-A domain. In COS-1 and HEK293T cells, we have shown that introducing a phosphomimic mutation (aspartate, D) to S117 and S124 (S117D, S124D) traffics PDE11A4 into punctate structures and shifts PDE11A4 from the cytosol to the membrane (Pathak et al. 2015). In contrast, a S162D mutation has the completely opposite effect, distributing PDE11A4 throughout the cytosol and shifting PDE11A4 from the membrane to the cytosol (Pathak et al. 2015). Interestingly, S162D completely blocks the effects of S117D/S124D (Pathak et al. 2015). The fact that S162D blocks the effect of S117D in the context of a full-length recombinant protein, yet potentiates the effect of S117D in the context of the chimeric protein, may suggest a complex interplay between these N-terminal phosphorylation events and the C-terminus. Consistent with the fact that S162D shifts PDE11A4 to the cytosol and blocks the ability of S117D/S124D to shift PDE11A4 toward the membrane, we find that wild-type PDE11A found in the cytosol can be phosphorylated at any of the three serines; whereas, PDE11A4 in the membrane shows phosphorylation at serines 117 and 124 but not 162 (Pathak et al. 2015). It will be important to determine whether the ability of these phosphorylation events to control the subcellular compartmentalization of PDE11A4 is related to conformational changes in the enzyme, changes in cGMP binding of the GAF-A domain, and/or the prevention or promotion of other post-transtional modifications (e.g., palmitoylation, ubiquitination, sumoylation).

The functional consequence of cyclic nucleotide binding of a PDE GAF domain differs by PDE family. cGMP binding the GAF-A domain can directly increase catalytic activity (PDE2A, Martinez et al. 2002; Beavo et al. 1971), increases substrate affinity (PDE5A, Francis et al. 2011), indirectly inhibit catalytic activity by strengthening specific inhibitory protein-protein interactions (PDE6, D'Amours and Cote 1999), or have no effect at all (PDE10A, Jager et al. 2012; Matthiesen and Nielsen 2009). Several laboratories have reported that cGMP binds the PDE11A4 GAF-A, but not GAF-B, domain (Gross-Langenhoff et al. 2008; Gross-Langenhoff et al. 2006; Jager et al. 2012; Matthiesen and Nielsen 2009), likely with a lower $K_i$ versus the catalytic domain (Matthiesen and Nielsen 2009). Although cGMP binding of the PDE11A4 GAF-A domain did stimulate catalytic activity of the PDE11A4-cyclase chimeric protein described above (Gross-Langenhoff et al. 2008; Gross-Langenhoff et al. 2006), it did not impact catalytic activity of recombinant full-length PDE11A4 (Jager et al. 2012; Matthiesen and Nielsen 2009). That said, it is interesting to note that the ability of cGMP to allosterically stimulate catalytic activity of the PDE11A4-cyclase chimera was dependent on the presence of an aspartate within a conserved NKFDE motif that is present in all mammlian PDE GAF domains (Gross-Langenhoff et al. 2006). Mutating D355 to an alanine abolished the intramolecular signaling events triggered by cGMP. It remains to be determined whether mutating D355 simply prevents cGMP from binding the GAF-A domain or prevents some downstream consequence of cGMP binding (e.g., a conformational change; Gross-Langenhoff et al. 2006). Although cGMP does not appear to allosterically regulate catalytic activity of PDE11A4, a cGMP analog

Rp-8-pCPT-PET-cGMPs does appear to allosterically increase the catalytic activity of both recombinant and native PDE11A4 (Jager et al. 2012). Unfortunately, Rp-8-pCPT-PET-cGMPs inhibits PKG and, likely, many other cGMP-binding molecules; thus, its use as a tool compound is limited. That said, the fact that Rp-8-pCPT-PET-cGMPs is capable of allosterically stimulating PDE11A function provides a key proof-of-concept for developing PDE11A4 activators.

GAF domains not only bind cyclic nucleotides, they also bind proteins, including other molecules of PDEs themselves. All PDE11A isoforms, indeed all PDEs (Francis et al. 2011; Heikaus et al. 2009), exist as oligomers (Weeks et al. 2007). The C-terminal portion of the GAF-B domain is required for dimerization of all PDE11A isoforms (Weeks et al. 2007). PDE11A1, with the shortest N-terminal region, tetramerizes; whereas, PDE11A2-4 homodimerize. It is not completely understood how oligomerization affects PDE11A function. Weeks *et al.* found that the dimeric PDE11A2 and the tetrameric PDE11A1 have nearly identical substrate affinities for cAMP and cGMP, suggesting that quaternary structure does not greatly impact affinity of the cyclic nucleotides for the catalytic site (Weeks et al. 2007). We have shown that homodimerization controls the subcellular compartmentalization of PDE11A4 (Pathak et al. 2016). A mutation within the GAF-B domain found in select mouse strains that strengthens homodimerization shifts PDE11A4 from the cytosol towards the membrane; whereas, disrupting homodimerization shifts PDE11A4 from the membrane to the cytosol (Pathak et al. 2016). Disrupting homodimerization also increases proteolytic degradation of PDE11A4 (Pathak et al. 2016). Although the mechanism responsible remains to be determined, it is interesting to note that PDE11A4 is predicted to be ubiquitinated and sumoylated (Kelly 2015). Thus, it is possible that disruption of homodimerization may make PDE11A4 more vulnerable to these particular posttranslational modifications that tag a protein for degradation. It remains to be determined whether or not homodimerization directly affects PDE11A4 catalytic activity as well. In vitro studies examining the PDE2, PDE4, and PDE5 families argue that dimerization is not required for catalytic activity; however, dimerization may influence posttranslational modifications of the enzymes, thereby altering subcellular localization and/or catalytic activity (Francis et al. 2011; Keravis and Lugnier 2010). Clearly, much work remains to understand the functional role of PDE11A oligomerization. That said, these studies suggest that homodimerization may be a novel mechanism by which we could therapeutically target PDE11A function, particularly in disease states where the enzyme may become mislocalized.

## 8.3   Tissue Expression Patterns for PDE11A

Understanding the tissue expression profile of an enzyme is key when considering it as a therapeutic target. As noted above, tissue expression profiling studies for PDE11A have proven highly inconsistent. Poor tools are likely to blame for many of these discrepant reports. We have shown that Western blots of peripheral tissues

probed with various commercially-available PDE11A antibodies demonstrate an abundance of non-specific bands at molecular weights that are consistent with the various PDE11A isoforms (Kelly 2015). The fact that the bands do not disappear in tissue from a PDE11A KO mouse shows these signals are non-specific. Some discrepancies may also be related to the fact that studies have not examined the correct sub-compartment of certain organs. For example, initial studies failed to detect PDE11A expression in brain (Fawcett et al. 2000; Yuasa et al. 2000). Subsequent studies, however, have convincingly shown that PDE11A4 is, in fact, expressed within a small, restricted region of the brain (particularly the ventral hippocampal formation, Kelly et al. 2010; Jager et al. 2012; Kelly et al. 2014). Finally, discrepancies could be related to species differences or a differential expression profile under normal versus disease conditions.

As we have extensively reviewed elsewhere (Kelly 2015), tissue expression profiling studies to date suggest PDE11A expression is relatively restricted throughout the body. PDE11A1 and/or PDE11A2 may be expressed at a moderate level in prostate, pancreas and kidney. PDE11A3 is likely expressed within specific compartments of the testes and seminal vesicles at moderate levels. PDE11A4 is certainly expressed at high levels in the ventral hippocampal formation of brain, and may be expressed at moderate levels in the human—but not mouse—adrenal gland. Limited evidence points to low levels of PDE11A4 being expressed in liver, heart, and pituitary, and moderate levels being expressed in human prostate, but our own studies employing 23 peripheral tissues from PDE11A KO mice as negative controls fail to detect PDE11A4 outside of brain (Kelly 2015). With such a limited tissue expression profile, a PDE11A-targeted therapeutic would stand to impact very selective systems of interest without eliciting wide-ranging toxicological side effects.

PDE11A4 mRNA in brain is almost exclusively expressed in neurons of CA1, possibly CA2, the subiculum and the adjacently connected amygdalohippocampal area (Kelly 2015; Kelly et al. 2010; Hegde et al. 2016a; Kelly et al. 2014; Kelly 2014) (Fig. 8.1). Within these neuronal populations, PDE11A4 protein is found in the cell bodies, axons, and select dendrites (Hegde et al. 2016a) (Fig. 8.2, 8.3, 8.4 and 8.5). Trafficking of PDE11A4 protein to the axons explains why PDE11A4 protein can be detected at miniscule levels in brain regions that receive VHIPP projection but, themselves, lack PDE11A4 mRNA (e.g., prefrontal cortex and striatum) (Kelly 2015; Hegde et al. 2016a). PDE11A4 is the only PDE whose expression in brain originates solely from the hippocampal formation (c.f., Kelly et al. 2014; Kelly 2014; Kelly and Brandon 2009; Xu et al. 2011). In the rodent hippocampus, PDE11A4 expression is minimal on postnatal day 7 but dramatically increases with each postnatal week, reaching young adulthood levels by postnatal day 28 (Hegde et al. 2016a). PDE11A expression stabilizes for a short period of time during young adulthood, but then again significantly increases between young, middle, and late adulthood (Kelly et al. 2014). The fact that PDE11A expression is restricted to the hippocampal formation, at least during young adulthood, suggests a PDE11A-targeted therapeutic may be capable of selectively targeting hippocampal function whilst leaving the rest of the brain undisturbed.
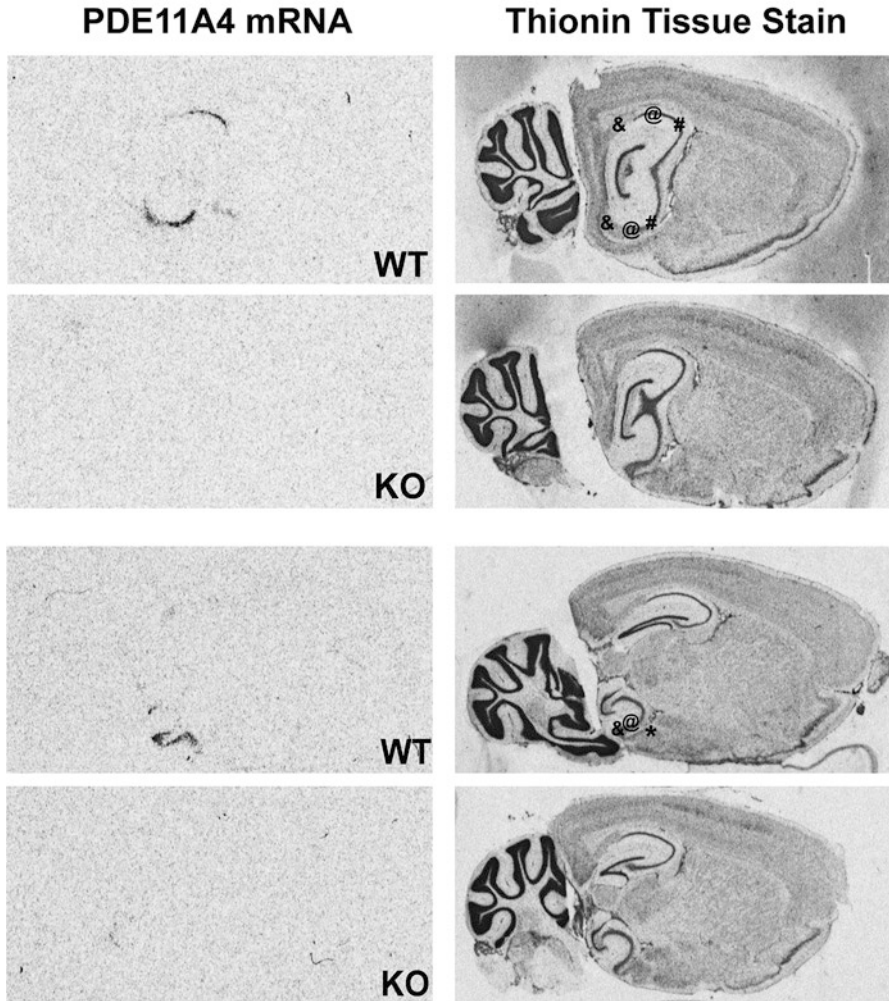
## PDE11A4 mRNA          ## Thionin Tissue Stain



**Fig. 8.1** PDE11A4 mRNA expression is restricted to the hippocampal formation, with enrichment in ventral versus dorsal hippocampus. Autoradiographic *in situ* hybridization was conducted using two ^{35}S-labeled antisense oligonucleotide probes with identical patterns of signal (shown: 5′-gccacctgtctggagatctcccacggtttggtcacggc-3′ recognizing nucleotides 2538-2501 of NM_001081033.1; not shown: 5′-cgcatcaagtaatcttcaaacaactctgggtgcct-3′ recognizing nucleotides 129-95 of NM_001081033.1). Note that no signal is observed in sections from PDE11A knockout (KO) mice, suggesting specificity of the signal detected in sections from PDE11A wild-type (WT) mice. When comparing the autoradiograph to the thionin tissue stain, it is clear that PDE11A mRNA expression is restricted to the hippocampal formation (CA1[@], possibly CA2[#], subiculum[&] and the adjacently connected amygdalohippocampal area*—regions indicated on thionin stain with corresponding symbols), with a two to tenfold enrichment in ventral versus dorsal hippocampus. *Top panels* show sections from ~2.76–2.88 mm lateral from Bregma, and *bottom panels* show sections from ~2.28–2.40 mm lateral from Bregma. Contrast and brightness were adjusted to enhance the graphical clarity of the images
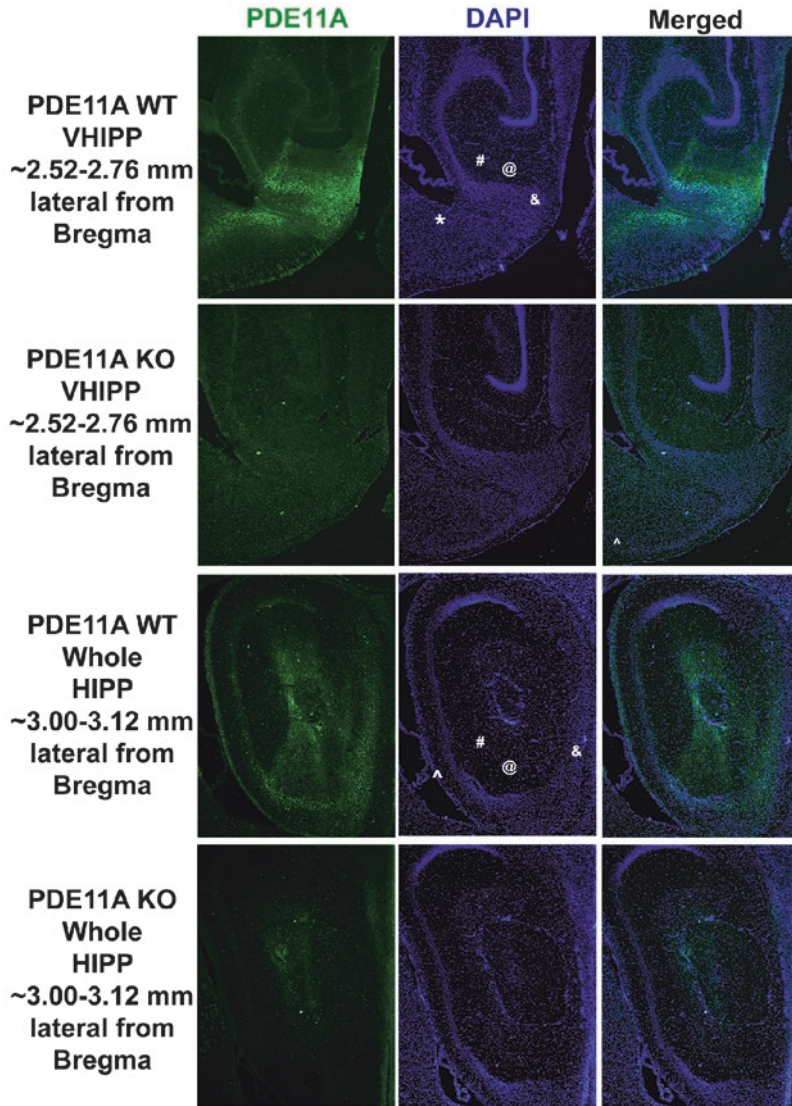
**Fig. 8.2** PDE11A4 protein expression is enriched in the ventral hippocampal formation, with expression throughout the stratum pyramidale, stratum radiatum, and fimbria. Identical staining for PDE11A was obtained in sections from PDE11A wild-type (WT) mice when sections were processed for immunofluorescence using an antibody that recognized all PDE11A isoforms (Fabgennix PD11-112 1:100, shown) or an antibody recognizing only PDE11A4 (AVES PDE11#1 1:5000; Hegde et al. 2016a). Note that minimal staining is observed in sections from PDE11A knockout (KO) mice, suggesting specificity of the signal detected in WT tissue. PDE11A protein is distinctly expressed in CA1[@], possibly CA2[#], subiculum[&], the adjacently connected amygdalo-hippocampal area[*], and the fimbria[^]), with a two to threefold enrichment in ventral versus dorsal hippocampus. Images collected using a 4× objective. Histogram stretch and gamma were corrected to enhance the graphical clarity of the images. *Green*—PDE11A, *Blue*—DAPI nuclear stain
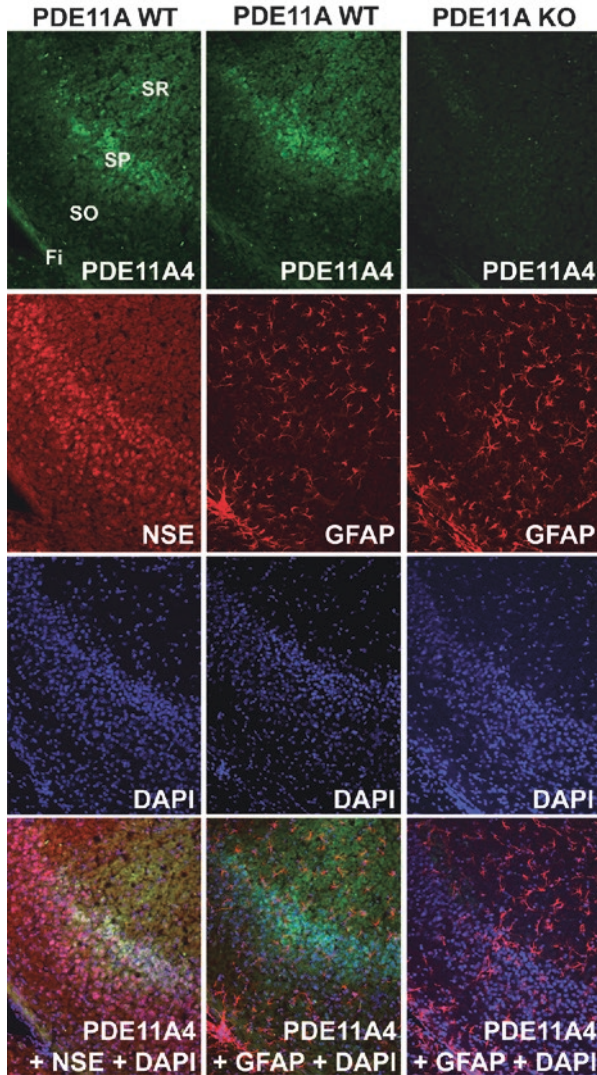
**Fig. 8.3** PDE11A4 protein expression within CA1 is found within a subset of neurons, not astrocytes. Immunofluorescence was conducted on sections from PDE11A wild-type (WT) and knockout (KO) mice collected ~2.76–2.88 mm lateral from Bregma. PDE11A protein expression (Fabgennix PD11-112 1:100) clearly colocalizes with a marker of neuronal cytoplasm (AVES neuronal specific enolase (NSE) 1:500) within a subset of neurons in CA1, and possibly CA2, stratum pyramidale (SP; i.e., cell body layer). Note: colocalization of *green + red = yellow*. PDE11A protein does not appear to colocalize with a marker of astrocytes (AVES glial acidic fibrillary protein (GFAP) 1:500) in SP, stratum radiatum (SR; i.e., the dendritic layer), stratum oriens (SO; i.e., axonal projection layer), or the fimbria (Fi; i.e., projecting axonal bundle). Images collected using a 20× objective. Histogram stretch and gamma were corrected to enhance the graphical clarity of the images. *Green*—PDE11A, *Blue*—DAPI nuclear stain, *Red*—either NSE or GFAP as indicated
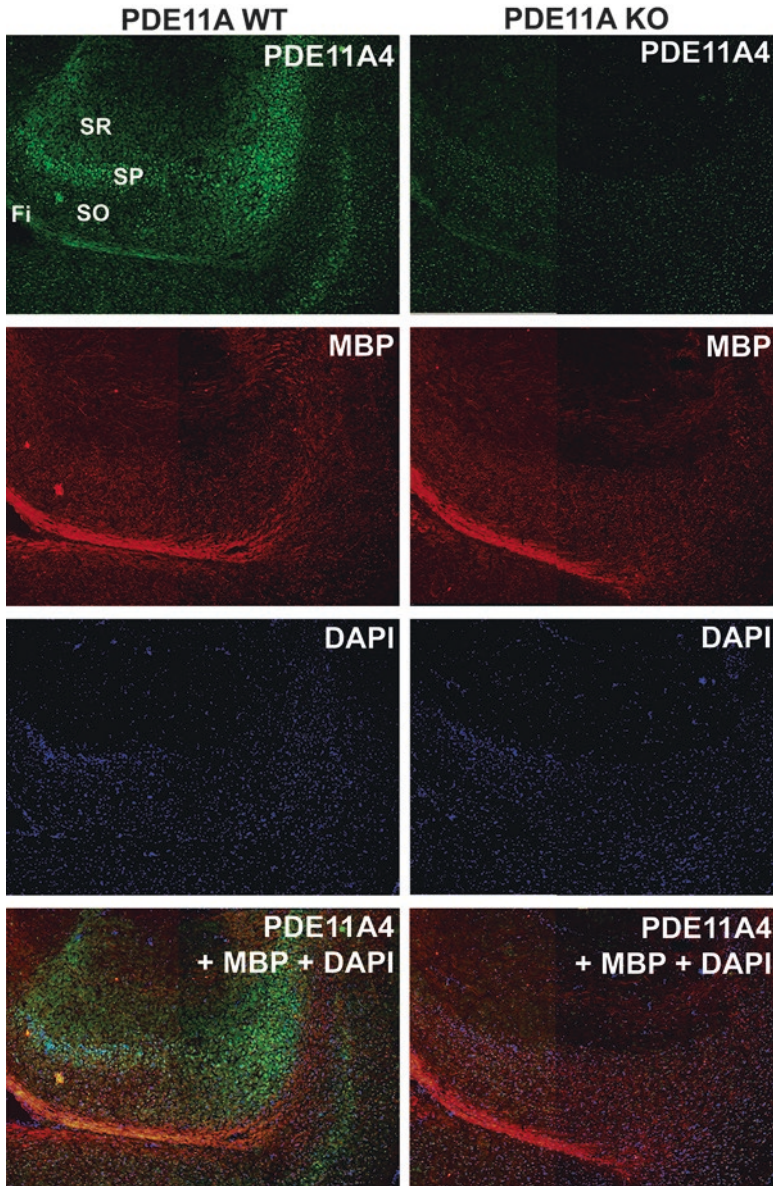
**Fig. 8.4** PDE11A4 protein expression is seen in the fimbria, a structure mostly composed of hippocampal efferents. Immunofluorescence was conducted on sections from PDE11A wild-type (WT) and knockout (KO) mice collected ~2.76 mm lateral from Bregma. PDE11A protein expression (Fabgennix PD11-112 1:100) is clearly found in the fimbria, as indicated by colocalization with a marker of myelin that labels axon bundles (AVES myelin basic protein (MBP) 1:100). Note: colocalization of *green + red = yellow*. Two images per section were collected using a 10× objective and then stitched together using Adobe Photoshop. Histogram stretch and gamma were corrected to enhance the graphical clarity of the images. *Green*—PDE11A, *Blue*—DAPI nuclear stain; *Red*—MBP
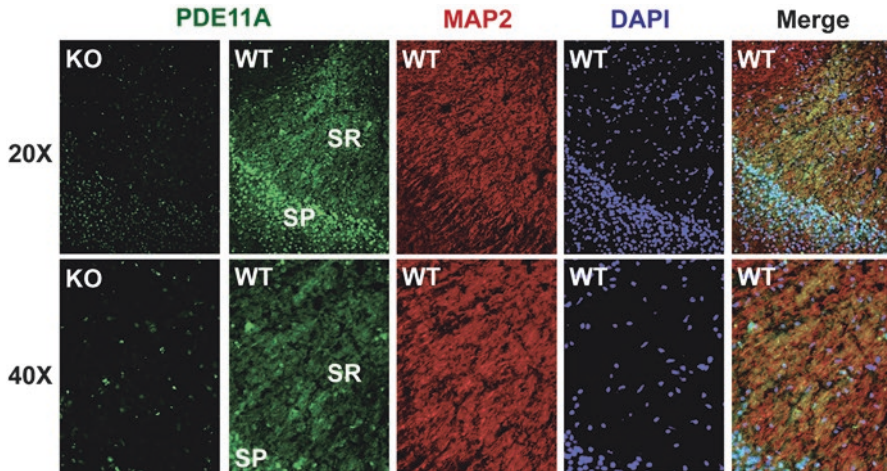
**Fig. 8.5** PDE11A4 protein expression is detected within a subset of dendrites in stratum radiatum. Immunofluorescence was conducted on sections from PDE11A wild-type (WT) and knockout (KO) mice collected ~3.00 mm lateral from Bregma. Punctate PDE11A protein expression (Fabgennix PD11-112 1:100) is clearly found in stratum pyramidale (cell body layer), as indicated by colocalization with a subset of DAPI staining. Fibril-like PDE11A labeling can be found in the stratum radiatum, a structure mostly composed of CA dendrites. Consistent with the fibril-like pattern of PDE11A staining in the stratum radiatum, PDE11A protein expression colocalizes with a marker of dendrites (Neuromics microtubule associated protein 2 (MAP2) 1:2000). Note: colocalization of *green + red = yellow*. Images were collected using a 20× or 40× objective, as indicated. Histogram stretch and gamma were corrected to enhance the graphical clarity of the images. *Green*—PDE11A, *Blue*—DAPI nuclear stain; *Red*—MAP2

Upon biochemical fractionation of the hippocampus, PDE11A4 can be found in nuclear, cytosolic and membrane compartments (both soluble and insoluble). This compartmentalization of PDE11A4 is modifiable in response to behavioral, genetic, and biochemical manipulations. Relative to single-housed mice, group-housed mice exhibit increased PDE11A4 protein expression in the soluble membrane compartment but not the cytosolic compartment of the VHIPP (Hegde et al. 2016b). Similarly, BALB/cJ mice express significantly more PDE11A4 protein than C57BL/6J mice in the soluble membrane but not cytosolic compartment of VHIPP (Pathak et al. 2016). Although it remains to be determined how social experience elicits such compartment-specific effects on PDE11A4 protein expression, the compartment-specific difference in PDE11A4 protein expression that is observed between C57BL/6J and BALB/cJ mice appears to be largely accounted for by a single point mutation at amino acid 499 within the GAF-B homodimerization domain (Pathak et al. 2016). In the C57BL/6J, 499 is a non-phosphorylatable alanine; however, in the BALB/cJ 499 is a phosphorylatable threonine (Pathak et al. 2016). We showed that the BALB/cJ 499T and corresponding phosphomimic mutation (T499D) shifts PDE11A4 from the cytosol to the membrane, relative to the C57BL/6J 499A, perfectly replicating the PDE11A4 protein expression differences noted between these mouse strains in VHIPP (Pathak et al. 2016). The ability of the

499T mutation to drive PDE11A4 into the membrane appears to be driven by an ability to increase homodimerization of PDE11A4, as 499T increases homodimerization of PDE11A4 relative to 499A and disrupting homodimerization has the opposite effect of the 499T mutation, shifting PDE11A4 from the membrane to the cytosol (Pathak et al. 2016). PDE11A4 can also be shifted between the cytosol and membrane in response to N-terminal phosphorylation events. We have shown that phosphorylation of serines 117 and 124 shifts PDE11A4 from the cytosol to the membrane, while phosphorylation of serine 162 keeps PDE11A4 in the cytosol (Pathak et al. 2016). The ability to therapeutically control the subcellular localization of PDE11A4 may become highly relevant as bipolar disorder, lithium responsiveness, and Alzheimer's disease have all been associated with subcellular compartment-specific differences in cyclic nucleotide signaling (Rahman et al. 1997; Fields et al. 1999; Chang et al. 2003; Mori et al. 1998; Jensen and Mork 1997; Casebolt and Jope 1991; Bonkale et al. 1999).

Not only is PDE11A4 expression restricted to the hippocampal formation, it is uniquely enriched three to tenfold in ventral versus dorsal hippocampus (Kelly 2015; Kelly et al. 2010; Hegde et al. 2016a; Kelly et al. 2014; Kelly 2014). The extent of the VHIPP versus DHIPP enrichment—that is, whether it is closer to three versus tenfold—depends on the mouse strain examined (Pathak et al. 2016). The ventral hippocampal formation in rodents is analogous to the anterior hippocampal formation in primates (Moser and Moser 1998). As such, we will use the term "ventral-anterior" hippocampal formation (VHIPP) and "dorsal-posterior" hippocampal formation (DHIPP) throughout the remainder of this chapter for consistent referencing of these anatomically and functionally distinct subregions across species.

The VHIPP and DHIPP are functionally, anatomically, and biochemically segregated (e.g., (Roman and Soumireu-Mourat 1988; Papatheodoropoulos and Kostopoulos 2000; Gusev et al. 2005; Bast and Feldon 2003; Fanselow and Dong 2010). While the VHIPP modulates sociality, emotion/affect, motivation, stress, behavioral flexibility, and sensorimotor gating, the DHIPP regulates learning, memory, contextual representation, and spatial navigation (c.f., Moser and Moser 1998; Bast and Feldon 2003; Fanselow and Dong 2010; Tseng et al. 2008; Behrendt 2011) also see (Roman and Soumireu-Mourat 1988; Marquis et al. 2008; Gruber et al. 2010). These separable functions are reflected in, if not driven by, differences in the extrahippocampal connectivity of VHIPP versus DHIPP. Whereas the VHIPP is highly interconnected with the prefrontal cortex, amygdala, olfactory bulb, hypothalamus, and the shell of the nucleus accumbens, the DHIPP is highly interconnected with thalamic subregions, sensory-related cortices, and the core of the nucleus accumbens (c.f., Bast and Feldon 2003; Fanselow and Dong 2010). Biochemical segregation of VHIPP versus DHIPP can easily be visualized when mapping expression of numerous gene products (Fanselow and Dong 2010), including PDE11A4 (Fig. 8.1). Consistent with its enrichment in the VHIPP, emerging evidence from human and rodent studies suggests PDE11A4 is a key regulator of social behaviors and mood stabilization.

## 8.4    A Role for PDE11A in Brain Function

Human studies to date largely implicate PDE11A dysfunction in mood disorders (Kelly 2015). Several studies associate PDE11A single nucleotide polymorphisms (SNPs) with major depressive disorder (Wong et al. 2006; Luo et al. 2009b; Cabanero et al. 2009) and 1 study associates an inactivating mutation in PDE11A with suicide risk (Coon et al. 2013). PDE11A has also been nominally associated with fluoxetine and desipramine response (Wong et al. 2006; Luo et al. 2009b), but not with citalopram or duloxetine response (Perlis et al. 2010; Cabanero et al. 2009). Whether the inconsistencies in the latter findings are related to differences in patient populations, differences in the specific antidepressants studied, or some unknown factor remains to be determined. PDE11A SNPs have also been associated with lithium responsiveness in both a retrospective and prospective cohort of patients with bipolar disorder (Couzin 2008; Kelsoe 2010). Further, lithium decreases PDE11A mRNA expression in IPSC-derived hippocampal neurons originating from lithium-responsive patients but not lithium-unresponsive patients (Mertens et al. 2015). As reviewed below, studies in rodents suggest PDE11A may be highly relevant to the social deficits that are associated with mood disorders, and may be particularly important for regulating lithium responsivity.

A link between PDE11A and lithium responsivity is consistent with studies that associate changes in the cAMP cascade with bipolar disorder (Rahman et al. 1997; Fields et al. 1999; Chang et al. 2003; Avissar et al. 1997; Avissar and Schreiber 2006; Schreiber and Avissar 1991; Schreiber et al. 1991; Alda et al. 2013; Dowlatshahi et al. 1999; Fatemi et al. 2010b; Fatemi et al. 2008), including cyclic nucleotide alterations restricted to specific subcellular compartments (Rahman et al. 1997; Fields et al. 1999; Chang et al. 2003) and changes associated with lithium responsivity (Alda et al. 2013; Sun et al. 2004). The link between PDE11A and lithium responsivity is also particularly intriguing in light of the study associating PDE11A SNPs and suicide risk (Coon et al. 2013) because lithium uniquely reduces suicide risk in patients with bipolar disorder (Malhi et al. 2013).

Deletion of PDE11A in mice elicits very selective behavioral deficits. PDE11A KO mice show no differences in basal anxiety- or depression-related behaviors (but see below for drug-induced changes in these behaviors), including elevated plus maze, stress-induced hyperthermia, four-plate, tail suspension test, and forced swim test (Kelly et al. 2010), as well as sucrose preference (WT, 80.3 ± 3.5%; KO, 78.2 ± 3.3%; n = 16-17/genotype; effect of genotype: F(1,28) = 0.022, P = 0.883). They also show no differences in contextual or cued fear conditioning or the motoric response to an acute dopaminergic challenge (Kelly et al. 2010). While single-housed PDE11A KO mice show increased locomotor activity in an open field and normal prepulse inhibition (PPI) of acoustic startle relative to WT littermates (Kelly et al. 2010), group-housed PDE11A KO mice show normal locomotor activity in an open field (WT,11,187 ± 455 cm; KO, 10,978 ± 486 cm; n = 21–25/genotype; effect of genotype (F(1,41) = 0.098, P = 0.756) and modestly lower PPI at the lowest

prepulse intensity relative to PDE11A WT mice (PPI at 4 db above background: WT, 16.49 ± 2.76%; KO, 3.85 ± 2.92%; n = 50–55/genotype; genotype × prepulse intensity: F(2207) = 3.59, P = 0.029; *Post hoc* WT vs. KO within 4 db above background, P = 0.02). The most notable and reliable phenotypes exhibited by PDE11A KO mice, however, are impairments in social behaviors (Kelly et al. 2010; Hegde et al. 2016a; Hegde et al. 2016b).

PDE11A is required for intact social interactions and is a key mechanism by which social experience, particularly social isolation, shapes the brain. Using Brodkin's version of the 3-chamber social approach assay, we found that deletion of PDE11A reduces social approach behaviors towards stranger mice but not towards cagemates (Kelly et al. 2010; Hegde et al. 2016b). The reduced social approach observed in PDE11A heterozygous (HT) and knockout (KO) mice appears somewhat sensitive to the effects of social buffering and depends on the social context (i.e., the strain of the stimulus mouse). Presence of a cagemate improves social approach behavior of PDE11A KO mice towards a novel mouse from the colony but not towards a novel C57BL/6J; whereas, presence of a cagemate improves social approach behavior of PDE11A HT mice towards a C57BL/6J but not a novel mouse from the colony (Hegde et al. 2016b). Other mice appear to be capable of detecting abnormalities in the social behavior of PDE11A KO mice, because male and female C57BL/6J spend significantly more time with a sex-matched PDE11A WT mouse vs its KO littermate (Hegde et al. 2016b), suggesting the PDE11A KO mice may be socially isolated. We believe this finding is particularly intriguing given the PDE11A SNP that has been associated with increased suicide risk in a Utah pedigree is an inactivating mutation (Coon et al. 2013). As noted above, social isolation decreases PDE11A4 protein expression within the membrane fraction of VHIPP samples relative to group-housed mice, and this isolation-induced decrease in PDE11A4 expression is sufficient to impair subsequent social behavior—both social approach and social memory formation (Hegde et al. 2016b). Consistent with these behavioral phenotypes, RNA sequencing of VHIPP from PDE11A KO and WT littermates shows that PDE11A regulates gene expression in the oxytocin signaling pathway (Hegde et al. 2016b), a key signaling cascade underlying social behaviors (c.f. Ebstein et al. 2012; Viero et al. 2010; Lukas and Neumann 2013; Stoesz et al. 2013).

We have also shown that PDE11A is required for the formation of social memories (Kelly et al. 2010; Hegde et al. 2016a). Although PDE11A KO mice show intact short-term memory for social odor recognition (SOR) or social transmission of food preference (STFP), PDE11A KO mice fail to show any long-term memory for SOR or STFP 24 h following training. Such a pattern suggests PDE11A KO mice retain the ability to learn and retrieve each memory but fail in their ability consolidate these memories to a long-lasting form (Hegde et al. 2016a). In contrast, PDE11A KO mice show perfectly intact contextual fear conditioning (Kelly et al. 2010) and non-social odor recognition memory 24 h after training (Hegde et al. 2016a), suggesting the SOR and STFP memory consolidation impairments are selective and due the social nature of the stimuli employed. There are several possible explanations for why PDE11A KO mice exhibit such a selective memory deficit. As noted above, the social deficits present in the PDE11A mutant mice are consistent with the

fact that PDE11A4 is enriched in the VHIPP. The social deficits are also consistent with our RNA sequencing study showing that PDE11A KO mice exhibit significantly altered gene expression in the oxytocin pathway (Hegde et al. 2016b). Indeed, like our PDE11A KO mice, oxytocin KO mice similarly show an inability to form social memories while their ability to form non-social memories remains intact (Ferguson et al. 2000). The memory impairments observed in PDE11A KO mice may also be related to altered glutamatergic signaling. Previously, we showed that PDE11A KO mice are more sensitive to the hyperactivating effects of the NMDA receptor antagonist MK-801 (Kelly et al. 2010). We have also shown that deleting PDE11A impairs *de novo* protein synthesis, which is required to transition memory from a short-term to a long-term state. PDE11A KO mice show significantly reduced expression of the ribosomal S6 kinase 2 (RSK2) and phosphorylation of the ribosomal protein S6 at serines 235/236 relative to WT littermates (Hegde et al. 2016a). It will be of interest to future studies to determine which of these mechanisms accounts for social memory deficits in PDE11A KO mice and if those deficits can be reversed.

Interestingly, the manifestation of social memory deficits precedes the manifestation of social approach deficits in PDE11A mutant mice. That is, adolescent PDE11A KO mice already have an inability to form social long-term social memories (Hegde et al. 2016a) but show no differences in their social approach behavior, relative to WT littermates (Hegde et al. 2016b). This raises the interesting possibility that adolescent PDE11A mutant mice have a fundamental inability to form long-term memories for what is and what is not a socially-acceptable behavior, which ultimately leads to alterations in social approach behavior at a later age. Such a relationship has been observed in humans where impaired social skills early in development predict lower quality friendships in adolescents with intellectual disabilities (Tipton et al. 2013). It will be of interest to future studies to determine if social interaction deficits observed in adult PDE11A mutant mice are, in fact, directly related to their inability to form social memories.

As noted above, PDE11A has been genetically and functionally associated with lithium responsivity in patients with bipolar disorder (Couzin 2008; Mertens et al. 2015; Kelsoe 2010). In mice, we have shown that PDE11A4 negatively regulates lithium responsivity (Pathak et al. 2016). PDE11A4 mRNA and protein expression negatively correlate with lithium responsivity such that C57BL/6J mice that respond well to lithium exhibit lower levels of PDE11A4 expression in hippocampus than do BALB/cJ mice that respond poorly to lithium (Pathak et al. 2016). Further, using PDE11A mutant mice, we have shown that decreasing PDE11A expression is, in fact, sufficient to increase lithium response (Pathak et al. 2016). At face value, this may suggest that a PDE11A inhibitor might augment the therapeutic effects of lithium. Indeed, AKT—an enzyme whose activation is required for lithium's behavioral effects (Pan et al. 2011)—is predicted to phosphorylate PDE11A at serines 117 and 124 (Kelly 2015). As noted above, phosphorylation of S117/S124 would shift PDE11A4 towards the membrane compartment (Pathak et al. 2016), thereby removing it from the cytosol where AKT is selectively located. Shifting PDE11A from the cytosol to the membrane could serve to extend the activation of AKT (i.e., its phosphorylation),

because PDE11A4 would no longer be in a position to negatively regulate the cytosolic pools of cAMP that lead to phosphorylation of AKT in neurons via Epac (Nijholt et al. 2008). Of course, deleting PDE11A4 would artificially augment such feedforward signaling. That said, it is equally possible that lowered PDE11A expression may simply trigger a specific pathophysiology that happens to be particularly well-treated by lithium (Pathak et al. 2016). Indeed, both PDE11A KO mice and IPSC-derived hippocampal neurons from bipolar patients exhibit altered signaling in the neuroactive-ligand receptor pathway and increased neural activity (Kelly et al. 2010; Hegde et al. 2016b; Mertens et al. 2015). Further, decreasing PDE11A4 expression is sufficient to upregulate the proinflammatory cytokine IL-6 (Pathak et al. 2016), increased signaling of which has been repeatedly measured in patients with mania, depression, and suicidal ideation (Dowlati et al. 2010; Maes et al. 1997; Maes et al. 1995; Brietzke et al. 2009; Simon et al. 2008; Niculescu et al. 2015; Khandaker et al. 2014) and is reversed by lithium (Watanabe et al. 2014). Thus, studies in mice are most consistent with the notion that lowered levels of PDE11A trigger a specific pathophysiology that is readily treated by lithium.

PDE11A inactivating mutations have been identified in patients with adrenocortical tumors (Vezzosi et al. 2012; Horvath et al. 2006a; Horvath et al. 2006b; Libe et al. 2008; Libe et al. 2011) but see (Bimpaki et al. 2009; Louiset et al. 2010), so it is also worth noting that one study has examined the anterior hippocampus in patients with Cushing Syndrome, albeit not patients genotyped with regard to PDE11A mutations. Maheu and colleagues (Maheu et al. 2008) found heightened functional activation of the VHIPP during encoding of an emotional-faces recognition test in patients with Cushing Syndrome. As noted above, PDE11A KO mice show deficits in social odor recognition memory and social transmission of food preference (Kelly et al. 2010; Hegde et al. 2016a). PDE11A KO mice also show heightened activation of ventral CA1 relative to WT littermates, as indicated by increased expression of the activity-regulated immediate-early gene Arc (Kelly et al. 2010). In this context, it is important to note that our PDE11A KO mice do not appear to develop any adrenal tumor pathology (Kelly et al. 2010), consistent with the fact that the mouse adrenal gland does not express PDE11A (Kelly 2015), suggesting it is the loss of PDE11A4 in the brain, as opposed to adrenal dysfunction, that is driving the neurocognitive deficits of PDE11A KO mice. Studies in patients with Cushing Syndrome have correlated overall hippocampal function with dysregulated cortisol levels (Starkman et al. 1999; Starkman et al. 1992; Forget et al. 2000; Starkman et al. 2001); however, a potential role for aberrant PDE11A signaling within the VHIPP has not yet been examined. Unfortunately, to our knowledge, hippocampal function has not been assessed in patients genotyped with PDE11A inactivating mutations. Thus, it remains to be determined whether hippocampal deficits observed in patients with Cushing Syndrome are simply related to the indirect effects of rising peripheral cortisol levels or the direct effects of PDE11A inactivation within the hippocampus.

Ectopic PDE11A expression in brain regions outside of the hippocampus may also be an important facet of disease pathophysiology. Fatemi and colleagues reported an increase in PDE11A mRNA expression in the cerebellum of patients

with bipolar disorder relative to controls (Fatemi et al. 2010a). We are unable to detect PDE11A expression in cerebellum taken from healthy humans or rodents, suggesting that a disease state may drive ectopic expression of PDE11A outside of the hippocampal formation (Kelly 2015). Our recent findings and ongoing studies in the lab suggest that aging drives ectopic expression of PDE11A4 outside of the hippocampal formation (Kelly et al. 2014), with negative consequences. If this holds true, it may be important to not simply modulate catalytic activity of PDE11A4 but rather to restore proper physiological control over the mechanisms controlling PDE11A4's unique tissue-specific expression profile.

## 8.5   PDE11A Pharmacological Tools

As extensively reviewed elsewhere (Kelly 2015), progress has been made in identifying pharmacological activators and inhibitors of PDE11A catalytic activity. Jager and colleagues used an in vitro FRET-based assay to screen compounds for their ability to bind to and initiate a conformational change in a fragment of PDE11A4 that included both GAF domains (Jager et al. 2012). While cAMP failed to bind the PDE11A4 GAF construct, both cGMP and the cGMP analog Rp-8-pCPT-PET-cGMPS did (Jager et al. 2012). In a catalytic activity assay, cGMP failed to stimulate PDE11A4 catalytic activity. In contrast, Rp-8-pCPT-PET-cGMPS stimulated PDE11A catalytic activity of both recombinant human PDE11A4 as well as native mouse PDE11A4 enriched from hippocampus approximately four to fivefold (Jager et al. 2012). Interestingly, Rp-8-pCPT-PET-cGMPS failed to activate PDE11A when the 196 amino acids upstream of the PDE11A4 GAF-A domain were deleted (Jager et al. 2012). This suggests that it will be important for PDE11A compound screens to employ full-length PDE11A4, as opposed to some truncated version of the protein. Although Rp-8-pCPT-PET-cGMPS does not appear to bind the GAF domains of PDE5A or PDE2A (Jager et al. 2010), suggesting specificity in its ability to target the GAF domains of PDE11A4, it is well known to have significant off-target activities, including inhibition of PKG and cGMP-gated ion channels (see product insert for Rp-8-pCPT-PET-cGMPS on www.biolog.de). Although this off-target activity severely limits the use of Rp-8-pCPT-PET-cGMPS as a tool PDE11A activator, this study provides critical proof-of-concept that it is possible to stimulate PDE11A4 catalytic activity.

Ceyhan *et al.* identified four PDE11A4 inhibitors using a yeast-based high-throughput assay (Ceyhan et al. 2012). All four compounds were fairly potent (IC50s = 0.11–0.33 μM) and BC11-28 and BC11-38, in particular, were highly selective for PDE11A4 versus other PDE families (>350-fold selective for PDE11A) (Ceyhan et al. 2012). One strength of this screen was the fact that it employed full-length PDE11A4, as opposed to an isolated catalytic domain; therefore, these compounds are likely to inhibit the native protein. That said, because the screen was conducted with the full-length PDE11A4, it is not possible to determine whether the inhibitors compete for the substrate binding pocket or modulate catalytic activity

via binding to an allosteric site (e.g., the GAF-A domain) (Ceyhan et al. 2012). PDE11A cGMP hydrolytic activity was inhibited by all four compounds in both the yeast-based assay and an enzyme assay. In an H295R cell-based assay, however, only BC11-38 was able to inhibit PDE11A cAMP hydrolytic activity (Ceyhan et al. 2012). The fact that all four compounds were able to inhibit cGMP-PDE11A activity in the yeast-based assay but only one was able to inhibit cAMP-PDE11A activity in the H295R-based assay may simply be related to differential availability of the four PDE11A inhibitors in the two different media employed in the respective assays (i.e, differences in solubility or freely available compound) (Ceyhan et al. 2012). An alternative possibility, reviewed elsewhere in great detail (Kelly 2015), is that certain compounds may be functionally selective in their ability to inhibit cAMP-PDE11A versus cGMP-PDE11A catalytic activity. While many compounds, such as IBMX, zaprinast, dipyrimadole, and a few PDE5A-preferring inhibitors, inhibit cAMP-PDE11A and cGMP-PDE11A activity with equal potency, several other PDE5A-preferring inhibitors require much higher concentrations to inhibit the cAMP-hydrolyzing activity of PDE11A versus its cGMP-hydrolyzing activity (Yuasa et al. 2000; Ahmed et al. 2011; Ahmed et al. 2012; Mohamed et al. 2011). Clearly the BC compounds are membrane-penetrant; however, their ability to cross the blood-brain-barrier has not been determined. Indeed no studies have yet reported in vivo activities of the compounds or their pharmacokinetic profiles. Although it remains to be determined whether these PDE11A inhibitors will prove useful for in vivo experiments, their identification certainly proves it is possible to inhibit PDE11A with a high degree of selectivity versus other PDEs.

## 8.6   Future Considerations for PDE11A Research

In recent years we have learned much about PDE11A4 function in the brain, but many questions remain. Considering the number of conflicting findings in the field regarding the tissue expression profile of PDE11A, it will be critical to continue carefully assessing which tissues and cell types express the various PDE11A iso-forms, and how those expression patterns may change with age or disease state. Given how dramatically PDE11A4 expression increases in the hippocampus across the lifespan (Kelly et al. 2010; Kelly et al. 2014), the "when and where" of PDE11A4 expression will be critically important when evaluating the efficacy and side effect potential of a PDE11A4-targeted therapeutic. It will also be key in understanding whether PDE11A4 may be considered a therapeutic target in the context of neuro-developmental, adulthood, or age-related disease. Although emerging evidence shows that phosphorylation events and homodimerization can alter the subcellular compartmentalization of PDE11A4 (Pathak et al. 2016; Pathak et al. 2015), it is not yet clear if these mechanisms also affect catalytic activity and/or whether they can be therapeutically exploited to restore aberrant subcellular localization of the enzyme (e.g., in the case of social isolation; Hegde et al. 2016b). That said, the GAF domains are highly intriguing from a drug target perspective because they are found

in no other mammalian proteins other than PDEs (Francis et al. 2011), and the PDE11A4 GAF domains are less than 50% homologous to those in other PDE families (Viero et al. 2010). This, together with the fact that PDE11A4 is the only PDE11A isoform with a full GAF-A domain, suggests it might not only be possible to selectively target PDE11A4 over other PDE families, but also selectively target PDE11A4 relative PDE11A3, A2 or A1. With such specific targeting, it might be possible to reduce, if not eliminate, side effect liability associated with targeting other PDEs or PDE11A signaling outside the brain. Finally, we need to gain a far better understanding of signaling events that lie upstream and downstream of PDE11A, and how coupling to those signaling events may change with age, disease, and acute versus chronic manipulations.

## 8.7  Summary

Evidence is mounting that PDE11A critically regulates select aspects of brain function. Our studies in PDE11A KO mice show that PDE11A plays a crucial role in the formation of social memories and lithium responsiveness and is a key mechanism by which social experience feeds back to shape the brain (Kelly et al. 2010; Hegde et al. 2016a; Pathak et al. 2016; Hegde et al. 2016b). These finding are consistent with the fact that human studies associate PDE11A with lithium responsiveness, MDD, and suicide risk (Couzin 2008; Wong et al. 2006; Mertens et al. 2015; Luo et al. 2009b; Cabanero et al. 2009; Coon et al. 2013; Kelsoe 2010; Aitchison et al. 2009). As extensively reviewed elsewhere (Kelly 2015), there are a large number of studies reporting VHIPP dysfunction as well as cyclic nucleotide dysregulation in patients with neuropsychiatric disease, particularly schizophrenia and Alzheimer's disease (Lee et al. 2004; Pegues et al. 2003; Suddath et al. 1990; Rametti et al. 2007; Schobel et al. 2009a; Shenton et al. 1992; Nesvaderani et al. 2009; Ghose et al. 2009; Zhou et al. 2008; Goldman et al. 2011; Schobel et al. 2009b; Jessen et al. 2003; Hall et al. 2010; Rajarethinam et al. 2001; Rusch et al. 2008; Laakso et al. 2000; Leube et al. 2008; Jansen et al. 1993; Quiroz et al. 2010; Yakushev et al. 2011a; Yakushev et al. 2011b; Yakushev et al. 2010; Rahman et al. 1997; Avissar et al. 1997; Garver et al. 1982; Kafka et al. 1979; Kafka et al. 1986; Kanof et al. 1986; Kafka and van Kammen 1983; Ofuji et al. 1989; Kaiya 1992; Kaiya et al. 1990; Kanof et al. 1989; Kang 1990; Kanof et al. 1987; Bowers and Study 1979; Belmaker et al. 1978; Gattaz et al. 1983; Ebstein et al. 1976; Turetsky and Moberg 2009; Memo et al. 1983; Avissar et al. 2001a; Avissar et al. 2001b; Edmunds et al. 2008; Young et al. 1991; Young et al. 1993; Young et al. 1994; Cowburn et al. 1994; Gurguis et al. 1999a; Gurguis et al. 1999b; Gurguis et al. 1997; Bonkale et al. 1996; Shanahan et al. 1997; Yamamoto et al. 2000; Fowler et al. 1995; Ohm et al. 1989; Baltrons et al. 2004; Ohm et al. 1991; Martinez et al. 1999). Certainly, a PDE11A-targeted therapeutic would be positioned to address both. Clearly, future studies should determine which, if any, neuropsychiatric disorders are associated with alterations in PDE11A expression, localization, and/or catalytic activity or if a

PDE11A-targeted therapeutic could compensate for upstream or downstream insults (e.g., at the AMPA receptor). Clearly more studies examining PDE11A in patient tissue are needed to drive a therapeutic indication for a PDE11A modulator, but we believe the data to date suggest PDE11A holds potential as a future therapeutic target (Kelly 2015).

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