Miao-Kun Sun and Daniel L. Alkon

Blanchette Rockefeller Neurosciences Institute, Morgantown, WV, USA

Activation of Protein Kinase C Isozymes for the Treatment of Dementias

Abstract

Memories are much more easily impaired than improved. Dementias, a lasting impairment of memory function, occur in a variety of cognitive disorders and become more clinically dominant as the population ages. Protein kinase C is one of the "cognitive kinases," and plays an essential role in both memory acquisition and maintenance. Deficits in protein kinase C (PKC) signal cascades in neurons represent one of the earliest changes in the brains of patients with Alzheimer's disease (AD) and other types of memory impairment, including those related to cerebral ischemia and ischemic stroke. Inhibition or impairment of PKC activity results in compromised learning and memory, whereas an appropriate activation of certain PKC isozymes leads to an enhancement of learning and memory and/or antidementic effects. In preclinical studies, PKC activators have been shown to increase the expression and activity of PKC isozymes, thereby restoring PKC signaling and downstream activity, including stimulation of neurotrophic activity, synaptic/structural remodeling, and synaptogenesis in the hippocampus and related cortical areas. PKC activators also reduce the accumulation of neurotoxic amyloid and tau protein hyperphosphorylation and support antiapoptotic processes in the brain. These observations strongly suggest that PKC pharmacology may represent an attractive area for the development of effective cognition-enhancing therapeutics for the treatment of dementias.

I. Introduction

Dementia, a lasting impairment of memory function, represents a major challenge to modern medicine. According to Alzheimer's Disease

Advances in Pharmacology, Volume 64
1054-3589/12 $00.00

http://dx.doi.org/10.1016/B978-0-12-394816-8.00008-8

International, the total worldwide cost of care for patients with dementias in 2010 is $604 billion (Alzheimer's Disease International, 2010), which is also set to soar as the population ages in the near future. Dementias—including Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia—are memory disorders that are caused by a variety of neural impairments or injuries that lead to compromised cognitive function. There are currently no curative therapeutics for any type of dementia, highlighting an unmet and urgent need for the development of new, cost-effective agents that can target the processes of neural injury that lead to cognitive dysfunction and memory impairment characteristic of dementia.

Cognition, including the formation and retention of memories, results from activity-generated (i.e., acquiring experience and maintaining knowledge of that experience) neuronal Ca^{2+} and other signals that promote gene transcription and protein synthesis in the brain. Protein kinase C (PKC) belongs to a multigene family of phospholipid-dependent serine–threonine kinases, and is part of an essential signaling network in the brain. PKC isoforms are critically involved in modulating synaptic function/transmission; neurite outgrowth/neuronal plasticity; functions of membrane proteins, including enzymes and channels; neuronal metabolism, inflammation, carcinogenesis, proliferation, and gene expression; neuroprotection and neurodegeneration; and behavior, learning, and memory (Alkon et al., 1998; Hama et al., 2004). PKC signaling cascades are impaired or become dysfunctional in many disease processes, and loss of normal PKC signaling may underlie the pathogenesis of various brain disorders, including dementias. Thus, the PKC signaling system represents an important target for discovering new therapeutics for dementias.

II. PKC Signaling System

A. PKC Isoforms

Twelve PKC isoforms have so far been identified in mammals. Based on their homology and sensitivity to activators, they are commonly divided into three subgroups (Fig. 1): (1) classical PKC (cPKC); (2) novel PKC (nPKC); and (3) atypical PKC (aPKC). The number of isoforms differs from other species. For example, in *Aplysia*, at least three isoforms, Apls I, II, and III, have been identified so far.

The cPKC subgroup members contain four homologous domains (C1, C2, C3, and C4) separated by isozyme-specific variable regions (labeled V; Fig. 1), and are activated by Ca^{2+} stimulating factors, such as diacylglycerol (DAG), phosphatidylserine (PS), or other PKC activators. The C-terminal active site contains the C3 and C4 domains and functions as a serine/threonine kinase. The C3 region includes the binding site for adenosine-5'-triphosphate

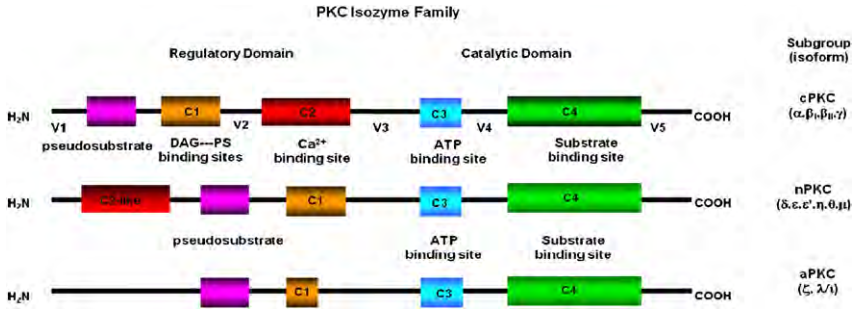

FIGURE 1 Domain structures of the PKC isoforms. The homologous domains (C1, C2, C3, and C4) are separated by isoform-unique (variable or V) regions. The C1 domain contains binding sites for diacylglycerol (DAG) and phosphatidylserine (PI). For color version of this figure, the reader is referred to the online version of this book.

(ATP) (as the phosphate donor for phosphotransferase activity), and the C4 region contains the substrate binding site. At the N-terminal, there are two main regulatory domains, the activator-binding C1 domain and the Ca^{2+}-binding C2 domain, which are also involved in membrane association. By contrast, the nPKC subgroup members contain a C2 domain that lacks the acidic Ca^{2+}-binding pocket; as a result, the Ca^{2+}-binding affinity of nPKCs is very low and Ca^{2+} is not required for activation. The aPKC subgroup members lack both the Ca^{2+}-binding site in the C2 domain and one-half of the C1 homologous domain (atypical C1 domain). aPKCs are insensitive to Ca^{2+}, DAG, phorbol esters, and some of the other PKC activators, but they can be activated by PS, arachidonic acid, and ceramide.

One important feature of the PKC isoforms is an N-terminal pseudosubstrate motif near the C1 domain. All of the PKC isoforms but PKCμ (human) and its murine homologue, PKD, contain this motif, which acts as an autoinhibitory domain that binds to the PKC catalytic domain, thereby maintaining an inactive state. Removal of this autoinhibitory fragment is one way by which PKC isoforms can be activated. Upon proteolytic cleavage of the autoregulatory region, the PKC isozymes can be transformed into a persistently active kinase (PKM). For example, PKCδ can be cleaved by caspase-3 to generate a catalytically active kinase (Emoto et al., 1995; Kanthasamy et al., 2003), an event that has been linked to dieldrin-induced dopaminergic degeneration, a potential environmental risk factor for development of Parkinson's disease (Kitazawa et al., 2003).

B. PKC Isoform Activation

PKC activation depends on the presence of required activators, membrane association and translocation, and binding to specific anchoring molecules. The phosphoinositide (PI) signaling pathway is one of the

major cascades that leads to activation of PKC. Stimulation of certain G-protein-coupled receptors activates phospholipase C (PLC, Fig. 2), which hydrolyzes phosphatidylinositol-4, 5-bis-phosphate to form inositol triphosphate (IP_3) and DAG. IP_3 binds to intracellular receptors, causing Ca^{2+} release from the endoplasmic reticulum, whereas DAG binds to and activates most PKC isozymes. The combination of the Ca^{2+} wave and DAG simulate the cPKC isoforms, while DAG alone activates the nPKC and aPKC isoforms. Thus, the concomitant release of intracellular Ca^{2+} release permits activation of all PKC isoforms.

PKC activation also requires membrane association and subcellular translocation. Activated PKCβI, for example, is found inside the nucleus of cardiac myocytes, whereas activated PKCβII is located at the perinucleus and cell periphery. The localization of different PKC isoforms to different areas of the cell appears to involve binding of the activated isoforms to their specific anchoring molecules, the receptors for activated C-kinase (RACKs). RACKs function by selectively anchoring activated PKC isozymes to their respective subcellular sites. They bind only activated PKC

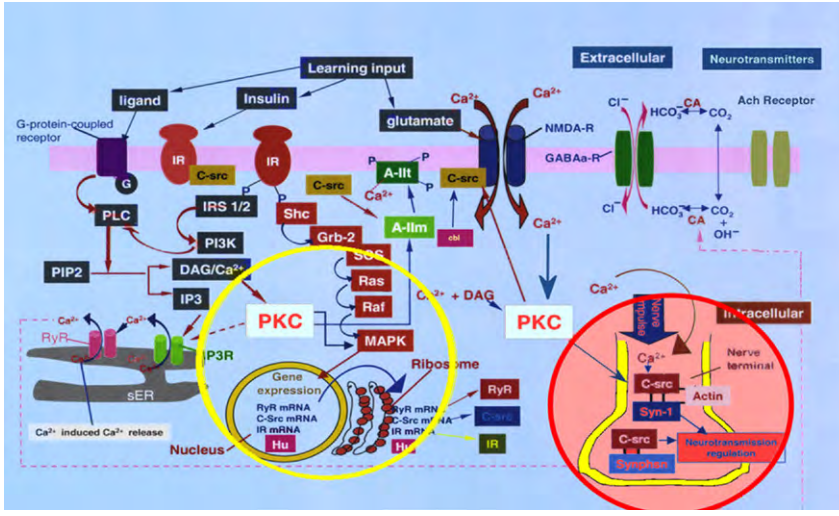

FIGURE 2 **Schematic summary of multimodal drug pathways in memory-enhancing and antidementic therapeutics.** PKC activators may affect neuronal functions through multiple signaling pathways, including regulation of synaptic transmission involved in cognitive processing, membrane channel functions, Ca^{2+} release, gene expression, and protein synthesis. Ach, acetylcholine; cbl, casitas b-lineage lymphoma protein(s); CA, carbonic anhydrase; DAG, diacylglycerol; IP3, inositol triphosphate; IR, insulin receptor; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol-4, 5-bis-phosphate; PLC, phospholipase C; RyR, ryanodine receptor; sER, smooth endoplasmic reticulum; SHC, Src homology domain-containing protein(s); Synphsn, synaptophysin. For color version of this figure, the reader is referred to the online version of this book.

but are not necessarily substrates of the enzyme, and PKC binding to RACKs is not mediated via the catalytic domain of the kinase. RACK binding is, however, required for PKC to mediate its cellular responses. Inhibition of PKC binding to RACKs *in vivo* has been shown to inhibit PKC translocation and PKC-mediated functions (Johnson et al., 1996; Ron & Mochly-Rosen, 1995; Smith & Mochly-Rosen, 1992). Aβ oligomers decrease RACK1 distribution in the membrane fraction of cortical neurons (Liu et al., 2011). Peptides that mimic either the PKC-binding site on RACKs or the RACK-binding site on PKC isozymes are isozyme-specific translocation inhibitors of PKCs. For example, an eight amino acid peptide derived from PKCε (εV1-2; Glu-Ala-Val-Ser-Leu-Lys-Pro-Thr) contains a part of the RACK-binding site on PKCε and selectively inhibits PKCε-mediated functions. The structural requirement for PKC isozyme-specific binding by RACKs is of particular interest for the development of PKC isozyme-selective nonpeptide inhibitors and activators.

Depending on the cell types and isoforms involved, activation of PKC isozymes results in phosphorylation of the hydroxyl moiety of serines and threonines within a variety of target proteins. Serine/threonine phosphorylation of a given protein can alter its stability, protein–protein interactions, cellular distribution, or catalytic activity, which in turn propagates signals from the plasma membrane to molecular targets in the cytoplasm and nucleus. One PKC target protein is GAP-43, a growth-associated protein with an approximate molecular weight of 43 kDa.

C. Synaptic and Neuronal Functions of PKC Isozymes

PKC is a known regulator of synaptic functions, including the synthesis, vesicle-refilling, and release of neurotransmitters in cholinergic, γ-aminobutyric acid (GABA)-ergic, dopaminergic, and glutamatergic systems (Dobransky et al., 2004; Malenka et al., 1986; Nicholls, 1998; Okada et al., 2004; Stevens & Sullivan, 1998). PKC also regulates gene expression in mature neurons (Roberson et al., 1999), and the activity and cell surface expression of several plasma membrane proteins, including G-protein-coupled receptors, neurotransmitter transporters (serotonin, dopamine, norepinephrine, glutamate, and GABA), and the Na^+/H^+ antiporter. Activation of PKC enhances Ca^{2+} action potentials, increases neurotransmitter release, and decreases voltage-gated Na^+ currents (Carr et al., 2002; Carr et al., 2003; Chen et al., 2005; Chen, Yu et al., 2006; González et al., 2002) through enhancement of intrinsic slow inactivation gating (Chen et al., 2006) and voltage-dependent K^+ currents (Alkon et al., 1986; Farley & Auerbach, 1986) and Ca^{2+}-activated K^+ currents in the hippocampus, and through inhibition of the delayed rectifier K^+ channel (PKCε, Song et al., 2011). Each of these PKC-mediated synaptic changes are relevant in cognition (Alkon et al., 1986, 1998; Bank et al., 1988; Farley & Auerbach, 1986; LoTurco et al., 1988; Zhang

et al., 2005). PKC activation potentiates synaptic responses in a variety of preparations (Alkon & Rasmussen, 1988; Bank et al., 1988; Kaczmarek, 1987; LoTurco et al., 1988; Stevens & Sullivan, 1998; Zhang et al., 2005).

1. Glutamatergic System

The glutamatergic system, with glutamate as the major excitatory transmitter in the mammalian brain, interacts with PKC signaling pathways. In cultured cerebellar granule neurons, *N*-methyl-D-aspartic acid receptor (NMDAR) activity has been shown to regulate PKC activity (Wang et al., 2004). PKC mediates (–)-epigallocatechin gallate, the main polyphenolic constituent of green tea, to induce Ca^{2+}-dependent glutamate release in the rat cerebral cortex (Chou et al., 2007). PKC also mediates brain-derived neurotrophic factor (BDNF)-mediated modulation of NMDAR subunit 1 in the dorsal horn of the rat spinal cord (Salck et al., 2004). The α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) receptor subunits glutamate receptor (GluR)1 and GluR2 contain type I and type II postsynaptic density protein of 95 kDa/Discs-large/ZO-1 (PDZ) binding motifs, respectively, as does the metabotropic GluR (mGluR)7α. The C-terminus of PKCα has a type I PDZ binding motif, where GluR2 has a type II PDZ binding motif. Both motifs are recognized by the PDZ domain of protein interacting with C kinase 1 (PICK1). The PDZ domain of PICK1 appears to have distinct PKCα and GluR2 binding subsites and PICK1-PKCα-controlled phosphorylation regulates the synaptic expression and function of GluR2 (Dev et al., 2004). Knock-in mice lacking the PDZ-ligand motif of mGluR7α show an impaired PKC-dependent regulation of glutamate release and spatial working memory deficits (Zhang et al., 2008).

It has been shown that PKC activation leads to phosphorylation of GluR 2/3 (at serine 880) in the Purkinje cells. GluR 2/3 phosphorylation appears to be the critical step for parallel fiber long-term depression (LTD; Rekart et al., 2005). Phosphorylation of GluR1 on serine 818 by PKC controls synaptic incorporation of GluR1-containing AMPA receptors into the synapses during long-term potentiation (LTP; Boehm et al., 2006). Postsynaptic inhibition of PKC activity holds AMPARs at the perisynaptic regions, making both LTP and spine expansion labile (Yang et al., 2010). PKC mediates an AMPA receptor subtype switch (from GluR2-lacking [Ca^{2+}-permeable] to GluR2-containing [Ca^{2+}-impermeable] receptors) caused by activation of extrasynaptic NMDARs in mouse cerebellar stellate cells (Sun & Liu, 2007).

In pyramidal neurons of the rat prefrontal cortex, mGluR activity has been shown to enhance NMDAR currents via a PKC-dependent mechanism (Tyszkiewcz et al., 2003). In the perirhinal cortex, mGluR-LTD requires activation of the PKC-PICK1 signaling pathway (Jo et al., 2008). In the hippocampal CA1 pyramidal neurons, mGluR6-containing kainate

receptors are probably involved in PKC-mediated inhibition of the slow after-hyperpolarization (Melyan et al., 2002). Glutamate also desensitizes mGluR5a and mGluR5b via PKC-mediated phosphorylation of mGluR5 at multiple sites (Gereau & Heinemann, 1998).

2. *GABAergic System*

GABA is the major inhibitory neurotransmitter in the adult mammalian brain. In addition to the agents that act on GABA receptors (GABARs) as agonists or antagonists, GABAR currents can be modulated by positive and negative allosteric agents, such as benzodiazepines, barbiturates, neurosteriods, and zinc. PKC phosphorylates several GABAR subunits within their major intracellular domains, changing GABAR functions and their allosteric modulations. Phosphorylation of serine 443 by PKC increases α4 subunit-containing $GABA_AR$ cell surface expression and insertion into the plasma membrane of neurons in the hippocampus, thereby mediating tonic inhibition (Abramian et al., 2010). PKC activation may increase the clearance of GABA from synaptic and extrasynaptic sites into astrocytes (Vaz et al., 2011). PKC activation decreases GABAR function in most cases (Filippova et al., 2000; Krishek et al., 1994; Leidenheimer et al., 1993), but can also increase GABAR currents in some cases (Lin et al., 1994; Lin et al., 1996; Poisbeau et al., 1999). In the hippocampus, PKC activation increases miniature inhibitory postsynaptic current (mIPSC) peak amplitudes in granule cells but have no effect on the mIPSC in CA1 neurons (Poisbeau et al., 1999). In the NT2-N neurons, activation of PKC isozymes results in reduced apparent affinity of diazepam to the GABARs and decreased allosteric enhancement by benzodiazepines (Gao & Greenfield, 2005).

3. *Cholinergic System*

The cholinergic system in the brain plays an important role in learning and memory. Functional deficits in the cholinergic system and neuronal injury are among the earliest detectable abnormalities in neurotransmitter systems in AD. Arachidonic acid stimulates choline acetyltransferase activity through PKC activation (Chalimoniuk et al., 2004). Choline acetyltransferase phosphorylation in neurons is mediated predominantly by PKC at Ser 476 (which is required for phosphorylation at other serine residues to proceed), with PKC activation also increasing phosphorylation at Ser 440 and enhancing choline acetyltransferase activity (Dobransky et al., 2004).

Functional interaction between the cholinergic system and PKC has also been noted. Muscarinic activation of G-protein-coupled receptors leads to stimulation of PLC, which cleaves the membrane phospholipids phosphatidyl-inositol-4,5-bisphosphate to form the PKC activators IP_3 and DAG. As described previously, IP_3 initiates Ca^{2+} release from intracellular stores, and

high Ca^{2+} levels are required for cPKC activation. PKC activation, on the other hand, enhances acetylcholine release from rat hippocampal slices (Chaki et al., 1994). Activation of the presynaptic α7 acetylcholine receptors on the glutamatergic terminals in the CA1 region of the rat hippocampus facilitates glutamate release via an action on PKC (Yamamoto et al., 2005). Based on these observations, another promising approach to developing antidementic therapies would involve targeting PKC-induced presynaptic facilitation (Nishizaki et al., 2000).

4. Dopaminergic System

Dopaminergic activity in the brain is associated with many types of cognition, particularly emotion-associated memory and reward decision-making. The dopamine-mediated enhancement of spike firing in nucleus accumbens shell medium spiny neurons can be prevented by the PKC inhibitor bisindolymaleimide but not by the phospholipase C inhibitor 1-[6-((17b-3-methoxyestra-1,3,5(10)-trien-17-yl) amino)hexyl]-1H-pyrrole-2,5-dione, suggesting a role for the DAG-independent aPKCs (Hopf et al., 2005). In PKCε knockout mice, nicotinic regulation of dopamine release is reduced in the brain reward network (Lee & Messing, 2011), most likely due to a down-regulation of α_6 nAChR subunit mRNA in the ventral midbrain and striatum (Exley et al., 2008). Morphine-induced reward memory, however, may involve the PKCγ isoform (Ping et al., 2012). The protein levels of PKCγ, but not PKCα, βI, βII, and/or ε, were significantly up-regulated in membrane functions of the limbic forebrain obtained from morphine-conditioned mice (Narita et al., 2001). In both porcine aortic endothelial and HeLa cells, PKC activation results in rapid degradation of dopamine transporter ($t_{1/2}$ of approximately 1–2 h; Miranda et al., 2005), through accelerated internalization and probably lysosomal degradation. In C6 glioma cells, internalization is mediated by PKCε, whereas degradation is mediated by PKCα through PI3K (Davis et al., 1998; Gonzalez et al., 2002).

D. Synaptogenesis

Synapses, located on dendritic spines, are polarized structures in which proteins and mRNA become asymmetrically localized. PKC isoforms, including PKCε, are involved in regulation of dendritic spine and synapse structure and function. Activation of PKCε results in synaptogenesis as well as prevents synaptic loss related to brain injury in adult rodents (Hongpaisan & Alkon, 2007; Sun et al., 2008; Sun et al., 2009). PKCε activation leads to an increased expression of BDNF, which initiates complex signaling pathways that modify/repair synaptic structure and function (Adasme et al., 2011). BDNF-induced spine formation and growth require functional RyR (Adasme et al., 2011). At *Drosophila* glutamatergic presynaptic structures,

aPKC regulates the stability of microtubules by promoting their association with the MAP1B-related protein Futsch. At the postsynaptic structure, aPKC regulates the synaptic cytoskeleton by controlling the extent of actin-rich and microtubule-rich areas (Ruiz-Canada et al., 2004). Neurons overexpressing PKMζ, an independent C-terminal domain of PKCζ, exhibit shorter spines, primarily the stubby type, with no differences in terms of spine density, dendritic arborization, or overall viability (Ron et al., 2012). Activation of PKC with 12-myristate 13-acetate, an analogue of DAG, induces rapid morphological plasticity and formation of dendritic lamellae in dendrites of cultured hippocampal neurons (Pilpel & Segal, 2004). PKC inhibitors block neurite outgrowth in retinal axons (Heacock & Agranoff, 1997), dorsal root ganglion neurons (Theodore et al., 1995), sympathetic neurons (Campenot et al., 1994), PC12 cells (Kolkova et al., 2000), and hippocampal organotypic cultures (Toni et al., 1997). These inhibitors also promote dendritic growth in Purkinje cells in cerebellar slice cultures (Metzger & Kapfhammer, 2000) and the extension of dorsal root ganglion cell filopodia (Bonsall & Rehder, 1999).

There is evidence that astrocytes are active participants in synaptic formation and modification (Haydon, 2001). Local astrocytic contact with cultured rat hippocampal neurons via integrin receptors promotes global synaptogenesis (Hama et al., 2004). The astrocyte-neuron contact activates PKC through an arachidonic acid cascade in neurons, triggering excitatory synaptogenesis, a process that can be blocked by inhibitors of both integrins and PKC (Hama et al., 2004).

E. Neuronal Survival

PKC isoforms influence the process of neurite outgrowth or the induction of apoptosis. In general, PKCα, β, ε, and ζ function as suppressors of apoptosis (Khadra et al., 2011), whereas PKC δ and θ are pro-apoptotic (Basu & Pal, 2010). In neuroblastoma cells, for example, PKCε induces neurite outgrowth, whereas PKCδ and PKCθ evoke apoptosis. Plasmalemmal repair/sealing is necessary for survival of damaged neurons, and involves nPKC isoforms (Spaeth et al., 2010). An inhibitor of an nPKC (an nPKCη, pseudosubstrate fragment) decreases the frequency and rate of plasmalemmal sealing in B104 hippocampal cells (Spaeth et al., 2010). There is also evidence that PKC may play an important role in the survival of the spiral ganglion neurons. After deafferentation, activation of PKCβ1 with either phorbol esters or bryostatin-1 induces survival and neurite regrowth and rescues spinal ganglion neurons from cell death (Lallemend et al., 2005).

Nerve growth factor activates phospholipase C-γ, which, upon binding to phosphorylated Tyr^{785} in Trka, is itself phosphorylated and activated, hydrolyzing phosphatidylinositol 4,5-biphosphate to produce DAG and IP_3

and thus activating PKC (Parekh et al., 2000; Toker, 2000). Nerve growth factor activates phosphatidylinositol 3-kinase and PKC in sympathetic neurons, and PKC activation can rescue neurons from apoptosis induced by the withdrawal of nerve growth factor (Favit et al., 1998; Pierchla et al., 2004). PKC may also mediate the neuroprotective effects of estrogen and protect neurons against amyloid beta (Aβ) neurotoxicity (Cordey, Gundimeda, Gopalakrishna, & Pike, 2003). There is a direct neuroprotective effect of PKC against Aβ, demonstrated in culture when the effect of exogenous $A\beta_{42}$ (25 μM, 24 h) is blocked by PKC inhibitors (Cordey et al., 2003). Estrogen activates cPKC and/or nPKC in a variety of cell types nongenomically and can induce translocation of PKCγ through G-protein-coupled estrogen receptors (Qiu et al., 2003).

Kainic acid administration induces upregulation of PKCδ mRNA and protein in the cortex and hippocampus in rats (Kaasinne et al., 2002). Kainate at 50 μM also induces PKCδ translocation from the soluble to the particulate fraction (Jung et al., 2005). Inhibition of PKCδ with rottlerin significantly increases kainite-induced neuronal death, while phorbol 12-myristate 13-acetate attenuates kainite-induced neuronal death (Nitti et al., 2005), suggesting a protective role of PKCδ against kainite toxicity. On the other hand, PKCδ has been found to mediate glycoxidation-dependent apoptosis in NT2 human neurons, since rottlerin protects neurons from glycoxidation-dependent apoptosis (Nitti et al., 2005). Nuclear translocation of PKCζ, a predominantly cytosolic enzyme, is sensitive to caspase-3 inhibition and is believed to mediate NMDA-induced death of cortical neurons. The nuclear translocation of PKCζ induced by NMDA involves caspase-3-dependent PKCζ degradation. Like other aPKC isozymes, PKCζ is not activated by Ca^{2+}, DAG, phorbol esters, or bryostatin; however, it is activated by several lipid mediators, including phosphatidic acid, phosphatidylinositol 3,4,5-triphosphate, arachidonic acid, and ceramide. Aspirin directly inhibits PKCζ activity, thereby protecting against NMDA-induced death of cortical neurons (Crisanti et al., 2005).

III. Memory and Alzheimer's Dementia

PKC isoforms play a critical role in learning and memory. PKCε activation results in an enhanced BDNF activity, which increases hippocampal expression of the Ca^{2+} release channel isoforms ryanodine receptor RyR2, RyR3 (Fig. 2), and PKMζ in the hippocampus (Adasme et al., 2011). PKMζ is believed to play key roles in hippocampal memory maintenance (Shema et al., 2011), through several mechanisms, including persistent inhibition of GluR2-AMPAR removal from the surface of postsynaptic sites (Migues et al., 2010; Yao et al., 2008) and/or alterations

in spine structure (Ron et al., 2012). Overexpressing PKMζ in the rat neocortex enhances long-term memory, whereas a dominant negative PKMζ disrupts memory, even long after memory has been established (Shema et al., 2011).

PKC inhibition or dysfunction, which occurs in neurodegenerative disorders including AD, lead to cognitive impairments in the majority of patients. AD is characterized by a devastating and progressive decline of memory and other cognitive functions. The main histopathological hallmarks of the AD brain are extracellular senile plaques formed by deposits of Aβ peptide and intracellular neurofibrillary tangles consisting of paired helical filaments formed by hyperphosphorylated tau. Aβ occurs in two predominant forms with different COOH-termini, Aβ40 and Aβ42, through cleavage of amyloid precursor protein (APP) by β-secretases and γ-secretases (Fig. 3). Aβ is hydrophobic and prone to aggregation, forming oligomers and plaques. β-secretase cleaves APP at its NH_2-terminus, releasing a soluble NH_2-terminal fragment of approximately 100 kD (sAPPβ) and a 12-kD membrane-bound C99 fragment. On the other hand, cleavage of APP by α-secretase (Postina, 2011), which includes a disintegrin and metalloprotease 10 (ADAM10) as the constitutive α-secretase in neurons (Lichtenthaler, 2011), produces a large soluble fragment and a 10-kD membrane-bound C83 fragment. C99 and C83 can be further cleaved by one or more γ-secretases, resulting in Aβ and a nonpathological p3 peptide, respectively. Synaptotoxic Aβ oligomers inhibit PKC isoforms, decrease RyR2 protein expression, and block BDNF-induced RyR-dependent spine remodeling in hippocampal neurons (Paula-Lima et al., 2011). Tau is a microtubule-associated protein typically found in the axon of neurons and involved in microtubule assembly and the stabilization of growth axons (Mailliot et al., 2000). The hyperphosphorylation of tau prevents its binding to taxol-stabilized microtubules and disrupts microtubule assembly from tau and tubulin (Mandelkow & Mandelkow, 1998). A number of protein kinases and protein phosphatases have been implicated in tau hyperphosphorylation, including glycosynthetase kinase 3β (GSK-3β), phosphokinase A (PKA), phosphokinase C, and Src protein kinase.

The Aβ hypothesis of AD pathogenesis facilitated a strong hope that the ability to halt or reverse AD was possible. However, results from large clinical trials have been disappointing thus far, since patients with dramatic clearance of amyloid showed no clear change in clinical course (Holmes et al., 2008; Schenk et al., 2005; Serrano-Pozo et al., 2010). Patients who received a γ-secretase inhibitor in a recent clinical trial also showed apparently worse cognitive functions (Lilly, 2011). For several reasons, PKC isoforms may represent a potential therapeutic target for the treatment of dementias such as AD. First, PKC isoforms are important signaling molecules in learning and memory (Alkon et al., 1998; Alkon et al., 2007;

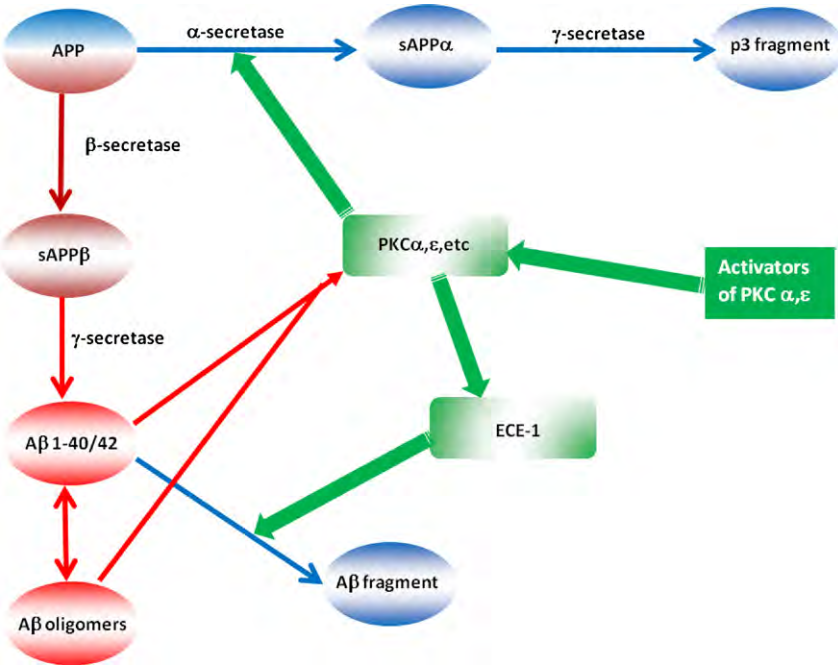

FIGURE 3 **Schematic summary of interaction between Aβ production/clearance and PKC isoform-specific activators.** PKC isoform-specific activators produce antidementic effects through antagonism of the neurotoxic effects of amyloids on PKC, activating α-secretase and endothelin-converting enzyme (ECE). For color version of this figure, the reader is referred to the online version of this book.

Bank et al., 1988; Lorenzetti et al., 2008; Nelson et al., 2008; Sacktor, 2008, 2011; Serrano et al., 2008). PKC is activated by synaptic inputs and intracellular signals that are involved in information processing in cognition, including glutamatergic inputs (Hasham et al., 1997), cholinergic inputs (Chen et al., 2005), serotonergic inputs (Carr et al., 2002, 2003), dopaminergic inputs (Maurice et al., 2001), intracellular calcium and DAG elevation, and other hormonal stimulation (Sato et al., 2004). Memory task learning is associated with PKC immunoreactivity in the principal hippocampal neurons (Van der Zee et al., 1995) and stimulation of muscarinic cholinergic receptors is associated with an increase in PKCγ immunoreactivity (Van der Zee et al., 1992). PKC activation leads to synaptogenesis in the hippocampus (Hongpaisan & Alkon, 2007). Changes in the activity of PKC downstream signaling molecules are also involved. The expression of GAP-43 (Holahan & Routtenberg, 2008), for instance, is up-regulated during spatial learning and memory (Pascale et al., 2004). Transgenic mice overexpressing GAP-43 (Rekart et al., 2004) exhibit enhanced memory in a maze task (Routtenberg et al., 2000), while heterozygous GAP-43

knockout mice have impaired hippocampus-dependent memory (Chung et al., 2003) and contextual fear conditioning (Rekart et al., 2005). PKC signaling cascades are essential for spatial memory acquisition (Colombo et al., 1997; Olds et al., 1989; Olds et al., 1990; Paylor et al., 1991; Paylor et al., 1992; Sun & Alkon, 2005, 2008; Vázquez and de Ortiz, 2004) and consolidation of spatial memory (Bonini et al., 2007), learning and memory of eye blink conditioning (Alkon et al., 1998; Bank et al., 1988; Schreurs et al., 1996; Schreurs et al., 1997; Van der Zee et al., 1997; Wang et al., 2008), olfactory discrimination learning (Olds et al., 1994), conditioned taste aversion (Nunez-Jaramillo et al., 2007; Yasoshima & Yamamoto, 1997), fear memory (Ahi et al., 2004; Levenson et al., 2004; Sacco & Sacchetti, 2010), conditioned avoidance (Jerusalinsky et al., 1994), and drug-associated reward memory (Li et al., 2011; Nimitvilai et al., 2012; Ping et al., 2012). PKC activation with bryostatin-1 induces the *de novo* synthesis of proteins necessary and sufficient for subsequent long-term memory consolidation and enhances memory in *Hermissenda* (Alkon et al., 2005; Kuzirian et al., 2006). Overactivation of PKC may, however, lead to memory impairments, such as working memory in young and old animals (Brennan et al., 2007).

Second, PKC deficiency may underlie many forms of dementias. Expression of PKC isozymes and their functions, especially those in the hippocampus and related brain structures, are plastic and vulnerable to various factors, including stress and neurotoxic amyloid. Inhibition of PKC or impairment of PKC functions consistently leads to deficits in learning and memory (one exception is the report that curcumin-induced PKCδ degradation is associated with enhanced spatial learning in adult and aged rats; Conboy et al., 2009). Intracerebroventricular injection of PKC inhibitors causes marked memory impairment in the passive avoidance task and the water maze task (Takashima et al., 1991). In mice with a deficit in PKCβ, learning of both cued and contextual fear conditioning are impaired, although brain anatomy and hippocampal synaptic transmission, paired-pulse facilitation, and synaptic LTP are all normal (Weeber et al., 2000).

The PKC signaling pathway is impaired in AD (Cole et al., 1988; Govoni et al., 1993; Wang et al., 1994), consistent with evidence that Aβ reduces PKC isozyme levels (Desdouits et al., 1996; Pakaski et al., 2002; Wang et al., 1994). Aβ contains a putative PKC pseudosubstrate domain and can directly inhibit PKC isoforms, including PKCα and PKCε (Lee et al., 2004). Aβ treatment of 1 μM for 1 h induces PKC inhibition that lasts for several hours (Lee et al., 2004). Through binding to PKC, Aβ blocks PKC activation and induces PKC degradation (Cordey et al., 2003), reduces PKC-mediated phosphorylation (Chauhan et al., 1991; Govoni et al., 1993), and decreases PKC membrane translocation (Pakaski et al., 2002). This mechanism of action suggests that the type of interaction between PKC and Aβ

would affect all the PKC isozymes that contain the pseudosubstrate binding site and that the soluble form of Aβ, including oligomers, would be most active. Aβ40, for instance, has been shown to induce translocation of PKC from membrane fraction to cytosol in cultured endothelial cells (Pakaski et al., 2002).

Third, PKCα and ε isoforms regulate the α-processing of APP (Etcheberrigaray et al., 2004; Ibarreta et al., 1999; Jolly-Tornetta & Wolf, 2000; Khan et al., 2009; Kinouchi et al., 1995; Kozikowski et al., 2003; Nelson et al., 2009; Rossner et al., 2001; Yeon et al., 2001; Zhu et al., 2001) and Aβ degradation (Choi et al., 2006; Nelson & Alkon, 2009). α-Processing of APP, mediated by the action of α-secretase, generates a large extracellular soluble APP fragment (sAPPα) and a smaller membrane-bound intracellular fragment, C83. These fragments appear to exhibit no toxic properties to neurons. Evidence has been provided that the administration of bryostatin-1, a partial agonist of cPKC and nPKC isozymes, reduces Aβ40 in the brains of AD transgenic mice and both brain Aβ40 and Aβ42 in AD double-transgenic mice (Kozikowski et al., 2003). Bryostatin-1 at subnanomolar concentrations enhances the secretion of the α-secretase product sAPPα in fibroblasts from AD patients. In APP[V7171] transgenic mice, PKC activation reduces Aβ40 accumulation in the brain (Kozikowski et al., 2003), and in APP transgenic mice, overexpression of PKCε has been shown to selectively increase the activity of endothelin-converting enzyme (ECE, Choi et al., 2006), which degrades Aβ and is expressed in several populations of neurons including the hippocampal cells (Eckman et al., 2001; Funalot et al., 2004). Furthermore, PKC activation inhibits glycogen synthase 3 kinase (Fang et al., 2002; Lavoie et al., 1999), thereby reducing tau protein hyperphosphorylation (Cho & Johnson, 2004).

The combination of memory-enhancing action with reduction in brain amyloid burden and tau protein hyperphosphorylation opens up the possibility for a multitarget strategy with PKC isoform-selective activation that may be an effective therapeutic approach against AD. The therapeutic approach is not expected to interfere with vascular function, as those dysfunctions associated with an enhanced clearance of Aβ from the brains of late-stage AD patients, since the mechanisms of PKC activators, thorough α-secretase and ECE, do not involve an enhanced vascular Aβ clearance. The downside of potent PKC activation may arise due to overactivation of α-processing of APP and/or Aβ degradation, since APP (through an interaction with β1 integrin) and Aβ (including monomers and oligomers) may function in normal physiology by mediating neuronal adhesion and migration (Siemes et al., 2006; Young-Pearse et al., 2007), and promoting neurite outgrowth (Hoareau et al., 2008; Hoe et al., 2009; Perez et al., 1997; Small et al., 1999) and synaptic plasticity and memory (Puzzo et al., 2008).

IV. Ischemic Dementia

It has been well established that ischemia and hypoxia dramatically impair cognitive function. Not only are synapses and neural structures directly impaired by ischemia, but also the process of acquiring and maintaining knowledge that requires energy. PKC is involved in synaptic dysfunction and memory impairments in patients surviving ischemic events (cerebral ischemia, cardiac arrest, etc.; Perez-Pinzon et al., 2005). Global cerebral ischemia triggers DAG kinase (DGK)ξ translocation from the nucleus to the perikaryal cytoplasm of CA1 pyramidal cells during the very early phase of an ischemic insult, probably resulting in a sustained increase in DAG levels and PKC activity in the nucleus (Ali et al., 2004). Cerebral ischemia increases PKCδ mRNA and protein levels in the cortex and hippocampus (Koponen et al., 2000; Miettinen et al., 1996). The increased PKCδ expression in the penumbral area may be responsible for delayed neuronal damage (Phan et al., 2002). Activation of PKCδ by cerebral ischemia results in cytochrome C release from the mitochondria and apoptosis (Dave et al., 2011). A selective PKCδ peptide inhibitor, for example, has been found to reduce cellular injury in a rat hippocampal slice model of cerebral ischemia. The inhibitor decreased infarct size *in vivo* in rats with transient middle cerebral artery occlusion when administered at the onset, at 1 h, or at 6 h of reperfusion (Bright et al., 2004). Hypoxia activates PKC, leading to phosphorylation of NMDA NR1 subunits and an enhancement of GluR activity and Ca^{2+} influx (Bickler et al., 2004). In acutely dissociated rat CA1 neurons, oxygen and glucose deprivation after removal of extracellular Ca^{2+} can still activate PKC through endogenous Ca^{2+} release (Larsen et al., 2004), suggesting that a brief period of cerebral ischemia without exposure to excitotoxicity is sufficient to activate PKC.

On the other hand, PKCε mediates ischemic tolerance (Liu et al., 2012). Activation of PKCε, as a vital part of adenosine/ NMDA-activated signal transduction pathway, protects neurons from ischemia-reperfusion injury (Di-Capua et al., 2003; Raval et al., 2003) and oxygen-glucose deprivation damage, whereas selective inhibition of PKCβI enhances astrocyte cell death induced by oxygen-glucose deprivation (Wang et al., 2004). PKCε phosphorylates and inhibits GSK3β, the inhibition of which during reperfusion promotes glycogen synthesis, thus decreasing glycolysis and associated harmful H^+ production during reperfusion (Takeishi et al., 2000). Ischemic preconditioning is associated with PKCε-mediated phosphorylation of the mitochondrial K^+_{ATP} channels (Raval et al., 2007) and increased synaptosomal mitochondrial respiration (Dave et al., 2008). PKCε knockout mice lose the preconditioning effect of ischemia-reperfusion (Raval et al., 2007). Electroacupuncture pretreatment has been shown to produce PKCε-mediated anti-apoptosis and rapid tolerance to focal cerebral ischemia (MCAO) in rats (Wang et al., 2011). Postischemic activation in rats with intermittent doses of bryostatin-1, which is a relatively specific activator of PKCε, has been found

to restore neurotrophic activity and synaptogenesis in the hippocampus and spatial learning and memory performance after global cerebral ischemia (Sun et al., 2008, 2009). The protective action of bryostatin-1 may involve alterations in cerebral blood flow (Della-Morte et al., 2011). Thus, an appropriate activation of PKC isozymes with targeted PKC activators may represent an effective therapeutic approach to stroke/ischemia-reperfusion injury and associated memory impairment, through activation of ischemic preconditioning responses and enhancement of neurotrophic activity, synaptogenesis and synaptic remodeling.

Female animals are less vulnerable to ischemia-induced neuronal damage (Alkayed et al., 1998; Zhang et al., 1998) and estrogen treatment protects the brain from experimental stroke (McCullough & Hurn, 2003; Yang et al., 2000). PKCε preferentially stimulates the transcriptional activity of estrogen-related receptor α, which regulates mitochondrial homeostasis (Lu et al., 2011). Transient unilateral middle cerebral artery occlusion (90 min) followed by 22.5 h reperfusion has been shown to produce smaller total infarct size in C57BL/6 female mice than in the male mice, but no difference was observed in PKCγ knockout mice (Hayashi et al., 2005). Injection of estrogen (i.p.) after the start of reperfusion can significantly reduce the infarct volume in males but again, the protective effect was attenuated in PKCγ-knockout mice (Hayashi et al., 2005). These data suggest that the neuroprotective effect of estrogen against cerebral ischemia is present in rodents; however, in humans, the clinical evidence for stroke prevention with hormone replacement therapy remains inconclusive.

V. Conclusion

PKC isoforms are distributed in neuronal structures and involved in a broad range of vital functions (Brenner et al., 2004; Lee et al., 2006; Pascale et al., 2007). PKC is ubiquitously and densely expressed in the brain (Saito et al., 1988) and activated by Ca^{2+}, phospholipids and DAG, phorbol esters, and other PKC activators.

PKC activators, such as DAG, arachidonic acid, phorbol esters, bryostatins, aplysiatoxins, and teleocidins, bind to a hydrophilic cleft in a largely hydrophobic surface of the C1 domains, resulting in an enhanced hydrophobicity of the surface and promoting the interaction between the C1 domain and the phospholipid bilayer of the cell membranes and driving removal of the pseudosubstrate region from the catalytic site of the enzyme. When dosed appropriately, these activators may produce memory-enhancing and antidementic effects.

In addition to its inhibitory action on GSK3β, the PKCα and ε activator bryostatin-1 increases soluble APP fragment production through α-secretase in tissues obtained from AD patients and significantly improves spatial

learning and memory in rats. These actions have obvious therapeutic value for the treatment of AD amyloidosis and associated dementias. The availability of bryostatin is limited by their low natural abundance and difficulties with synthesis. 8-[2-(2-Pentylcyclopropyl-methyl)-cyclopropyl]-octanoic acid (DCP-LA), on the other hand, has been shown to selectively activate PKCε, possibly through binding to the PS binding site (Kanno et al., 2006; Nelson et al., 2009). These agents can activate the PKC isoforms and reverse Aβ-mediated neurotoxic effects in the presence of a high Aβ load (Hongpaisan et al., 2011; Khan et al., 2009), raising the possibility that they may be effective at all stages of the disorder. In addition, these agents can achieve therapeutic effects through oral administrations (at different dosing; Sun et al., unpublished observations). The potential values of PKC activators, especially isoform-specific activators, as antidementic therapeutics rely mainly on the following three pharmacological profiles:

1. Functional restoration/facilitation of the PKC signal cascades that are critically involved in memory acquisition and maintenance
2. Reduction of the pathological factors—Aβ accumulation and tau protein hyperphosphorylation—that are associated with or underlie dementia
3. Activation of endogenous neurorepair/protective mechanisms and synaptogenesis against neurodegenerative disorders and ischemic damage

The desired pharmacological profile for the treatment of dementias includes a selective activation of PKC isozymes (PKCε and probably PKCα, but not PKCδ), without inducing significant degradation. Activation of PKC, however, is also involved in the formation of conditioned cue-provoked cocaine memory (Lai et al., 2008), reward memory related to comorbid nicotine and alcohol addictions (Lee & Messing, 2011), and maintenance of persistent pain and pain hypersensitivity (Laferriere et al., 2011). Memories of negative events and unwanted fear may also be enhanced. It remains to be determined whether the involvement of PKC in methamphetamine-induced, long-lasting astrocytic activation and behavioral sensitization (Narita et al., 2005) would jeopardize clinical use of these agents as therapeutics for certain patients. In addition, inhibition of PKCα and β1 may underlie curcumin-induced attenuation of diabetic nephropathy (Soetikno et al., 2011). PKC activity is significantly increased in synpatosomal samples isolated from the forebrain, midbrain, and hindbrain of spontaneously hypertensive rats (Hughes-Darden et al., 2001), responsible for the enhanced basal neural activity in the anterior hypothalamic area (Kubo & Hagiwara, 2005). Many of the potential adverse and side effects may be reduced through the development of PKC region/isozyme-specific agents, such as DCP-LA and its derivatives, in the future.

Conflict of Interest: The authors have no conflicts of interest to declare.

Abbreviations

Aβ	amyloid β-peptide
AD	Alzheimer's disease
ADAM	a disintegrin and metalloprotease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate
aPKC	atypical PKC
APP	amyloid precursor protein
BDNF	brain-derived neurotrophic factor
cPKC	conventional PKC
DAG	diacylglycerol
ECE	endothelin-converting enzyme
GAP-43	growth-associated protein with an approximate molecular weight of 43 kDa
GluR	glutamate receptor
GSK-3β	glycogen synthetase kinase 3β
IP_3	inositol triphosphate
LDP	long-term depression
LTP	long-term potentiation
mGluR	metabotropic GluR
mIPSC	miniature inhibitory synaptic current
NMDAR	*N*-methyl-D-aspartic acid receptor
nPKC	novel PKC
PDZ	ostsynaptic density protein of 95 kDa/Discs-large/ZO-1
PI	phosphoinositide
PICK	protein interacting with C kinase
PKA	phosphokinase A
PKC	protein kinase C
PLC	phospholipase C
PS	phosphatidylserine
RACK	receptor for activated C-kinase
RyR	ryanodine receptor
V	variable (region)

References

Abramian, A. M., Comenencia-Ortiz, E., Vithlani, M., Tretter, E. V., Sieghart, W., et al. (2010). Protein kinase C phosphorylation regulates membrane insertion of $GABA_A$ receptor subtypes that mediate tonic inhibition. *The Journal of Biological Chemistry*, *285*, 41795–41805.

Adasme, T., Haeger, P., Paula-Lima, A. C., Espinoza, I., Casas-Alarcon, M. M., et al. (2011). Involvement of ryanodine receptors in neurotrophin-induced hippocampal synaptic plasticity and spatial memory formation. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 3029–3034.

Ahi, J., Radulovic, J., & Spiess, J. (2004). The role of hippocampal signaling cascades in consolidation of fear memory. *Behavioural Brain Research*, *149*, 17–31.

Ali, H., Nakano, T., Saino-Saito, S., Hozumi, Y., Katagiri, Y., et al. (2004). Selective translocation of diacylglycerol kinase ξ in hippocampal neurons under transient forebrain ischemia. *Neuroscience Letters*, *372*, 190–195.

Alkayed, N. J., Harukuni, I., Kimes, A. S., London, E. D., Traystman, R. J., et al. (1998). Gender-linked brain injury in experimental stroke. *Stroke*, *29*, 159–165.

Alkon, D. L., & Rasmussen, H. (1988). A spatial-temporal model of cell activation. *Science*, *239*, 998–1005.

Alkon, D. L., Epstein, H., Kuzirian, A., Bennett, M. C., & Nelson, T. J. (2005). Protein synthesis required for long-term memory is induced by PKC activation on days before associative learning. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 16432–16437.

Alkon, D. L., Sun, M. -K., & Nelson, T. J. (2007). PKC signaling deficits: A mechanistic hypothesis for the origins of Alzheimer's disease. *Trends in Pharmacological Sciences*, *28*, 51–60.

Alkon, D. L., Neary, J. T., Naito, S., Coulter, D., Kubota, M., et al. (1986). C-kinase activation prolongs CA-dependent inactivation of K currents. *Biochemical and Biophysical Research Communications*, *134*, 1245–1253.

Alkon, D. L., Nelson, T. J., Zhao, W. Q., & Cavallaro, S. (1998). Time domains of neuronal Ca2+ signaling and associative memory: Steps through a calexcitin, ryanodine receptor, K+ channel cascade. *Trends in Neurosciences*, *21*, 529–537.

Alzheimer's Disease International. (2010). *World Alzheimer Report 2010. The global economic impact of dementia*. London: Alzheimer's Disease International.

Bank, B., DeWeer, A., Kuzirian, A. M., Rasmussen, H., & Alkon, D. L. (1988). Classical conditioning induces long-term translocation of protein kinase C in rabbit hippocampal CA1 cells. *Proceedings of the National Academy of Sciences of the United States of America*, *85*, 1988–1992.

Basu, A., & Pal, D. (2010). Two faces of protein kinase Cδ: The contrasting roles of PKCδ in cell survival and cell death. *The Science World Journal*, *10*, 2272–2284.

Bickler, P. E., Fahlman, C. S., & Ferriero, D. M. (2004). Hypoxia increases calcium flux through cortical neuron glutamate receptor via protein kinase C. *Journal of Neurochemistry*, *88*, 878–884.

Boehm, J., Kang, M.-G., Johnson, R. C., Esteban, J., Huganir, R. L., et al. (2006). Synaptic incorporation of AMPA receptors during LTP is controlled by a PKC phosphorylation site on GluR1. *Neuron*, *51*, 213–225.

Bonini, J. S., da Silva, W. C., Bevilaqua, L. R. M., Medina, J. H., Izquierdo, I., et al. (2007). On the participation of hippocampal PKC in acquisition, consolidation and reconsolidation of spatial memory. *Neuroscience*, *147*, 37–45.

Bonsall, J., & Rehder, V. (1999). Regulation of chick dorsal root ganglion growth cone filopodia by protein kinase C. *Brain Research*, *839*, 120–132.

Brennan, A. R., Yuan, P., Dickstein, D. L., Rocher, A. B., Hof, P. R., et al. (2007). Protein kinase C activity is associated with prefrontal cortical decline in aging. *Neurobiology of Aging*, *30*, 782–792.

Brenner, G., Ji, R.-R., Shaffer, S., & Woolf, C. J. (2004). Peripheral noxious stimulation induces phosphorylation of the NMDA receptor NR1 subunit at the PKC-dependent site, serine-896, in spinal cord dorsal horn neurons. *The European Journal of Neuroscience*, *20*, 375–384.

Bright, R., Raval, A. P., Dembner, J. M., Pérez-Pinzón, M. A., Steinberg, G. K., et al. (2004). Protein kinase C delta mediates cerebral reperfusion injury *in vivo*. *Journal of Neuroscience*, *24*, 6880–6888.

Campenot, R. B., Draker, D. D., & Senger, D. L. (1994). Evidence that protein kinase C activates involved in regulating neurite growth are localized to distal neuritis. *Journal of Neuroscience*, *63*, 868–878.

Carr, D. B., Cooper, D. C., Ulrich, S. L., Spruston, N., & Surmeier, D. J. (2002). Serotonin receptor activation inhibits sodium current and dendritic excitability in prefrontal cortex via a protein kinase C-dependent mechanism. *Journal of Neuroscience*, *22*, 6846–6855.

Carr, D. B., Day, M., Cantrell, A. R., Held, J., Scheuer, T., et al. (2003). Transmitter modulation of slow, activity-dependent alterations in sodium channel availability endows neurons with a novel form of cellular plasticity. *Neuron*, *39*, 793–806.

Chaki, S., Muramatsu, M., & Otomo, S. (1994). Involvement of protein kinase C activation of acetylcholine release from rat hippocampal slices by minaprine. *Neurochemistry International*, *24*, 37–41.

Chalimoniuk, M., King-Pospisil, K., Pedersen, W. A., Malecki, A., Wylegala, E., et al. (2004). Arachidonic acid increases choline acetyltransferase activity in spinal cord neurons through a protein kinase C-mediated mechanism. *Journal of Neurochemistry*, *90*, 629–636.

Chauhan, A., Chauhan, V. P., Brockerhoff, H., & Wisniewski, H. M. (1991). Action of amyloid beta-protein on protein kinase C activity. *Life Sciences*, *49*, 1555–1562.

Chen, Y., Cantrell, A. R., Messing, R. O., Scheuer, T., & Catterall, W. A. (2005). Specific modulation of Na+ channels in hippocampal neurons by protein kinase C epsilon. *Journal of Neuroscience*, *25*, 507–513.

Chen, Y., Yu, F. H., Surmeier, J., Scheuer, T., & Catterall, W. A. (2006). Neuromodulation of Na+ channel slow inactivation via cAMP-dependent protein kinase and protein kinase C. *Neuron*, *49*, 409–420.

Cho, J. H., & Johnson, G. V. (2004). Glycogen synthase kinase 3 beta induces caspase-cleaved tau aggregation in situ. *The Journal of Biological Chemistry*, *279*, 54716–54723.

Choi, D.-S., Wang, D., Yu, G. Q., Zhu, G. F., Kharazia, V. N., et al. (2006). PKCε increases endothelin converting enzyme activity and reduces amyloid plaque pathology in transgenic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 8215–8220.

Chou, C.-W., Huang, W.-J., Tien, L.-T., & Wang, S.-J. (2007). (-)-Epigallocatechin gallate, the most active polyphenolic catechin in green tea, presynaptically facilitates Ca2þ-dependent glutamate release via activation of protein kinase C in rat cerebral cortex. *Synapse*, *61*, 889–902.

Chung, H. J., Steinberg, J. P., Huganir, R. L., & Linden, D. J. (2003). Requirement of AMPA receptor GluR2 phosphorylation for cerebellar long-term depression. *Science*, *300*, 1751–1755.

Cole, G., Dobkins, K. R., Hansen, L. A., Terry, R. D., & Saitoh, T. (1988). Decreased levels of protein kinase C in Alzheimer brain. *Brain Research*, *452*, 165–174.

Colombo, P. J., Wetsel, W. C., & Gallagher, M. (1997). Spatial memory is related to hippocampal subcellular concentrations of calcium-dependent protein kinase C isoforms in young and aged rats. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 14195–14199.

Conboy, L., Foley, A. G., O'Boyle, N. M., Lawlor, M., Gallagher, H. C., et al. (2009). Curcumin-induced degradation of PKC delta is associated with enhanced dentate NCAM PSA expression and spatial learning in adult and aged Wistar rats. *Biochemical Pharmacology*, *77*, 1254–1265.

Cordey, M., Gundimeda, U., Gopalakrishna, R., & Pike, C. J. (2003). Estrogen activates protein kinase C in neurons: Role in neuroprotection. *Journal of Neurochemistry*, *84*, 1340–1348.

Crisanti, P., Leon, A., Lim, D. M., & Omri, B. (2005). Aspirin prevention of NMDA-induced neuronal death by direct protein kinase Cζ inhibition. *Journal of Neurochemistry*, *93*, 1587–1593.

Dave, K. R., DeFazio, R. A., Raval, A. P., Torraco, A., Saul, I., et al. (2008). Ischemic preconditioning targets the respiration of synaptic mitochondrial via protein kinase C epsilon. *Journal of Neurochemistry*, *28*, 4172–4182.

Dave, K. R., Bhattacharya, S. K., Saul, I., DeFazio, R. A., Dezfulian, C., et al. (2011). Activation of protein kinase C delta following cerebral ischemia leads to release of cytochrome C from the mitochondria via Bad pathway. *PloS One*, *6*, e22057.

Davis, K. E., Straff, D. J., Weinstein, E. A., Bannerman, P. G., Correale, D. M., et al. (1998). Multiple signaling pathways regulate cell surface expression and activity of the excitatory amino acid carrier 1 subtype of Glu transporter in C6 glioma. *Journal of Neurochemistry*, *18*, 2475–2485.

Della-Morte, D., Raval, A. P., Dave, K. R., Lin, H. W., & Perez-Pinzon, M. A. (2011). Post-ischemic activation of protein kinase C epsilon protects the hippocampus from cerebral ischemic injury via alterations in cerebral blood flow. *Neuroscience Letters*, *487*, 158–162.

Desdouits, F., Buxbaum, J. D., Desdouits-Magnen, J., Nairn, A. C., & Greengard, P. (1996). Amyloid alpha peptide formation in cell-free preparations. Regulation by protein kinase C, calmodulin, and calcineurin. *The Journal of Biological Chemistry*, *271*, 24670–24674.

Dev, K., Nakanishi, S., & Henley, J. M. (2004). The PDZ domain of PICK1 differentially accepts protein kinase C-α and GluR2 as interacting ligands. *The Journal of Biological Chemistry*, *279*, 41393–41397.

Di-Capua, N., Sperling, O., & Zoref-Shani, E. (2003). Protein kinase C-ε is involved in the adenosine-activated signal transduction pathway conferring protection against ischemia-reperfusion injury in primary rat neuronal cultures. *Journal of Neurochemistry*, *84*, 409–412.

Dobransky, T., Doherty-Kirby, A., Kim, A., Brewer, D., Lajoie, G., et al. (2004). Protein kinase C isoforms differentially phosphorylate human choline acetyltransferase regulating its catalytic activity. *Journal of Neurochemistry*, *279*, 52059–52068.

Eckman, E. A., Reed, D. K., & Eckman, C. B. (2001). Degradation of the Alzheimer's amyloid β peptide by endothelin-converting enzymes. *The Journal of Biological Chemistry*, *276*, 24540–24548.

Emoto, Y., Manome, Y., Meinhardt, G., Kisaki, H., Kharbanda, S., et al. (1995). Proteolytic activation of protein kinase C delta by an ICE-like protease in apoptotic cells. *The EMBO Journal*, *14*, 6148–6156.

Etcheberrigaray, R., Tan, M., Dewachter, I., Kuipéri, C., Van der Auwera, I., et al. (2004). Therapeutic effects of PKC activators in Alzheimer's disease transgenic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 11141–11146.

Exley, R., Clements, M. A., Hartung, H., McIntosh, J. M., & Cragg, S. J. (2008). α6-Containing nicotinic acetylcholine receptors dominate the nicotine control of dopamine neurotransmission in nucleus accumbens. *Neuropsychopharmacology*, *33*, 2158–2166.

Fang, X., Yu, S., Tanyi, J. L., Lu, Y., Woodgett, J. R., et al. (2002). Convergence of multiple signaling cascades at glycogen synthase kinase 3: Edg receptor-mediated phosphorylation and inactivation by lysophosphatidic acid through a protein kinase C-dependent intracellular pathway. *Molecular Cell Biology*, *22*, 2099–2110.

Farley, J., & Auerbach, S. (1986). Protein kinase C activation induces conductance changes in Hermissenda photoreceptors like those seen in associative learning. *Nature*, *319*, 220–223.

Favit, A., Grimaldi, T., Nelson, T. J., & Alkon, D. L. (1998). Alzheimer's-specific effects of soluble beta-amyloid on protein kinase C-alpha and -gamma degradation in human fibroblasts. *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 5562–5567.

Filippova, N., Sedelnikova, A., Zong, Y., Fortinberry, H., & Weiss, D. S. (2000). Regulation of recombinant gamma-aminobutyric acid (GABA)(A) and GABA(C) receptors by protein kinase C. *Molecular Pharmacology*, *57*, 847–856.

Funalot, B., Quimet, T., Claperon, A., Fallet, C., Delacourte, A., et al. (2004). Endothelin-converting enzyme-1 is expressed in human cerebral cortex and protects against Alzheimer's disease. *Molecular Psychiatry*, *9*, 1122–1128.

Gao, L., & Greenfield, L. J. (2005). Activation of protein kinase C reduces benzodiazepine potency at GABAA receptors in NT2-N neurons. *Neuropharmacology*, *48*, 333–342.

Gereau, R. W., IV, & Heinemann, S. F. (1998). Role of protein kinase C phosphorylation in rapid desensitization of metabolic glutamate receptor 5. *Neuron*, *20*, 143–151.

González, M., Kazanietz, M. G., & Robinson, M. B. (2002). Regulation of the neuronal glutamate transporter excitatory amino acid carrier-1 (EAAC1) by different protein kinase C subtypes. *Molecular Pharmacology*, *62*, 901–910.

Govoni, S., Bergamaschi, S., Racchi, M., Battaini, F., Binetti, G., et al. (1993). Cytosol protein kinase C downregulation in fibroblasts from Alzheimer's disease patients. *Neurology*, *43*, 2581–2586.

Hama, H., Hara, C., Yamaguchi, K., & Miyawaki, A. (2004). PKC signaling mediates global enhancement of excitatory synaptogenesis in neurons triggered by local contact with astrocytes. *Neuron*, *41*, 405–415.

Hasham, M. I., Pelech, S. L., & Krieger, C. (1997). Glutamate-mediated activation of protein kinase C in hippocampal neurons. *Neuroscience Letters*, *228*, 115–118.

Hayashi, S., Ueyama, T., Kajimoto, T., Yagi, K., Kohmura, E., et al. (2005). Involvement of γ protein kinase C in estrogen-induced neuroprotection against focal brain ischemia through G protein-coupled estrogen receptor. *Journal of Neurochemistry*, *93*, 883–891.

Haydon, P. G. (2001). Glia: Listening and talking. *Nature Reviews. Neuroscience*, *2*, 185–193.

Heacock, A. M., & Agranoff, B. W. (1997). Protein kinase inhibitors block neurite outgrowth from explants of goldfish retina. *Neurochemical Research*, *22*, 1179–1185.

Hoareau, C., Borrell, V., Soriano, E., Krebs, M. O., Prochiantz, A., et al. (2008). Amyloid precursor protein cytoplasmic domain antagonizes reelin neurite outgrowth inhibition of hippocampal neurons. *Neurobiology of Aging*, *29*, 542–553.

Hoe, H.-S., Lee, K. J., Carney, R. S. E., Lee, J., Markova, A., et al. (2009). Interaction of reelin with amyloid precursor protein promotes neurite outgrowth. *Journal of Neuroscience*, *29*, 7459–7473.

Holmes, C., Boche, D., Wilkinson, D., Yadegarfar, G., Hopkins, V., et al. (2008). Long-term effects of Abeta42 immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled phase I trial. *Lancet*, *372*, 216–223.

Hongpaisan, J., & Alkon, D. L. (2007). A structural basis for enhancement of long-term associative memory in single dendritic spines regulated by PKC. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 19571–19576.

Hongpaisan, J., Sun, M. -K., & Alkon, D. L. (2011). PKCε activation prevents synaptic loss, Aβ elevation, and cognitive deficits in Alzheimer's disease transgenic mice. *Journal of Neuroscience*, *31*, 630–643.

Holahan, M., & Routtenberg, A. (2008). The protein kinase C phosphorylation site on GAP-43 differentially regulates information storage. *Hippocampus*, *18*, 1099–1102.

Hopf, F. W., Mailliard, W. S., Gonzalez, G. F., Diamond, I., & Bonci, A. (2005). Atypical protein kinase C is a novel mediator of dopamine-enhanced firing in nucleus accumbens neurons. *Journal of Neuroscience*, *25*, 985–989.

Hughes-Darden, C. A., Wachira, S. J., Denaro, F. J., Taylor, C. V., Brunson, K. J., et al. (2001). Expression and distribution of protein kinase C isozymes in brain tissue of spontaneously hypertensive rats. *Cellular and Molecular Biology*, *47*, 1077–1088.

Ibarreta, D., Duchen, M., Ma, D., Qiao, L., Kozikowski, A. P., et al. (1999). Benzolactam (BL) enhances sATP secretion in fibroblasts and in PC12 cells. *Neuroreport*, *10*, 1035–1040.

Jerusalinsky, D., Quillfeldt, J. A., Walz, R., Da Silva, R. C., Medina, J. H., et al. (1994). Post-training intrahippocampal infusion of protein kinase C inhibitors causes amnesia in rats. *Behavioral and Neural Biology*, *61*, 107–109.

Jo, J., Heon, S., Kim, M. J., Son, G. H., Park, Y., et al. (2008). Metabotropic glutamate receptor-mediated LTD involves two interacting Ca2+ sensors, NCS-1 and PICK1. *Neuron*, *60*, 1095–1111.

Johnson, J. A., Gray, M. O., Chen, C. H., & Mochly-Rosen, D. (1996). A protein kinase C translocation inhibitor as an isozyme-selective antagonist of cardiac function. *The Journal of Biological Chemistry*, *271*, 24962–24966.

Jolly-Tornetta, C., & Wolf, B. A. (2000). Regulation of amyloid precursor protein (APP) secretion by protein kinase Cα in human Ntera 2 neurons (NT2N). *Biochemistry*, *39*, 7428–7435.

Jung, Y.-S., Lee, B. K., Park, H.-S., Shim, J. K., Kim, S. U., et al. (2005). Activation of protein kinase C-δ attenuates kainite-induced cell death of cortical neurons. *Neuroreport*, *16*, 741–744.

Kaasinne, S. K., Goldsteins, G., Alhonen, L., Jänne, J., & Koistinaho, J. (2002). Induction and activation of protein kinase C-δ in the hippocampus and cortex after kainic acid treatment. *Experimental Neurology*, *176*, 203–212.

Kaczmarek, L. K. (1987). The role of protein kinase C in the regulation of ion channels and neurotransmitter release. *Trends in Neurosciences*, *10*, 30–34.

Kanno, T., Yamamoto, H., Yaguchi, T., Hi, R., Mukasa, T., et al. (2006). The linoleic acid derivative DCP-LA selectively activates PKC-epsilon, possibly binding to the phosphatidylserine binding site. *Journal of Lipid Research*, *47*, 1146–1156.

Kanthasamy, A. G., Kitazawa, M., Kanthasamy, A., & Anantharam, V. (2003). Role of proteolytic activation of protein kinase Cδ in oxidative stress-induced apoptosis. *Antioxidants & Redox Signaling*, *5*, 609–620.

Khadra, N., Bresson-Bepoldin, L., Penna, A., Chaigne-dDelalande, C., Segui, B., et al. (2011). CD95 triggers orai1-mediated localized Ca^{2+} entry, regulates recruitment of protein kinase C (PKC) β2, and prevents death-inducing signaling complex formation. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 19072–19077.

Khan, T. K., Nelson, T. J., Verma, V. A., Wender, P. A., & Alkon, D. L. (2009). A cellular model of Alzheimer's disease therapeutic efficacy: PKC activation reverses Abeta-induced biomarker abnormality on cultured fibroblasts. *Neurobiology of Disease*, *34*. 332–329.

Kinouchi, T., Sorimachi, H., Maruyama, K., Mizuno, K., Ohno, S., et al. (1995). Conventional protein kinase C (PKC)-alpha and novel PKC epsilon, but not–delta, increase the secretion of an N-terminal fragment of Alzheimer's disease amyloid precursor protein from PKC cDNA transfected 3Y1 fibroblasts. *FEBS Letters*, *364*, 203–206.

Kitazawa, M., Anantharam, V., & Kanthasamy, A. G. (2003). Dieldrin induces apoptosis by promoting caspase-3-dependent proteolytic cleavage of protein kinase Cδ in dopaminergic cells: Relevance to oxidative stress and dopaminergic degeneration. *Neuroscience*, *119*, 945–964.

Kolkova, K., Novitskaya, V., Pedersen, N., Berezin, V., & Bock, E. (2000). Neural cell adhesion molecule-stimulated neurite outgrowth depends on activation of protein kinase C and the Ras-mitogen-activated protein kinase pathway. *Journal of Neuroscience*, *20*, 2238–2246.

Koponen, S., Goldsteins, G., Keinanen, R., & Koistinaho, J. (2000). Induction of protein kinase Cdelta subspecies in neurons and microglia after transient global brain ischemia. *Journal of Cerebral Blood Flow and Metabolism*, *20*, 93–102.

Kozikowski, A. P., Nowak, I., Petukhov, P. A., Etcheberrigaray, R., Mohamed, A., et al. (2003). New amide-bearing benzolactam-based protein kinase C modulators induce enhanced secretion of the amyloid precursor protein metabolic sAPPalpha. *Journal of Medicinal Chemistry*, *46*, 364–373.

Krishek, B. J., Xie, X., Blackstone, C., Huganir, R. L., Moss, S. J., et al. (1994). Regulation of GABAA receptor function by protein kinase C phosphorylation. *Neuron*, *12*, 1081–1095.

Kubo, T., & Hagiwara, Y. (2005). Protein kinase C activation-induced increases of neural activity are enhanced in the hypothalamus of spontaneously hypertensive rats. *Brain Research*, *1033*, 157–163.

Kuzirian, A. M., Epstein, H. T., Gagliardi, C. J., Nelson, T. J., Sakakibara, M., et al. (2006). Bryostatin enhancement of memory in Hermissenda. *The Biological Bulletin*, *210*, 201–214.

Laferriere, A., Pitcher, M. H., Haldane, A., Huang, Y., Cornea, V., et al. (2011). PKMzeta is essential for spinal plasticity underlying the maintenance of persistent pain. *Molecular Pain*, 7:99. doi:10.1186/1744-8069-7-99

Lai, Y.-T., Fan, H.-Y., Cheng, C. G., Chiang, C.-Y., Kao, G.-S., et al. (2008). Activation of amygdaloid PKC pathway is necessary for conditioned cues-provoked cocaine memory performance. *Neurobiology of Learning and Memory*, *90*, 164–170.

Lallemend, F., Hadjab, S., Hans, G., Moonen, G., Lefebvre, P. P., et al. (2005). Activation of protein kinase CbetaI constitutes a new neurotrophic pathway for deafferented spiral ganglion neurons. *Journal of Cell Science*, *118*, 4511–4525.

Larsen, G. A., Berg-Johnsen, J., Moe, M. C., & Vinje, M. L. (2004). Calcium-dependent protein kinase C activation in acutely isolated neurons during oxygen and glucose deprivation. *Neurochemical Research*, *29*, 1931–1937.

Lavoie, L., Band, C. J., Kong, M., Bergeron, J. J. M., & Posner, B. I. (1999). Regulation of glycogen synthase in rat hepatocytes. Evidence for multiple signaling pathway. *The Journal of Biological Chemistry*, *274*, 28279–28285.

Lee, A. M., & Messing, R. O. (2011). Protein kinase C epsilon modulates nicotine consumption and dopamine reward signals in the nucleus accumbens. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 16080–16085.

Lee, C.-Y., Robinson, K. J., & Doe, C. Q. (2006). Lgl, pins, and aPKC regulate neuroblast self-renewal versus differentiation. *Nature*, *439*, 594–598.

Lee, W., Boo, J. H., Jung, M. W., Park, S. D., Kim, Y. H., Kim, S. U, et al. (2004). Amyloid beta peptide directly inhibits PKC activation. *Molecular and Cellular Neurosciences*, *26*, 222–231.

Leidenheimer, N. J., Whiting, P. J., & Harris, R. A. (1993). Activation of calcium-phospholipid-dependent protein kinase enhances benzodiazepine and barbiturate potentiation of the GABAA receptors. *Journal of Neurochemistry*, *60*, 1972–1975.

Levenson, J. M., O'Riordan, K. J., Brown, K. D., Trinh, M. A., Molfese, D. L., et al. (2004). Regulation of histone acetylation during memory formation in the hippocampus. *The Journal of Biological Chemistry*, *279*, 40545–40559.

Li, Y. Q., Xue, Y. X., He, Y. Y., Li, F. Q., Xue, L. F., et al. (2011). Inhibition of PKMζ in nucleus accumbens core abolishes long-term drug reward memory. *Journal of Neuroscience*, *31*, 5436–5446.

Lichtenthaler, S. F. (2011). Alpha-secretase in Alzheimer's disease: Molecular identity, regulation and therapeutic potential. *Journal of Neurochemistry*, *116*, 10–21.

Lilly (2011). Lilly halts development of semagacestat for Alzheimer's disease based on preliminary results of phase III clinical trials. http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=499794. Accessed March 13, 2012.

Lin, Y. F., Browning, M. D., Dudek, E. M., & MacDonald, R. L. (1994). Protein kinase C enhances recombinant bovine alpha 1 beta 1 gamma 2L GABAA receptor whole-cell currents expressed in L929 fibroplasts. *Neuron*, *13*, 1421–1431.

Lin, Y. F., Angelotti, T. P., Dudek, E. M., Browning, M. D., & MacDonald, R. L. (1996). Enhancement of recombinant alpha 1 beta 1 gamma 2L gamma-aminobutyric acid: A receptor whole-cell current by protein kinase C is mediated through phosphorylation of both beta 1 and gamma 2L subunits. *Molecular Pharmacology*, *50*, 185–195.

Liu, W., Dou, F., Feng, J., & Yan, Z. (2011). RACK1 is involved in beta-amyloid impairment of muscarinic regulation of GABAergic transmission. *Neurobiology of Aging*, *32*, 1818–1826.

Liu, C., Peng, Z., Zhang, N., Yu, L., Hna, S., et al. (2012). Identification of differentially expressed microRNAs and their PKC-isoform specific gene network prediction during hypoxic preconditioning and focal cerebral ischemia of mice. *Journal of Neurochemistry*.

Lorenzetti, F. D., Baxter, D. A., & Byrne, J. H. (2008). Molecular mechanisms underlying a cellular analog of operant reward learning. *Neuron*, *59*, 815–828.

LoTurco, J. L., Coulter, D. A., & Alkon, D. L. (1988). Enhancement of synaptic potentials in rabbit CA1 pyramidal neurons following classical conditioning. *Proceedings of the National Academy of Sciences of the United States of America*, *85*, 1672–1676.

Lu, N., Wang, W. X., Liu, J. S., & Wong, C. W. (2011). Protein kinase C epsilon affects mitochondrial function through estrogen-related receptor alpha. *Cell Signaling*, *23*, 1473–1478.

Mailliot, C., Bussiere, T., Hamdane, M., Sergeant, N., Caillet, M. L., et al. (2000). Pathological tau phenotypes. The weight of mutations, polymorphisms, and differential neuronal vulnerabilities. *Annals of the New York Academy of Sciences*, *920*, 107–114.

Malenka, R. C., Madison, D. V., & Nicoll, R. A. (1986). Potentiation of synaptic transmission in the hippocampus by phorbol esters. *Nature*, *321*, 175–177.

Mandelkow, E. M., & Mandelkow, E. (1998). Tau in Alzheimer's disease. *Trends in Cell Biology*, *8*, 425–427.

Maurice, N., Tkatch, T., Meisler, M., Sprunger, L. K., & Surmeier, D. J. (2001). D1/D5 dopamine receptor activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex. *Journal of Neuroscience*, *21*, 2268–2277.

McCullough, L. D., & Hurn, P. D. (2003). Estrogen and ischemic neuroprotection: An integrated view. *Trends in Endocrinology and Metabolism*, *14*, 228–235.

Melyan, Z., Wheal, H. V., & Lancaster, B. (2002). Metabolic-mediated kainite receptor regulation of Is AHP and excitability in pyramidal cells. *Neuron*, *34*, 107–114.

Metzger, F., & Kapfhammer, J. P. (2000). Protein kinase C activity modulates dendritic differentiation of rat Purkinje cells in cerebellar cultures. *The European Journal of Neuroscience*, *12*, 1993–2005.

Miettinen, S., Roivainen, R., Keinanen, R., Hokfelt, T., & Koistinaho, J. (1996). Specific induction of protein kinase C delta subsepecies after transient middle cerebral artery occlusion in the rat brain: Inhibition by MK-801. *Journal of Neuroscience*, *16*, 6236–6245.

Migues, P. V., Hardt, O., Wu, D. C., Gamache, K., Sacktor, T. C., et al. (2010). PKMzeta maintains memories by regulating GluR2-dependent AMPA receptor trafficking. *Nature Neuroscience*, *13*, 630–634.

Miranda, M., Wu, C. C., Sorkin, T., Korstjens, D. R., & Sorkin, A. (2005). Enhanced ubiquitylation and accelerated degradation of the dopamine transporter mediated by protein kinase C. *The Journal of Biological Chemistry*, *280*, 35617–35624.

Narita, M., Aoki, T., Ozaki, S., Yajima, Y., & Suzuki, T. (2001). Involvement of protein kinase Cgamma isoform in morphine-induced reinforcing effects. *Neuroscience*, *103*, 309–314.

Narita, M., Miyatake, M., Shibasaki, M., Tsuda, M., Koizumi, S., et al. (2005). Long-lasting change in brain dynamics induced by methamphetamine: Enhancement of protein kinase C-dependent astrocytic response and behavioral sensitization. *Journal of Neurochemistry*, *93*, 1383–1392.

Nelson, T. J., & Alkon, D. L. (2009). Neuroprotective versus tumorigenic protein kinase C activators. *Trends in Biochemical Sciences*, *34*, 136–145.

Nelson, T. J., Sun, M.-K., Hongpaisan, J., & Alkon, D. L. (2008). Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. *European Journal of Pharmacology*, *585*, 76–87.

Nelson, T. J., Cui, C., Luo, Y., & Alkon, D. L. (2009). Reduction of beta-amyloid levels by novel PKC epsilon activators. *The Journal of Biological Chemistry*, *284*, 34514–34521.

Nicholls, D. G. (1998). Presynaptic modulation of glutamate release. *Progress in Brain Research*, *116*, 15–22.

Nimitvilai, S., Arora, D. S., & Brodie, M. S. (2012). Reversal of dopamine inhibition of dopaminergic neurons of the ventral terminal area is mediated by protein kinase C. *Neuropharmacology*, *37*, 543–556.

Nishizaki, T., Nomura, T., Matuoka, T., Kondoh, T., Enikolopov, G., et al. (2000). The anti-dementia drug nefiracetam facilitates hippocampal synaptic transmission by functionally targeting presynaptic nicotinic ACh receptors. *Brain Research. Molecular Brain Research*, *80*, 53–62.

Nitti, M., d'Abramo, C., Traverso, N., Verzola, D., Garibotto, G., et al. (2005). Central role of PKCδ in glycoxidation-dependent apoptosis of human neurons. *Free Radical Biology & Medicine*, *38*, 846–856.

Nunez-Jaramillo, L., Delint-Ramirez, I., & Bermudez-Rattoni, F. (2007). PKC blockade differentially affects aversive but not appetitive gustatory memories. *Brain Research*, *1148*, 177–182.

Okada, M., Zhu, G., Yoshida, S., Hirose, S., & Kaneko, S. (2004). Protein kinase associated with gating and closing transmission mechanisms in temporoammonic pathway. *Neuropharmacology*, *47*, 485–504.

Olds, J. L., Anderson, M. L., McPhie, D. L., & Alkon, D. L. (1989). Imaging of memory-specific changes in the distribution of protein kinase C in the hippocampus. *Science*, *245*, 866–869.

Olds, J. L., Golski, S., McPhie, D. L., Olton, D., Mishkin, M., & Alkon, D. L. (1990). Discrimination learning alters the distribution of protein kinase C in the hippocampus of rats. *Journal of Neuroscience*, *10*, 3707–3713.

Olds, J. L., Bhalla, U. S., McPhie, D. L., Lester, D. S., Bower, J. M., & Alkon, D. L. (1994). Lateralization of membrane-associated protein kinase C in rat piriform cortex: Specific to operant training cues in the olfactory modality. *Behavioural Brain Research*, *61*, 37–46.

Pakaski, M., Balaspiri, L., Checler, F., & Kasa, P. (2002). Human amyloid-beta causes changes in the levels of endothelial protein kinase C and its alpha isoform *in vitro*. *Neurochemistry International*, *41*, 409–414.

Parekh, D. B., Ziegler, W., & Parker, P. J. (2000). Multiple pathways control protein kinase C phosphorylation. *The EMBO Journal*, *19*, 495–503.

Pascale, A., Gusev, P. A., Amadio, M., Dottorini, T., Govoni, S., et al. (2004). Quattrone A. Increase of the RNA-binding protein HuD and posttranscriptional up-regulation of the GAP-43 gene during spatial memory. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 1217–1222.

Pascale, A., Amadio, M., Govoni, S., & Battaini, F. (2007). The aging brain, a key target for the future: The protein kinase C involvement. *Pharmacological Research*, *55*, 560–569.

Paula-Lima, A. C., Adasme, T., SanMartín, C., Sebollela, A., Hetz, C., et al. (2011). Amyloid β-peptide oligomers stimulate RyR-mediated Ca^{2+} release inducing mitochondrial fragmentation in hippocampal neurons and prevent RyR-mediated dendritic spine remodeling produced by BDNF. *Antioxidants & Redox Signaling*, *14*, 1209–1223.

Paylor, R., Rudy, J. W., & Wehner, J. M. (1991). Acute phorbol ester treatment improves spatial learning performance in rats. *Behavioural Brain Research*, *45*, 189–193.

Paylor, R., Morrison, S. K., Rudy, J. W., Waltrip, L. T., & Wehner, J. M. (1992). Brief exposure to an enriched environment improves performance on the Morris water task and increases hippocampal cytosolic protein kinase C activity in young rats. *Behavioural Brain Research*, *52*, 49–59.

Perez, R. G., Zheng, H., Van der Ploeg, L. H., & Koo, E. H. (1997). The β-amyloid precursor protein of Alzheimer's disease enhances neuron viability and modulates neuronal polarity. *Journal of Neuroscience*, *17*, 9407–9414.

Perez-Pinzon, M. A., Raval, A. P., & Dave, K. P. (2005). Protein kinase C and synaptic dysfunction after cardiac arrest. *Pathophysiology*, *12*, 29–34.

Phan, T. G., Wright, P. M., Markus, R., Howells, D. W., Davis, S. M., et al. (2002). Salvaging the ischaemic penumbra: More than just reperfusion? *Clinical and Experimental Pharmacology & Physiology*, *29*, 1–10.

Pierchla, B. A., Ahrens, R. C., Paden, A. J., & Johnson, E. M., Jr. (2004). Nerve growth factor promotes the survival of sympathetic neurons through the cooperative function of the protein kinase C and phosphatidylinositol 3-kinase pathways. *The Journal of Biological Chemistry*, *279*, 27986–27993.

Pilpel, Y., & Segal, M. (2004). Activation of PKC induces rapid morphological plasticity in dendrites of hippocampal neurons via Rac and Rho-dependent mechanisms. *The European Journal of Neuroscience*, *19*, 3151–3164.

Ping, X. J., Ma, Y. Y., Li, Y. J., Qi, C., Sun, X. W., et al. (2012). Essential role of protein kinase C in morphine-induced rewarding memory. *Neuropharmacology*.

Poisbeau, P., Cheney, M. C., Browning, M. D., & Mody, I. (1999). Modulation of synaptic GABAA receptor function by PKA and PKC in adult hippocampal neurons. *Journal of Neuroscience*, *19*, 674–683.

Postina, R. (2011). Activation of α-secretase cleavage. *Journal of Neurochemistry*, *120*, 46–54.

Puzzo, D., Privitera, L., Leznik, E., Fa, M., Staniszewski, A., et al. (2008). Picomolar amyloid-β positively modulates synaptic plasticity and memory in hippocampus. *Journal of Neuroscience*, *28*, 14537–14545.

Qiu, J., Bosch, M. A., Tobias, S. C., Grandy, D. K., Scanlan, T. S., et al. (2003). Rapid signaling of estrogen in hypothalamic neurons involves a novel G-protein-coupled estrogen receptor that activates protein kinase C. *Journal of Neuroscience*, *23*, 9529–9540.

Raval, A. P., Dave, K. R., Mochly-Rosen, D., Sick, T. J., & Pérez-Pinzón, M. A. (2003). εPKC is required for the induction of tolerance by ischemic and NMDA-mediated preconditioning in the organotypic hippocampal slice. *Journal of Neuroscience*, *23*, 384–391.

Raval, A. P., Dave, K. R., deFazio, R. A., & Perez-Pinzon, M. A. (2007). EpsilonPKC phosphorylates the mitochondrial K(+)(ATP) channel during induction of ischemic preconditioning in the rat hippocampus. *Brain Research*, *1184*, 345–353.

Rekart, J. L., Quinn, B., Mesulam, M.-M., & Routtenberg, A. (2004). Increased brain growth protein in a subfield of hippocampus from Alzheimer's patients. *Neuroscience*, *126*, 579–584.

Rekart, J. L., Meiri, K., & Routtenberg, A. (2005). Hippocampal-dependent memory is impaired in heterozygous GAP-43 knockout mice. *Hippocampus*, *15*, 1–7.

Roberson, E. D., English, J. D., Adams, J. P., Selcher, J. C., Kondratick, C., et al. (1999). The mitogen-activated protein kinase cascade couples PKA and PKC to cAMP response element binding protein phosphorylation in area CA1 of hippocampus. *Journal of Neuroscience*, *19*, 4337–4348.

Ron, D., & Mochly-Rosen, D. (1995). An autoregulatory region in protein kinase C: The pseudoanchoring site. *Proceedings of the National Academy of Sciences of the United States of America*, *92*, 492–496.

Ron, S., Dudai, Y., & Segal, M. (2012) (in press). Overexpression of PKMζ alters morphology and function of dendritic spines in cultured cortical neurons. Cerebral Cortex.

Rossner, S., Mendla, K., Schliebs, R., & Bigl, V. (2001). Protein kinase C alpha and beta1 isoforms are regulators of alpha-secretory proteolytic processing of amyloid precursor protein *in vitro*. *The European Journal of Neuroscience*, *13*, 1644–1648.

Routtenberg, A., Cantallops, I., Zaffuto, S., Serrano, P., & Namgung, U. (2000). Enhanced learning after genetic overexpression of a brain growth protein. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 9657–9662.

Ruiz-Canada, C., Ashley, J., Moeckel-Cole, S., Drier, E., Yin, J., et al. (2004). New synaptic bouton formation is disrupted by misregulation of microtubule stability in aPKC mutants. *Neuron*, *42*, 567–580.

Sacco, T., & Sacchetti, B. (2010). Role of secondary sensory cortices in emotional memory storage and retrieval in rats. *Science*, *329*, 649–656.

Sacktor, T. C. (2008). PKMzeta, LTP maintenance, and the dynamic molecular biology of memory storage. *Progress in Brain Research*, *169*, 27–40.

Sacktor, T. C. (2011). How does PKMζ maintain long-term memory? *Nature Reviews. Neuroscience*, *12*, 9–15.

Saito, N., Kikkawa, U., Nishizuka, Y., & Tanaka, C. (1988). Distribution of protein kinase C-like immunoreactive neurons in rat brain. *Journal of Neuroscience*, *8*, 369–382.

Salck, S. E., Pezet, S., McMahon, S. B., Thompson, S. W. N., & Malcangio, M. (2004). Brain-derived neurotrophic factor induces NMDA receptor subunit one phosphorylation via ERK and PKC in the rat spinal cord. *The European Journal of Neuroscience*, *20*, 1769–1778.

Sato, T., Tanaka, K., Teramoto, T., Ohnishi, Y., Hirate, K., et al. (2004). Facilitative effect of a novel AVP fragment analog, NC-1900, on memory retention and recall in mice. *Peptides*, *25*, 1139–1146.

Schenk, D. B., Seubert, P., Grundman, M., & Black, R. (2005). A beta immunotherapy: Lessons learned for potential treatment of Alzheimer's disease. *Neuro-Degenerative Diseases*, *2*, 255–260.

Schreurs, B. G., Oh, M. M., & Alkon, D. L. (1996). Pairing-specific long-term depression of Purkinje cell excitatory postsynaptic potentials results from a classical conditioning procedure in the rabbit cerebellar slice. *Journal of Neurophysiology*, *75*, 1051–1060.

Schreurs, B. G., Tomsic, D., Gusev, P. A., & Alkon, D. L. (1997). Dendritic excitability microzones and occluded long-term depression after classical conditioning of the rabbit's nictitating membrane response. *Journal of Neurophysiology*, *77*, 86–92.

Serrano, P., Friedman, E. L., Kenney, J., Taubenfeld, S. M., Zimmerman, J. M., et al. (2008). A.A. PKMzeta maintains spatial, instrumental, and classically conditioned long-term memories. *PLoS Biology*, *6*, 2698–2706.

Serrano-Pozo, A., William, C. M., Ferrer, I., Uro-Coste, E., Delisle, M. B., et al. (2010). Beneficial effect of human anti-amyloid-beta active immunization on neurite morphology and tau pathology. *Brain*, *133*, 1312–1327.

Shema, R., Haramati, S., Ron, S., Hazvi, S., Chen, A., et al. (2011). Enhancement of consolidated long-term memory by overexpression of protein kinase Mzeta in the neocortex. *Science*, *331*, 1207–1210.

Siemes, C., Quast, T., Kummer, C., Wehner, S., Kirfel, G., et al. (2006). Keratinocytes from APP/APLP2-deficient mice are impaired in proliferation, adhesion and migration *in vitro*. *Experimental Cell Research*, *312*, 1939–1949.

Small, D. H., Clarris, H. L., Williamson, T. G., Reed, G., Key, B., et al. (1999). Neurite-outgrowth regulating functions of the amyloid protein precursor of Alzheimer's disease. *Journal of Alzheimer's Disease*, *1*, 275–285.

Smith, B. L., & Mochly-Rosen, D. (1992). Inhibition of protein kinase C function by injection of intracellular receptor for the enzyme. *Biochemical and Biophysical Research Communications*, *188*, 1235–1240.

Soetikno, V., Watanabe, K., Sari, F. R., Harima, M., Thandavarayan, R. A., et al. (2011). Curcumin attenuates diabetic nephropathy by inhibiting PKC-α and PKC-β_1 activity in streptozotocin-induced type I diabetic rats. *Molecular Nutrition & Food Research*, *55*, 1655–1665.

Song, C. Y., Xi, H. J., Yang, L., Qu, L. H., Yue, Z. Y., et al. (2011). Propofol inhibited the delayed rectifier potassium current (I_k) via activation of protein kinase C epsilon in rat parietal cortical neurons. *European Journal of Pharmacology*, *653*, 16–20.

Spaeth, C. S., Boydston, E. A., Figard, L. R., Zuzek, A., & Bittner, G. D. (2010). A model for sealing plasmalemmal damage in neuron and other eukaryotic cells. *Journal of Neuroscience*, *30*, 15790–15800.

Stevens, C. F., & Sullivan, J. M. (1998). Regulation of the readily releasable vesicle pool by protein kinase C. *Neuron*, *21*, 885–893.

Sun, L., & Liu, S. J. (2007). Activation of extrasynaptic NMDA receptors induces a PKC-dependent switch in AMPA receptor subtypes in mouse cerebellar stellate cells. *Journal of Physiology*, *583*, 537–553.

Sun, M.-K., & Alkon, D. L. (2005). Dual effects of bryostatin-1 on spatial memory and depression. *European Journal of Pharmacology*, *512*, 43–51.

Sun, M.-K., & Alkon, D. L. (2008). Synergistic effects of chronic bryostatin-1 and alpha-tocopherol on spatial learning and memory in rats. *European Journal of Pharmacology*, *584*, 328–337.

Sun, M.-K., Hongpaisan, J., Nelson, T. J., & Alkon, D. L. (2008). Poststroke neuronal rescue and synaptogenesis mediated *in vivo* by protein kinase C in adult brains. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 13620–13625.

Sun, M.-K., Hongpaisan, J., & Alkon, D. L. (2009). Postischemic PKC activation rescues retrograde and anterograde long-term memory. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 14676–14689.

Takeishi, Y., Ping, P., Bolli, R., Kirkpatrick, D. L., Hoit, B. D., et al. (2000). Transgenic overexpression of constitutively active protein kinase C epsilon causes concentric cardiac hypertrophy. *Circulation Research*, *86*, 1218–1223.

Takashima, A., Yokota, T., Maeda, Y., & Itoh, S. (1991). Pretreatment with caerulein protects against memory impairment induced by protein kinase C inhibitors in the rat. *Peptides*, *12*, 699–703.

Theodore, L., Derossi, D., Chassaing, G., Llirbat, B., Kubes, M., et al. (1995). Intraneuronal delivery of protein kinase C pseudosubstrate leads to growth cone collapse. *Journal of Neuroscience*, *15*, 7158–7167.

Toker, A. (2000). Protein kinases as mediators of phosphoinositide 3-kinase signaling. *Molecular Pharmacology*, *57*, 652–658.

Toni, N., Stoppini, L., & Muller, D. (1997). Staurosporine but not chelerythrine inhibits regeneration in hippocampal organotypic cultures. *Synapse*, *27*, 199–207.

Tyszkiewcz, J. P., Gu, Z., Wang, X., Cai, X., & Yan, Z. (2003). Group II metabotropic glutamate receptor enhance NMDA receptor currents via a protein kinase C-dependent mechanism in pyramidal neurons of rat prefrontal cortex. *Journal of Physiology*, *554*, 765–777.

Van der Zee, E. A., Compaan, J. C., de Beer, M., & Luiten, P. G. (1992). Changes in PKC gamma immunoreactivity in mouse hippocampus induced by spatial discrimination learning. *Journal of Neuroscience*, *12*, 4808–4815.

Van der Zee, E. A., Compaan, J. C., Bohus, B., & Luiten, P. G. (1995). Alterations in the immuno-reactivity for muscarinic acetylcholine receptors and colocalized PKC gamma in mouse hippocampus induced by spatial discrimination learning. *Hippocampus*, *5*, 349–362.

Van der Zee, E. A., Kronforst-Collins, M. A., Maizels, E. T., Hunzicker-Dunn, M., & Disterhoft, J. F. (1997). Gamma isoform-selective changes in PKC immunoreactivity after trace eyeblink conditioning in the rabbit hippocampus. *Hippocampus*, *7*, 271–285.

Vaz, S. H., Jorgensen, T. N., Cristovao-Ferreira, S., Duflot, S., Ribeiro, J. A., et al. (2011). Brain-derived neurotrophic factor (BDNF) enhances GABA transport by modulating the trafficking of GABA transporter-1 (GAT-1) from the plasma membrane of rat cortical astrosytes. *The Journal of Biological Chemistry*, *286*, 40464–40476.

Vázquez, A., & de Ortiz, P. (2004). Lead (Pd(2+)) impairs long-term memory and blocks learning-induced increases in hippocampal protein kinase C activity. *Toxicology and Applied Pharmacology*, *200*, 27–39.

Wang, H.-Y., Pisano, M. R., & Friedman, E. (1994). Attenuated protein kinase C activity and translocation in Alzheimer's disease brain. *Neurobiology of Aging*, *15*, 293–298.

Wang, J., Bright, R., Mochly-Rosen, D., & Giffard, R. G. (2004). Cell-specific role for ε- and βI-protein kinase C isozymes in protecting cortical neurons and astrocytes from ischemia-like injury. *Neuropharmacology*, *47*, 136–145.

Wang, D., Darwish, D. S., Schreurs, B. G., & Alkon, D. L. (2008). Analysis of long-term cognitive-enhancing effects of bryostatin-1 on the rabbit (Oryctolagus cuniculus) nictitating membrane response. *Behavioural Pharmacology*, *19*, 245–256.

Wang, Q., Li, X. Y., Chen, Y. K., Wang, F., Yang, Q. Z., et al. (2011). Activation of epsilon protein kinase C-mediated anti-apoptosis is involved in rapid tolerance induced by electroacupuncture pretreatment through cannabinoid receptor type 1. *Stroke*, *42*, 389–396.

Weeber, E. J., Atkins, C. M., Selcher, J. C., Varga, A. W., Mirnikjoo, B., et al. (2000). A role for the β isoform of protein kinase C in fear conditioning. *Journal of Neuroscience*, *20*, 5906–5914.

Yamamoto, S., Kanno, T., Nagata, T., Yaguchi, T., Tanaka, A., et al. (2005). The linoleic acid derivative FR236924 facilitates hippocampal synaptic transmission by enhancing activity of presynaptic alpha7 acetylcholine receptors on the glutamatergic terminals. *Neuroscience*, *130*, 207–213.

Yang, S. H., Shi, J., Day, A. L., & Simpkins, J. W. (2000). Estrodiol exerts neuroprotective effects when administered after ischemic insult. *Stroke*, *31*, 745–749.

Yang, Y., Wang, X. B., & Zhou, Q. (2010). Perisynaptic GluR2-lacking AMPA receptors control the reversibility of synaptic and spine modifications. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 11999–112004.

Yao, Y., Kelly, M. T., Sajikumar, S., Serrano, P., Tian, D., et al. (2008). PKM zeta maintains late long-term potentiation by *N*-ethylmaleimide-sensitive factor/GluR2-dependent trafficking of postsynaptic AMPA receptors. *Journal of Neuroscience*, *26*, 7820–7827.

Yasoshima, Y., & Yamamoto, T. (1997). Rat gustatory memory requires protein kinase C activity in the amygdale and cortical gustatory area. *Neuroreport*, *8*, 1363–1367.

Yeon, S. W., Jung, M. W., Ha, M. J., Kim, S. U., Huh, K., et al. (2001). Blockade of PKC epsilon activation attenuates phorbol ester-induced increase of alpha-secretase-derived secreted form of amyloid precursor protein. *Biochemical and Biophysical Research Communications*, *280*, 782–787.

Young-Pearse, T. L., Bai, J., Chang, R., Zheng, J. B., LoTurco, J. J., et al. (2007). A critical function for β-amyloid precursor protein in neuronal migration revealed by in utero RNA interference. *Journal of Neuroscience*, *27*, 14459–14469.

Zhang, Y. Q., Shi, J., Rajakumar, G., & Day, A. L. (1998). Simpkins, J.W. Effects of gender and estrogen treatment on focal brain ischemia. *Brain Research*, *784*, 321–324.

Zhang, G.-R., Wang, X., Kong, L., Lu, X. G., Lee, B., et al. (2005). Genetic enhancement of visual learning by activation of protein kinase C pathways in small groups of rat cortical neurons. *Journal of Neuroscience*, *25*, 8468–8481.

Zhang, C. S., Bertaso, F., Eulenburg, V., Lerner-Natoli, M., Herin, G. A., et al. (2008). Knock-in mice lacking the PDZ-ligand motif of mGluR7a show impaired PKC-dependent autoinhibition of glutamate release, spatial working memory deficits, and increased susceptibility to pentylenetetrazol. *Neuron*, *28*, 8604–8614.

Zhu, G., Wang, D., Lin, Y. H., McMahon, T., Koo, E. H., et al. (2001). Protein kinase C epsilon suppresses Aβ production and promotes activation of α-secretase. *Biochemical and Biophysical Research Communications*, *285*, 997–1006.