



Published in final edited form as:

J Alzheimers Dis. 2015 ; 43(3): 711–724. doi:10.3233/JAD-141422.

Common Mechanisms of Alzheimer's Disease and Ischemic Stroke: The Role of Protein Kinase C in the Progression of Age-Related Neurodegeneration

Brandon P. Lucke-Wold^{a,b}, Ryan C. Turner^{a,b}, Aric F. Logsdon^{b,c}, James W. Simpkins^b, Daniel L. Alkon^d, Kelly E. Smith^{b,c}, Yi-Wen Chen^b, Zhenjun Tan^{a,b}, Jason D. Huber^{b,c}, and Charles L. Rosen^{a,b,*}

^aDepartment of Neurosurgery, West Virginia University School of Medicine, Morgantown, WV, USA

^bThe Center for Neuroscience, West Virginia University School of Medicine, Morgantown, WV, USA

^cDepartment of Basic Pharmaceutical Sciences, West Virginia University School of Pharmacy, Morgantown, WV, USA

^dBlanchette Rockefeller Neurosciences Institute, Morgantown, WV, USA

Abstract

Ischemic stroke and Alzheimer's disease (AD), despite being distinct disease entities, share numerous pathophysiological mechanisms such as those mediated by inflammation, immune exhaustion, and neurovascular unit compromise. An important shared mechanistic link is acute and chronic changes in protein kinase C (PKC) activity. PKC isoforms have widespread functions important for memory, blood-brain barrier maintenance, and injury repair that change as the body ages. Disease states accelerate PKC functional modifications. Mutated forms of PKC can contribute to neurodegeneration and cognitive decline. In some cases the PKC isoforms are still functional but are not successfully translocated to appropriate locations within the cell. The deficits in proper PKC translocation worsen stroke outcome and amyloid- β toxicity. Cross talk between the innate immune system and PKC pathways contribute to the vascular status within the aging brain. Unfortunately, comorbidities such as diabetes, obesity, and hypertension disrupt normal communication between the two systems. The focus of this review is to highlight what is known about PKC function, how isoforms of PKC change with age, and what additional alterations are consequences of stroke and AD. The goal is to highlight future therapeutic targets that can be applied to both the treatment and prevention of neurologic disease. Although the pathology of ischemic stroke and AD are different, the similarity in PKC responses warrants further investigation, especially as PKC-dependent events may serve as an important connection linking age-related brain injury.

© 2015 – IOS Press and the authors. All rights reserved

*Correspondence to: Charles L. Rosen, MD, PhD, Department of Neurosurgery, West Virginia University School of Medicine, One Medical Center Drive, Suite 4300, Health Sciences Center, PO Box 9183, Morgantown, WV 26506-9183, USA. Tel.: +1 304 293 5041; Fax: +1 304 293 4819; crosen@hsc.wvu.edu.

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=2418>).

Keywords

Alzheimer's disease; blood-brain barrier; immune exhaustion; innate immunity; ischemic stroke; protein kinase C

INTRODUCTION

The most prominent clinical symptom of Alzheimer's disease (AD) is progressive cognitive decline [1]. The characteristic loss of episodic memories is an area under focused investigation and heavily dependent on amyloid- β (A β) plaques and neurofibrillary tau tangles (NFTs) [2]. A promising field of study is the contribution of Protein Kinase C (PKC) to cognitive decline and how it changes with aging and during AD progression. PKC isoforms have been classified as "memory kinases" for the role they play in acquisition and modification of dendritic spines [3]. Recent findings have highlighted PKC dysfunction as a process of aging. A β contributes to accelerated PKC changes that lead to downregulation of AMPA receptors [4]. Overactivity of damaging PKC isoforms, α and δ , contributes to cognitive decline and dendritic shortening [5]. Neurite retraction from PKC activity has also been reported in neurons of the hippocampus [6]. Interestingly, selective pharmacologic activation of PKC ϵ can improve synaptogenesis [7]. PKC γ also contributes to the preservation of synaptic plasticity [8]. Besides the role that PKC isoforms play in memory formation, they also have important functions as tau kinases [9]. In particular, age-related changes in PKC translocation have been linked to tau hyperphosphorylation and the phosphorylation of glycogen synthase kinase 3 β (p-GSK3 β) [10]. Restoration of the PKC ϵ cytosol-to-cell membrane translocation and activity decrease both NFTs and A β deposition in transgenic animal models [11]. What has yet to be fully determined is which isoforms are protective with aging, at what time are they protective, and when should they be selectively targeted.

Ischemic stroke, another prominent age-related disease, is the leading cause of disability in the US [12]. The severity of ischemic stroke outcome is closely linked to the extent of blood-brain barrier (BBB) disruption. Several deleterious PKC isoforms are increased in the endothelial cells of the vasculature following ischemia [13]. PKC θ and ζ contribute to disruption of the tight junction proteins, claudin-5, occludin, and ZO1 [14]. The extent of BBB disruption is biphasic in that acute disruption is detrimental while some chronic disruption is required for recovery. Interestingly, extensive motor training following stroke increases neuroprotective isoforms of PKC in a time-dependent manner leading to decreased BBB permeability [15]. Likewise δ opioid agonists increase the translocation of the neuroprotective isoform PKC ϵ from the cytosol to nuclear membrane following stroke, thus providing protection for neurons [16].

The complex interrelations between AD and ischemic stroke include and are dependent on immune exhaustion. Atherosclerosis, cardiovascular disease, and AD are made worse by the inflammatory cascade released during immune exhaustion [17]. The risk for immune exhaustion is magnified in both AD and stroke with comorbidities such as diabetes, obesity, and hypertension [18, 19]. PKC activity is intimately linked to the immune system through

both the complement system and toll-like receptors [20, 21]. In this review, we highlight what is known about PKC isoforms in aging, stroke, and AD, discuss areas requiring further investigation in order to successfully advance toward PKC-activated treatment regimens, and evaluate the contribution of immune exhaustion to PKC activity modification.

BACKGROUND OF PKC IN THE CENTRAL NERVOUS SYSTEM

PKC isoforms are found throughout the body, but in the brain they regulate vesicle movement and synapse secretion [22]. The isoforms can be broadly grouped into three classes: conventional (α , β , γ), novel (δ , ϵ , η , θ), and atypical (ι , ζ , N1–N3). Conventional isoforms require diacylglycerol, Ca^{2+} , and diphorbol ester for activation. Novel isoforms require only diacylglycerol, and atypical isoforms do not require co-factors. Common PKC isoforms within the brain include PKC α , β , δ , ϵ , γ , and ζ [3]. PKC isoforms are differentiated according to structure and function. PKC α has an organized linear configuration consisting of N-terminal pseudosubstrate domains, a kinase domain, targeting domains, and inhibitory regulatory domains [23]. PKC α provides biochemical and structural support for synaptic architecture through activation of protein synthesis and has been associated with memory capacity [24, 25]. PKC β has a distinct active site with a Ca backbone surrounded by supportive side chains [26]. The active site plays important roles as a memory kinase that mediates cognition [27]. The characteristic features of PKC δ are a catalytic domain and a highly reactive regulatory domain, C1B, which interacts with diacylglycerol [28]. PKC δ plays important roles in the regulation of apoptosis [29]. PKC ϵ has a catalytic domain and two C1 domains that help direct translocation from the plasma membrane to nuclear membrane [30]. PKC ϵ contributes to recognition memory and wound healing [31, 32]. PKC γ has a flexible C1B domain that can be phosphorylated at serine 109 [33]. PKC γ plays a vital role in pain regulation and reward seeking behavior [34, 35]. PKC ζ has a series of N-terminal PB1 domains that have important roles in cellular processes [36]. PKC ζ contributes to memory consolidation and maintenance [37, 38].

PKC REGULATION

PKC isoforms can be upregulated or downregulated depending on which pathways are active [39]. Common regulators include ceramide, annexins, and ellagic acid [40–42]. In order for PKC isoforms to be activated, they must be externally phosphorylated at a threonine residue tightly coiled within the active site. Subsequently, PKC undergoes autophosphorylation to internalize its hydrophobic residues [43]. It is only at this point that the C2 domain can bind to the receptor for activated C-kinases (RACKs) [44]. RACKs play a vital role in transporting PKC isoforms from the cytosol to the membrane [45]. Each PKC isoform has a binding site for specific RACKs in order to facilitate the appropriate translocation destination [46]. Once at the membrane, A-kinase regulating-proteins (AKAPs) and heat shock proteins (HSPs) direct PKC isoforms into close proximity with substrates [41]. AKAP7 α enhances the speed by which PKC can phosphorylate substrates as well as stabilizes PKC activity over time [47]. HSP90 maintains the phosphorylation state of PKC for extended periods increasing its efficiency [48]. PKC is cleaved by caspase 3, transported in association with heat shock protein 70 (HSP70), and degraded by the

proteasome [48, 49]. An alternative pathway for PKC degradation involves the lysosomal system [50].

PKC AND AGING

Two predominant theories have been proposed to explain how PKC activity changes with age [51]. The first theory is that as aging occurs, PKC isoforms become dysfunctional resulting in a gradual downregulation of PKC isoforms over time [52, 53]. Epigenetic modification triggers PKC repression [54]. Repression of the PKC gene has been directly associated with neurodegeneration as well as impaired memory and learning [7, 55]. The second theory is that PKC isoforms are still viable but the translocation process is dysfunctional [52]. RACKs are downregulated with aging, which leads to decreased PKC stabilization at the membrane [56]. Age-related decreases in RACK1 may explain, at least in part, age-related decreases in memory function [57].

Both theories are most likely relevant to the process of neuroaging but depend heavily on isoform specific interactions. For example, age-related decreases in expression with age of PKC α and ε in the frontal cortex and hippocampus have been linked to poor spatial memory [58]. Dysfunctional PKC α can also lead to an increase in matrix metalloproteinases within the aged brain [59]. In contrast, PKC γ levels are maintained at a constant level in the aged hippocampus, but translocation of this isoform is impaired. Such deficits in PKC γ translocation leads to poor performance on cognitive tasks in aged-animal models [27]. Furthermore, age-related comorbidities confound the expression of various isoforms. PKC α and β are increased with diabetes leading to the enhanced formation of advanced glycosylated end products [60, 61]. PKC δ and β are increased with atherosclerosis and contribute to endothelial cell damage [62, 63]. PKC δ also contributes to aortic contraction and adipocyte apoptosis in obese individuals [64]. In addition, complement mediated immunity activates PKC isoforms and triggers neurodegeneration during aging [65]. PKC β accelerates inflammatory vascular disruption contributing to immune exhaustion [66]. What has yet to be fully elucidated is how age and co-morbidities alter PKC dynamics in diseases such as stroke and AD.

PKC AND STROKE

Following ischemic stroke, several PKC isoforms are altered within the brain [67]. PKC isoforms α , β , δ , θ , and ζ have an initial spike during the onset of ischemia, but are quickly degraded within the penumbra at later time points [68]. PKC isoforms ε and η are acutely downregulated but may play a role in recovery at extended time points [14]. PKC α has been linked to increased risk for hemorrhagic transformation following ischemic stroke [69]. PKC δ contributes to a release of reactive oxygen species and apoptosis following ischemia [70, 71]. PKC δ likewise contributes to increased BBB permeability via activation of matrix metalloproteinase-9 and phosphorylation of occludin [72, 73]. PKC ε is downregulated leaving neuronal mitochondria susceptible to injury [74]. PKC ζ and PKC β contribute to tight junction disruption within the BBB during hypoxia (Fig. 1) [14, 75]. Of significance, PKC mediated vasoconstriction is disrupted allowing an influx of inflammatory markers and cytokines into the cerebrovasculature [76]. Similarly PKC isoforms likewise inhibit BBB

transport proteins leaving the brain permeable to inflammatory toxins [77] such that the P-glycoprotein efflux capability is eventually overwhelmed and the tissue succumbs to infarct [78].

PKC is initially activated by increased intracellular calcium and adenosine following ischemia, but a delayed induction is also seen due to changes in gene expression [68, 79]. PKC β , in particular, quickly increases the RhoA/myosin-regulated light chain 2 pathway leading to increased brain edema following stroke [80]. Some isoforms are unable to translocate following ischemic injury and trigger intracellular pathways that contribute to neuronal death or injury [81]. One such response is activation of NADPH oxidase [82]. PKC ζ triggers NADPH oxidase, which subsequently causes the release of superoxide. Superoxide changes the conformation of NMDA receptors predisposing the cell to excitotoxicity [83]. PKC activity also increases the permeability of chloride channels resulting in increased neuronal death following ischemia and triggers increased expression of nitric oxide synthase [84, 85]. If PKC ϵ is increased, however, scavenging molecules that protect cells from reactive oxygen species are elevated [86]. The level of PKC ϵ activity is inversely correlated with infarct volume [87]. PKC ϵ exerts its protective effects through mitochondrial stabilization [88].

If the brain is reperfused by thrombolytics, PKC δ can contribute to injury expansion by triggering an influx of neutrophils and activating platelets within compromised vasculature [89]. PKC isoforms α , δ , ϵ , and ζ are intimately involved in toll-like receptor signaling linking PKC activity closely with the innate immune system [90]. Comorbidities can also exacerbate stroke outcome and injury. Hyperglycemia in diabetes primes PKC δ allowing for more extensive BBB disruption following stroke [91]. Obesity increases PKC ζ , which predisposes the body to the development of the metabolic syndrome [92]. Hypertension can develop following obesity due to PKC specific activation of mitogen activated protein kinases. Such activation, leads to chronic vascular smooth muscle constriction in arteries [93]. Besides age itself, hypertension is the biggest risk factor for stroke [94]. Alternatively, ischemic preconditioning increases PKC ϵ and decreases PKC δ , which has been shown to decrease infarct volume in animal models of stroke [95, 96]. PKC ϵ is coupled with toll-like receptor 4 through MyD88. Toll-like receptor 4 exerts protective effects through downstream activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) [97]. PKC activity during stroke is ultimately time dependent and heavily mediated by vascular changes that are associated with comorbidities.

PKC AND AD

The process of memory formation and memory failure is an issue that has gained resurgence in the past few years with the increased prevalence of AD in the aging population [98]. PKC activity has recently been shown to be essential for memory formation and learning [3]. Memory in its basic form is dependent on synaptic remodeling, formation of dendritic spines, and mitochondria functionality [99, 100]. Isoforms of PKC are involved in multiple synaptic transmissions, including those involving glutamate, dopamine, acetylcholine, and serotonin [101–104]. The synaptic connections are intimately linked to cognitive processing and learning with different PKC isoforms being involved in distinct memory domains.

PKC α is linked to the formation of aversive and high-impact memories, whereas PKC ϵ is important in spatial memory formation and object recognition [25, 31]. Additionally, PKC ζ is essential in maintenance and storage of long-term memory, and overexpression of this isoform has been shown to improve memory processes [105].

Stress-related dysfunction of PKC isoforms with age is linked to a progressive decline of memory and cognition with the potential for dementia and tau-related pathology [10]. In a transgenic PKC β knockout model, animals did worse than controls on fear conditioning and cued learning [106], both tests detecting the neuroplasticity of the basolateral nucleus of the amygdala [107–109]. These data suggests that PKC β is essential in normal amygdala synaptic plasticity, limbic driven memory, and learning. Transgenic animals with a PKC ζ knockout have disrupted memory formation as well as poor memory recall [110]. In addition to dysfunction, downregulation of PKC isoforms is associated with AD, but not other types of dementia such as multi-infarct dementia and corticobasal degeneration [111]. PKC downregulation is also independent of other extraneous factors such as hydrocephalus and gender [112]. PKC downregulation may therefore be closely tied to the cognitive decline seen in AD [111]. A defect in PKC anchoring is associated with impairment of TNF- α production linking PKC dysfunction to immune senescence [113]. Moreover, the intracellular aggregation of hyperphosphorylated tau and extracellular amyloid accumulation are known to be detrimental to neurons and are suggested to be both directly and indirectly mediated by PKC [114] (Fig. 2).

PKC α is known to upregulate α -secretase, an enzyme important in non-pathogenic amyloid processing. Activation of α -secretase degrades amyloid- β protein precursor (A β PP), promotes the formation of soluble A β PP α (sA β PP α), and prevents A β accumulation. α -secretase is believed to be activated directly by PKC α and PKC ϵ , and indirectly through the mitogen-activated protein kinase (MAPK) pathway [115]. Dysfunctional PKC α is deficient in activating α -secretase leading to disrupted A β PP processing and subsequent A β accumulation. It is important to note that sA β PP α , formed by the α -secretase cleavage of A β PP, also promotes translocation of PKC β to the plasma membrane by RACK1 [116]. If PKC β is not translocated, it can hyperphosphorylate tau and substantially contribute to AD pathology [117]. Intracellular PKC has recently been proposed as an AD biomarker because dysfunctional PKC translocation can be successfully detected in red blood cells thereby mimicking the activation state of PKC within the brain [118].

Another isoform, PKC ϵ , when fully functional reduces A β accumulation. PKC ϵ knockout mice display poor reward seeking behavior and have severe cognitive decline on memory tasks indicating the importance of this isoform [119]. PKC ϵ induces the endothelin-converting enzyme to degrade A β ₄₀ and A β ₄₂ to small fragments [120], and facilitates the clearance of the A β fragments [115]. A β fragment clearance is associated with improved histological findings as well as potential neurological and cognitive benefits. In PKC ϵ transgenic knock-in mice, the amyloid plaque burden is significantly reduced as well as a reduction in neuritic dystrophy, reactive astrogliosis, and other neurodegenerative changes [115]. This isoform acts through the MAPK dependent Ets-1 pathway. MAPK induces the formation of Ets protein complexes, and acts to promote the activation of endothelin-converting enzyme. Ets-1 also forms protein complexes that act as important transcription

factors [121]. Further work is needed in order to determine the full extent that the PKC triggered Ets-1 pathway plays in AD pathophysiology.

Extracellular amyloid buildup can itself interfere with PKC function. A β is known to downregulate PKC activity [112, 122]. A β decreases PKC in a dose-dependent manner by binding to the PKC pseudosubstrate domain and inhibiting activation [123]. A β also disrupts cytosol to membrane translocation of PKC α and PKC ϵ . The disrupted translocation prevents the clearance of A β [122]. Improving RACK1 translocation can drastically decrease the A β burden by allowing protective PKC isoforms to stimulate the degradation and reduction of A β . Novel PKC isoforms, including PKC δ and PKC θ , are heavily involved in mediating A β ₄₂ processing. A β ₄₂ triggers changes in phosphatidylinositol 3-kinase, phosphoinositol-dependent kinase, and Rac 1 that ultimately result in cell lysis and the release of reactive oxygen species [124]. It is not yet known if the increase in novel isoforms is strictly an age-dependent adjustment or an indication of accumulated neural injuries. What is known is that increased expression of these isoforms is detrimental to neurons within the brain and leads to an increase in vascular endothelial growth factor [125, 126].

Baseline levels of amyloid and tau within the brain are dependent on protein clearance and cellular metabolism. Imbalances in amyloid metabolism and tau regulation are believed to be critical to AD pathophysiology. Although the toxic effects of A β are widely known, the study into the evolutionary benefit of A β as an antioxidant is in its infancy [127]. PKC isoforms also serve as potent regulators of tau phosphorylation at serine 199–202 [9]. Importantly, PKC α regulates tau binding to tubulin within axons. If PKC α activity is dysfunctional, tau readily dissociates from tubulin leading to increased tau pathology [6]. Another well-known tau kinase, GSK3 β , downregulates the neuroprotective isoform PKC ϵ during AD [128].

INTERRELATING PKC, STROKE, AND AD

Common disease mechanisms link AD and stroke. Loss of synapses is common to both AD and stroke and in AD is most closely correlated with cognitive impairment [129, 130]. Hypoxia is also important for both AD and ischemic disease and increases with age, hypertension, diabetes, and congestive heart failure [131]. AD and ischemic stroke not surprisingly are both independent risk factors for one another [132]. Iron mediated inflammation can activate PKC pathways through glutamate activity in both diseases (Fig. 3) [133]. Toxic iron can be released by microhemorrhages, red blood cell breakdown in the peripheral vasculature, or contusions [134]. Iron contributes to inflammation in the caudate nucleus of AD brains [135]. Through PKC activation, iron enhances the toxicity of A β [136]. In stroke, iron overload contributes to peroxynitrate formation and the release of reactive oxygen species [137]. The similarities in injury response between the two diseases are the result of early immune suppression. The development of dementia and atherosclerosis takes a heavy burden on the body's immune system with inevitable immune exhaustion over time [17]. The heightened state of inflammation and susceptibility to injury is likely due to an altered innate immune response seen in the elderly who are most at risk for these diseases. Toll-like receptors play important roles in neurogenesis and axonal growth in the adult brain, but have also been implicated in the pathology of both stroke and

AD [138]. Toll-like receptor 4 contributes to microglia activation in a healthy brain [139]. Toll-like receptor 4 also activates PKC δ leading to neuronal apoptosis, which eliminates damaged cells [140]. It is therefore likely that immune exhaustion, characteristic of AD and ischemic stroke, has broad reaching implications for PKC activity and localization. Such detriments may in part account for functional deficits seen in both of those diseases. Future therapeutics should be targeting both a reconstitution of the immune system as well as directly modulating PKC activity.

Additionally, the neurovascular unit plays an important role in both AD and ischemic stroke. PKC remodeling of the neurovascular unit has been proposed as a mechanism by which blood-borne products enter and accumulate within the brain [141]. Pericytes, astrocytes, and endothelial cells can become damaged during stroke onset and AD progression [142]. A key role of PKC is regulation of tight junction proteins. Tight junction complexes are altered with disease and the integrity of these complexes becomes compromised [143]. Abnormal vascular phenotypes may account for why PKC activity increases in at risk individuals. Vascular phenotypes more susceptible to injury can be driven into a pro-inflammatory state by obesity and diabetes [144]. A recent meta-analysis found that obesity and diabetes are independent risk factors for AD [145]. The important association of PKC changes in specific brain regions during disease and aging is a topic of ongoing investigation (Table 1). Markers such as cyclooxygenase 2 and interleukin 6 interact with PKC through toll-like receptors [21]. Modulation of toll-like receptor 4 acutely will likely decrease BBB disruption, help prevent immune exhaustion, and preserve the neurovascular unit. PKC ϵ would likely be increased at later time points preserving neuronal function and slowing the decline seen in AD and stroke.

Melatonin administered post-stroke inhibits PKC δ in a rat model, effectively reducing aquaporin-1, brain edema, and infarct size [146]. Curcumin inhibits neuroinflammation by mitigating PKC induced toll-like receptor activation [147]. Our laboratory has shown that the PKC modulator, bryostatin-1, given post-MCAO increased PKC ϵ in an aged-female rat model, improves survival, decreases infarct volume, and leads to an increase in salvageable tissue [148]. At low doses bryostatin activates PKC isoforms, but in excess it has an inhibitory effect. Histamine administration likewise increases PKC ϵ and improves function after stroke [149]. Another approach is to deliver HSP90 or the PKC ϵ specific RACK in order to facilitate enhanced translocation to the mitochondrial membrane, which was shown to reduce stroke infarct volume in a mouse model [74]. PKC mediated platelet aggregation can be inhibited by the phospholipase D inhibitor, FIPI. FIPI decreased the coagulability of platelets following middle cerebral artery occlusion [150]. Further work is required before PKC modulators are ready for clinical treatment. Meanwhile it will be necessary to determine when and where PKC activity is beneficial after stroke and at what time points PKC modification may prove detrimental.

Since PKC isoforms are closely connected to changes in amyloid and tau, PKC modulators are promising therapeutics warranting further investigation. PKC modulators are known to alter concentrations of hyperphosphorylated tau and A β . For instance, bryostatin-1, a potent modulator of classic and novel PKC isoforms, effectively reduces A β ₄₀ and A β ₄₂ plaques and improves behavioral outcomes [151, 152]. In addition, the effect of bryostatin-1 is

significantly greater for transgenic AD mice compared to non-pathologic controls [152]. Bryostatin-1 is not solely dependent on functional PKC in that it directly activates α -secretase as well by increasing PKC ϵ [153]. Low dose bryostatin-1 is currently being used in phase II clinical trials for the treatment of AD. Omega-3 polyunsaturated fatty acids reduce PKC mediated oxidative stress in a transgenic A β model [154]. Yessotoxin, a PKC activator, also decreases both hyperphosphorylated tau and A β accumulation [10]. It works by inhibiting the tau kinase, GSK3 β [155]. GSK3 β has an important association with PKC in that both contribute to tau hyperphosphorylation and eventually the development of neurofibrillary tangles in the diseased brain [156, 157]. Alternatively, (1H-indol-3-yl)-maleimide, a selective PKC inhibitor, can increase A β accumulation. Increased A β disrupts BBB transport and cellular metabolism contributing to rapid AD progression [158]. Many of the available compounds that target PKC have broad reaching endpoints that modulate several different isoforms. Future work will require the development of PKC isoform-specific compounds as well as increased use of transgenic models to tease out the exact role of PKC in AD pathology.

CONCLUSION

PKC isoforms have varied roles in normal and age-related physiology. Alterations in these isoforms contribute to the development of ischemic stroke and AD. Once ischemic stroke has occurred, altered PKC β , δ , and ζ contribute to BBB disruption and reperfusion injury. If PKC ϵ is properly translocated, it can provide neuroprotection. Often, however, pre-existing comorbidities lead to disrupted PKC translocation and worse outcome following ischemic infarction. PKC ϵ is also protective against memory decline in AD, but toxic A β contributes to epigenetic downregulation of PKC isoforms with time. Shared pathways between the two diseases such as iron mediated toxicity and immune suppression highlight important targets in injury development and progression. Although much work is yet to be done to increase our understanding about PKC activity in the brain, modulating PKC activity/translocation will enhance neuroprotective strategies for treating neurodegenerative diseases. Future studies are needed to investigate the time points at which PKC isoforms are neuroprotective, and furthermore when they switch to being detrimental.

Acknowledgments

We would like to thank West Virginia University School of Medicine for use of its facility. Funding for this project was provided by a WVU research funding and development grant and funding from the WVU Department of Neurosurgery.

References

1. Cai HY, Holscher C, Yue XH, Zhang SX, Wang XH, Qiao F, Yang W, Qi JS. Lixisenatide rescues spatial memory and synaptic plasticity from amyloid beta protein-induced impairments in rats. *Neuroscience*. 2014; 277C:6–13. [PubMed: 24583037]
2. Sutovsky S, Blaho A, Kollar B, Siarnik P, Csefalvay Z, Dragasek J, Turceni P. Clinical accuracy of the distinction between Alzheimer's disease and frontotemporal lobar degeneration. *Bratisl Lek Listy*. 2014; 115:161–167. [PubMed: 24579686]
3. Sun MK, Alkon DL. The “memory kinases”: Roles of PKC isoforms in signal processing and memory formation. *Prog Mol Biol Transl Sci*. 2014; 122:31–59. [PubMed: 24484697]

4. Liu SJ, Gasperini R, Foa L, Small DH. Amyloid-beta decreases cell-surface AMPA receptors by increasing intracellular calcium and phosphorylation of GluR2. *J Alzheimers Dis.* 2010; 21:655–666. [PubMed: 20571220]
5. Dickstein DL, Weaver CM, Luebke JI, Hof PR. Dendritic spine changes associated with normal aging. *Neuroscience.* 2013; 251:21–32. [PubMed: 23069756]
6. Korulu S, Yildiz-Unal A, Yuksel M, Karabay A. Protein kinase C activation causes neurite retraction via cyclinD1 and p60-katanin increase in rat hippocampal neurons. *Eur J Neurosci.* 2013; 37:1610–1619. [PubMed: 23489891]
7. Hongpaisan J, Xu C, Sen A, Nelson TJ, Alkon DL. PKC activation during training restores mushroom spine synapses and memory in the aged rat. *Neurobiol Dis.* 2013; 55:44–62. [PubMed: 23545166]
8. Menard C, Bastianetto S, Quirion R. Neuroprotective effects of resveratrol and epigallocatechin gallate polyphenols are mediated by the activation of protein kinase C gamma. *Front Cell Neurosci.* 2013; 7:281. [PubMed: 24421757]
9. De Montigny A, Elhiri I, Allyson J, Cyr M, Massicotte G. NMDA reduces Tau phosphorylation in rat hippocampal slices by targeting NR2A receptors, GSK3beta, and PKC activities. *Neural Plast.* 2013; 2013:261593. [PubMed: 24349798]
10. Alonso E, Vale C, Vieytes MR, Botana LM. Translocation of PKC by yessotoxin in an *in vitro* model of Alzheimer's disease with improvement of tau and beta-amyloid pathology. *ACS Chem Neurosci.* 2013; 4:1062–1070. [PubMed: 23527608]
11. Sun MK, Alkon DL. Activation of protein kinase C isozymes for the treatment of dementias. *Adv Pharmacol.* 2012; 64:273–302. [PubMed: 22840750]
12. Magkou D, Tziomalos K. Antidiabetic treatment, stroke severity and outcome. *World J Diabetes.* 2014; 5:84–88. [PubMed: 24748923]
13. Xu YL, Gao L, Shi L, Li J, Liu WH, Du YH. Effect of electroacupuncture intervention on expression of vascular PKC in the ischemic cerebral tissue in rats with cerebral infarction. *Zhen Ci Yan Jiu.* 2012; 37:218–223. [PubMed: 22934393]
14. Willis CL, Meske DS, Davis TP. Protein kinase C activation modulates reversible increase in cortical blood-brain barrier permeability and tight junction protein expression during hypoxia and posthypoxic reoxygenation. *J Cereb Blood Flow Metab.* 2010; 30:1847–1859. [PubMed: 20700133]
15. Schneider A, Rogalewski A, Wafzig O, Kirsch F, Gretz N, Kruger C, Diederich K, Pitzer C, Laage R, Plaas C, Vogt G, Minnerup J, Schabitz WR. Forced arm use is superior to voluntary training for motor recovery and brain plasticity after cortical ischemia in rats. *Exp Transl Stroke Med.* 2014; 6:3. [PubMed: 24528872]
16. Yang L, Shah K, Wang H, Karamyan VT, Abbruscato TJ. Characterization of neuroprotective effects of biphalin, an opioid receptor agonist, in a model of focal brain ischemia. *J Pharmacol Exp Ther.* 2011; 339:499–508. [PubMed: 21856861]
17. Brod SA. Unregulated inflammation shortens human functional longevity. *Inflamm Res.* 2000; 49:561–570. [PubMed: 11131295]
18. Pinti M, Cevenini E, Nasi M, De Biasi S, Salvioli S, Monti D, Benatti S, Gibellini L, Cotichini R, Stazi MA, Trenti T, Franceschi C, Cossarizza A. Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for “inflammaging”. *Eur J Immunol.* 2014; 44:1552–1562. [PubMed: 24470107]
19. Purkayastha S, Cai D. Neuroinflammatory basis of metabolic syndrome. *Mol Metab.* 2013; 2:356–363. [PubMed: 24327952]
20. Yang XS, Liu MY, Zhang HM, Xue BZ, Shi H, Liu DX. Protein kinase C-delta mediates sepsis-induced activation of complement 5a and urokinase-type plasminogen activator signaling in macrophages. *Inflamm Res.* 2014; 63:581–589. [PubMed: 24682410]
21. Mesquita RF, Paul MA, Valmaseda A, Francois A, Jabr R, Anjum S, Marber MS, Budhram-Mahadeo V, Heads RJ. Protein kinase Cepsilon-calcineurin cosignaling downstream of toll-like receptor 4 downregulates fibrosis and induces wound healing gene expression in cardiac myofibroblasts. *Mol Cell Biol.* 2014; 34:574–594. [PubMed: 24298017]

22. Xu SZ, Bullock L, Shan CJ, Cornelius K, Rajanna B. PKC isoforms were reduced by lead in the developing rat brain. *Int J Dev Neurosci*. 2005; 23:53–64. [PubMed: 15730887]
23. Ziemba BP, Li J, Landgraf KE, Knight JD, Voth GA, Falke JJ. Single-molecule studies reveal a hidden key step in the activation mechanism of membrane-bound protein kinase C- α . *Biochemistry*. 2014; 53:1697–1713. [PubMed: 24559055]
24. Takigami S, Sunada H, Lukowiak K, Kuzirian AM, Alkon DL, Sakakibara M. Protein kinase C mediates memory consolidation of taste avoidance conditioning in *Lymnaea stagnalis*. *Neurobiol Learn Mem*. 2014; 111:9–18. [PubMed: 24613854]
25. de Quervain DJ, Kolassa IT, Ackermann S, Aerni A, Boesiger P, Demougin P, Elbert T, Ertl V, Gschwind L, Hadziselimovic N, Hanser E, Heck A, Hieber P, Huynh KD, Klarhofer M, Luechinger R, Rasch B, Scheffler K, Spalek K, Stippich C, Vogler C, Vukojevic V, Stetak A, Papas-sotiropoulos A. PKC α is genetically linked to memory capacity in healthy subjects and to risk for post-traumatic stress disorder in genocide survivors. *Proc Natl Acad Sci U S A*. 2012; 109:8746–8751. [PubMed: 22586106]
26. Vijayakumar B, Velmurugan D. Designing of Protein Kinase C beta-II Inhibitors against Diabetic complications: Structure Based Drug Design, Induced Fit docking and analysis of active site conformational changes. *Bioinformation*. 2012; 8:568–573. [PubMed: 22829732]
27. Li L, You L, Sunyer B, Patil S, Hoger H, Pollak A, Stork O, Lubec G. Hippocampal protein kinase C family members in spatial memory retrieval in the mouse. *Behav Brain Res*. 2014; 258:202–207. [PubMed: 24075976]
28. Shanmugasundararaj S, Das J, Sandberg WS, Zhou X, Wang D, Messing RO, Bruzik KS, Stehle T, Miller KW. Structural and functional characterization of an anesthetic binding site in the second cysteine-rich domain of protein kinase C δ *. *Biophys J*. 2012; 103:2331–2340. [PubMed: 23283232]
29. Kim YA, Kim MY, Jung YS. Glutathione depletion by L-buthionine-S,R-sulfoximine induces apoptosis of cardiomyocytes through activation of PKC- δ . *Biomol Ther (Seoul)*. 2013; 21:358–363. [PubMed: 24244823]
30. Cheeseman KL, Ueyama T, Michaud TM, Kashiwagi K, Wang D, Flax LA, Shirai Y, Loegering DJ, Saito N, Lennartz MR. Targeting of protein kinase C- ϵ during Fc γ receptor-dependent phagocytosis requires the epsilonC1B domain and phospholipase C- γ 1. *Mol Biol Cell*. 2006; 17:799–813. [PubMed: 16319178]
31. Zisopoulou S, Asimaki O, Leondaritis G, Vasilaki A, Sakellaridis N, Pitsikas N, Mangoura D. PKC- ϵ activation is required for recognition memory in the rat. *Behav Brain Res*. 2013; 253:280–289. [PubMed: 23911427]
32. Zhou Y, Zhang M, Sun GY, Liu YP, Ran WZ, Peng L, Guan CX. Calcitonin gene-related peptide promotes the wound healing of human bronchial epithelial cells via PKC and MAPK pathways. *Regul Pept*. 2013; 184:22–29. [PubMed: 23501044]
33. Lauer J, Banerjee D, Shanks D, Dai H, Gong YX, Prakash O, Takemoto D. NMR structure/function relationships of peptides corresponding to the C1B1 Region of PKC γ . *Protein Pept Lett*. 2010; 17:1–10. [PubMed: 20214626]
34. Sanna MD, Quattrone A, Ghelardini C, Galeotti N. PKC-mediated HuD-GAP43 pathway activation in a mouse model of antiretroviral painful neuropathy. *Pharmacol Res*. 2014; 81C:44–53. [PubMed: 24565699]
35. Schmidt HD, Schassburger RL, Guercio LA, Pierce RC. Stimulation of mGluR5 in the accumbens shell promotes cocaine seeking by activating PKC γ . *J Neurosci*. 2013; 33:14160–14169. [PubMed: 23986250]
36. Ren J, Wang J, Wang Z, Wu J. Structural and biochemical insights into the homotypic PB1-PB1 complex between PKC ζ and p62. *Sci China Life Sci*. 2014; 57:69–80. [PubMed: 24369353]
37. Furini CR, Myskiw JC, Benetti F, Izquierdo I. New frontiers in the study of memory mechanisms. *Rev Bras Psiquiatr*. 2013; 35:173–177. [PubMed: 23904024]
38. Kwapis JL, Helmstetter FJ. Does PKM(ζ) maintain memory? *Brain Res Bull*. 2014; 105:36–45. [PubMed: 24076105]

39. Solstad T, Bjorgo E, Koehler CJ, Strozynski M, Torgersen KM, Tasken K, Thiede B. Quantitative proteome analysis of detergent-resistant membranes identifies the differential regulation of protein kinase C isoforms in apoptotic T cells. *Proteomics*. 2010; 10:2758–2768. [PubMed: 20486122]
40. Tanabe F, Nakajima T, Ito M. The thiol proteinase inhibitor E-64-d ameliorates amyloid-beta-induced reduction of sAPP α secretion by reversing ceramide-induced protein kinase C down-regulation in SH-SY5Y neuroblastoma cells. *Biochem Biophys Res Commun*. 2013; 441:256–261. [PubMed: 24141119]
41. Hoque M, Rentero C, Cairns R, Tebar F, Enrich C, Grewal T. Annexins – Scaffolds modulating PKC localization and signaling. *Cell Signal*. 2014; 26:1213–1225. [PubMed: 24582587]
42. Mishra S, Vinayak M. Ellagic acid inhibits PKC signaling by improving antioxidant defense system in murine T cell lymphoma. *Mol Biol Rep*. 2014; 41:4187–4197. [PubMed: 24574001]
43. Kim HR, Gallant C, Morgan KG. Regulation of PKC autophosphorylation by calponin in contractile vascular smooth muscle tissue. *Biomed Res Int*. 2013; 2013:358643. [PubMed: 24350264]
44. Farah CA, Sossin WS. The role of C2 domains in PKC signaling. *Adv Exp Med Biol*. 2012; 740:663–683. [PubMed: 22453964]
45. Miller LD, Lee KC, Mochly-Rosen D, Cartwright CA. RACK1 regulates Src-mediated Sam68 and p190RhoGAP signaling. *Oncogene*. 2004; 23:5682–5686. [PubMed: 15184885]
46. Liron T, Chen LE, Khaner H, Vallentin A, Mochly-Rosen D. Rational design of a selective antagonist of epsilon protein kinase C derived from the selective allosteric agonist, pseudo-RACK peptide. *J Mol Cell Cardiol*. 2007; 42:835–841. [PubMed: 17337000]
47. Greenwald EC, Redden JM, Dodge-Kafka KL, Saucerman JJ. Scaffold state switching amplifies, accelerates, and insulates protein kinase C signaling. *J Biol Chem*. 2014; 289:2353–2360. [PubMed: 24302730]
48. Lum MA, Balaburski GM, Murphy ME, Black AR, Black JD. Heat shock proteins regulate activation-induced proteasomal degradation of the mature phosphorylated form of protein kinase C. *J Biol Chem*. 2013; 288:27112–27127. [PubMed: 23900841]
49. Cui ZG, Piao JL, Kondo T, Ogawa R, Tsuneyama K, Zhao QL, Feril LB Jr, Inadera H. Molecular mechanisms of hyperthermia-induced apoptosis enhanced by docosa-hexaenoic acid: Implication for cancer therapy. *Chem Biol Interact*. 2014; 215:46–53. [PubMed: 24661947]
50. Cone AC, Cavin G, Ambrosi C, Hakozaki H, Wu-Zhang AX, Kunkel MT, Newton AC, Sosinsky GE. Protein kinase C δ -mediated phosphorylation of connexin43 gap junction channels causes movement within gap junctions followed by vesicle internalization and protein degradation. *J Biol Chem*. 2014; 289:8781–8798. [PubMed: 24500718]
51. Turner, RC.; Lucke-Wold, B.; Tan, Z.; Rosen, CL.; Huber, JD. Modulation of protein kinase C isoforms: A potential therapeutic for ischemic stroke?. In: Lakatos, V.; Somogyi, B., editors. *Ischemic Stroke: Symptoms, Prevention and Recovery (Neuroscience Research Progress)*. Nova Science Publishers Inc; Hauppauge, NY: 2012. p. 171-190.
52. Pascale A, Amadio M, Govoni S, Battaini F. The aging brain, a key target for the future: The protein kinase C involvement. *Pharmacol Res*. 2007; 55:560–569. [PubMed: 17553691]
53. Poulouse SM, Bielinski DF, Carrihill-Knoll K, Rabin BM, Shukitt-Hale B. Exposure to 16O-particle radiation causes aging-like decrements in rats through increased oxidative stress, inflammation and loss of autophagy. *Radiat Res*. 2011; 176:761–769. [PubMed: 21962006]
54. Patterson AJ, Chen M, Xue Q, Xiao D, Zhang L. Chronic prenatal hypoxia induces epigenetic programming of PKC ϵ gene repression in rat hearts. *Circ Res*. 2010; 107:365–373. [PubMed: 20538683]
55. Yang S, Huang S, Gaertig MA, Li XJ, Li S. Age-dependent decrease in chaperone activity impairs MANF expression, leading to Purkinje cell degeneration in inducible SCA17 mice. *Neuron*. 2014; 81:349–365. [PubMed: 24462098]
56. Battaini F, Pascale A, Lucchi L, Pasinetti GM, Govoni S. Protein kinase C anchoring deficit in postmortem brains of Alzheimer's disease patients. *Exp Neurol*. 1999; 159:559–564. [PubMed: 10506528]

57. Liu W, Dou F, Feng J, Yan Z. RACK1 is involved in beta-amyloid impairment of muscarinic regulation of GABAergic transmission. *Neurobiol Aging*. 2011; 32:1818–1826. [PubMed: 19954860]
58. Perovic M, Tesic V, Mladenovic Djordjevic A, Smiljanic K, Loncarevic-Vasiljkovic N, Ruzdijic S, Kanazir S. BDNF transcripts, proBDNF and proNGF, in the cortex and hippocampus throughout the life span of the rat. *Age (Dordr)*. 2013; 35:2057–2070. [PubMed: 23255148]
59. Lin CC, Hsieh HL, Shih RH, Chi PL, Cheng SE, Chen JC, Yang CM. NADPH oxidase 2-derived reactive oxygen species signal contributes to bradykinin-induced matrix metalloproteinase-9 expression and cell migration in brain astrocytes. *Cell Commun Signal*. 2012; 10:35. [PubMed: 23176293]
60. Vetri F, Chavez R, Xu HL, Paisansathan C, Pelligrino DA. Complex modulation of the expression of PKC isoforms in the rat brain during chronic type 1 diabetes mellitus. *Brain Res*. 2013; 1490:202–209. [PubMed: 23103504]
61. Zhang L, Huang D, Shen D, Zhang C, Ma Y, Babcock SA, Chen B, Ren J. Inhibition of protein kinase C betaII isoform ameliorates methylglyoxal advanced glycation endproduct-induced cardiomyocyte contractile dysfunction. *Life Sci*. 2014; 94:83–91. [PubMed: 24269213]
62. Klymenko K, Novokhatska T, Kizub I, Parshikov A, Dosenko V, Soloviev A. PKC-delta isozyme gene silencing restores vascular function in diabetic rat. *J Basic Clin Physiol Pharmacol*. 2014; 26:1–9. [PubMed: 24468620]
63. Fan Y, Li J, Zhang YQ, Jiang LH, Zhang YN, Yan CQ. Protein kinase C delta mediated cytotoxicity of 6-Hydroxydopamine via sustained extracellular signal-regulated kinase 1/2 activation in PC12 cells. *Neurol Res*. 2014; 36:53–64. [PubMed: 24107416]
64. Liu L, Liu J, Gao Y, Yu X, Dou D, Huang Y. Protein kinase Cdelta contributes to phenylephrine-mediated contraction in the aortae of high fat diet-induced obese mice. *Biochem Biophys Res Commun*. 2014; 446:1179–1183. [PubMed: 24667603]
65. Yang P, Baciuc P, Parker Kerrigan B, Etheridge M, Sung E, Toimil BA, Berchuck JE, Jaffe GJ. Retinal pigment epithelial cell death by the alternative complement cascade: Role of membrane regulatory proteins, calcium, PKC and oxidative stress. *Invest Ophthalmol Vis Sci*. 2014; 55:3012–3021. [PubMed: 24677108]
66. Kong L, Shen X, Lin L, Leitges M, Rosario R, Zou YS, Yan SF. PKCbeta promotes vascular inflammation and acceleration of atherosclerosis in diabetic ApoE null mice. *Arterioscler Thromb Vasc Biol*. 2013; 33:1779–1787. [PubMed: 23766264]
67. Gebremedhin D, Gopalakrishnan S, Harder DR. Endogenous events modulating myogenic regulation of cerebrovascular function. *Curr Vasc Pharmacol*. 2013; 11:1–11.
68. Bright R, Mochly-Rosen D. The role of protein kinase C in cerebral ischemic and reperfusion injury. *Stroke*. 2005; 36:2781–2790. [PubMed: 16254221]
69. Cui GY, Gao XM, Qi SH, Gillani A, Gao L, Shen X, Zhang YD. The action of thrombin in intracerebral hemorrhage induced brain damage is mediated via PKCalpha/PKCdelta signaling. *Brain Res*. 2011; 1398:86–93. [PubMed: 21172324]
70. Jeong C, Shin T. Immunohistochemical localization of protein kinase C (PKC) beta I in the pig retina during postnatal development. *Acta Histochem*. 2012; 114:18–23. [PubMed: 21474165]
71. Rex EB, Rankin ML, Yang Y, Lu Q, Gerfen CR, Jose PA, Sibley DR. Identification of RanBP 9/10 as interacting partners for protein kinase C (PKC) gamma/delta and the D1 dopamine receptor: Regulation of PKC-mediated receptor phosphorylation. *Mol Pharmacol*. 2010; 78:69–80. [PubMed: 20395553]
72. Wang HH, Hsieh HL, Wu CY, Yang CM. Oxidized low-density lipoprotein-induced matrix metalloproteinase-9 expression via PKC-delta/p42/p44 MAPK/Elk-1 cascade in brain astrocytes. *Neurotox Res*. 2010; 17:50–65. [PubMed: 19554388]
73. Angelow S, Zeni P, Hohn B, Galla HJ. Phorbol ester induced short- and long-term permeabilization of the blood-CSF barrier *in vitro*. *Brain Res*. 2005; 1063:168–179. [PubMed: 16271356]
74. Sun X, Budas GR, Xu L, Barreto GE, Mochly-Rosen D, Giffard RG. Selective activation of protein kinase C in mitochondria is neuroprotective *in vitro* and reduces focal ischemic brain injury in mice. *J Neurosci Res*. 2013; 91:799–807. [PubMed: 23426889]

75. Kim YA, Park SL, Kim MY, Lee SH, Baik EJ, Moon CH, Jung YS. Role of PKC β II and PKC δ in blood-brain barrier permeability during aglycemic hypoxia. *Neurosci Lett*. 2010; 468:254–258. [PubMed: 19900507]
76. Payne GW, Smeda JS. Cerebrovascular alterations in pressure and protein kinase C-mediated constriction in Dahl salt-sensitive rats. *J Hypertens*. 2002; 20:1355–1363. [PubMed: 12131532]
77. Zhou F, Lee AC, Krafczyk K, Zhu L, Murray M. Protein kinase C regulates the internalization and function of the human organic anion transporting polypeptide 1A2. *Br J Pharmacol*. 2011; 162:1380–1388. [PubMed: 21133891]
78. Ji BS, Cen J, He L, Liu M, Liu YQ, Liu L. Modulation of P-glycoprotein in rat brain microvessel endothelial cells under oxygen glucose deprivation. *J Pharm Pharmacol*. 2013; 65:1508–1517. [PubMed: 24028618]
79. Yagami T, Yamamoto Y, Koma H. The role of secretory phospholipase A2 in the central nervous system and neurological diseases. *Mol Neurobiol*. 2014; 49:863–876. [PubMed: 24113843]
80. Srivastava K, Shao B, Bayraktutan U. PKC- β exacerbates *in vitro* brain barrier damage in hyperglycemic settings via regulation of RhoA/Rho-kinase/MLC2 pathway. *J Cereb Blood Flow Metab*. 2013; 33:1928–1936. [PubMed: 23963366]
81. Mizutani K, Sonoda S, Wakita H, Katoh Y, Shimpo K. Functional recovery and alterations in the expression and localization of protein kinase C following voluntary exercise in rat with cerebral infarction. *Neurol Sci*. 2014; 35:53–59. [PubMed: 23793170]
82. Shao B, Bayraktutan U. Hyperglycaemia promotes cerebral barrier dysfunction through activation of protein kinase C- β . *Diabetes Obes Metab*. 2013; 15:993–999. [PubMed: 23617822]
83. Brennan-Minnella AM, Shen Y, El-Benna J, Swanson RA. Phosphoinositide 3-kinase couples NMDA receptors to superoxide release in excitotoxic neuronal death. *Cell Death Dis*. 2013; 4:e580. [PubMed: 23559014]
84. Zhang YP, Zhang H, Duan DD. Chloride channels in stroke. *Acta Pharmacol Sin*. 2013; 34:17–23. [PubMed: 23103617]
85. Katakam PV, Snipes JA, Steed MM, Busija DW. Insulin-induced generation of reactive oxygen species and uncoupling of nitric oxide synthase underlie the cerebrovascular insulin resistance in obese rats. *J Cereb Blood Flow Metab*. 2012; 32:792–804. [PubMed: 22234336]
86. Gundimeda U, McNeill TH, Elhiani AA, Schiffman JE, Hinton DR, Gopalakrishna R. Green tea polyphenols precondition against cell death induced by oxygen-glucose deprivation via stimulation of laminin receptor, generation of reactive oxygen species, and activation of protein kinase C ϵ . *J Biol Chem*. 2012; 287:34694–34708. [PubMed: 22879598]
87. Feng S, Li D, Li Y, Yang X, Han S, Li J. Insight into hypoxic preconditioning and ischemic injury through determination of nPKC ϵ -interacting proteins in mouse brain. *Neurochem Int*. 2013; 63:69–79. [PubMed: 23665338]
88. Ye Z, Guo Q, Wang N, Xia P, Yuan Y, Wang E. Delayed neuroprotection induced by sevoflurane via opening mitochondrial ATP-sensitive potassium channels and p38 MAPK phosphorylation. *Neurol Sci*. 2012; 33:239–249. [PubMed: 21720900]
89. Chou WH, Choi DS, Zhang H, Mu D, McMahon T, Kharazia VN, Lowell CA, Ferriero DM, Messing RO. Neutrophil protein kinase C δ as a mediator of stroke-reperfusion injury. *J Clin Invest*. 2004; 114:49–56. [PubMed: 15232611]
90. Loegering DJ, Lennartz MR. Protein kinase C and toll-like receptor signaling. *Enzyme Res*. 2011; 2011:537821. [PubMed: 21876792]
91. Geraldine P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. *Circ Res*. 2010; 106:1319–1331. [PubMed: 20431074]
92. Farese RV, Sajan MP. Metabolic functions of atypical protein kinase C: “good” and “bad” as defined by nutritional status. *Am J Physiol Endocrinol Metab*. 2010; 298:E385–E394. [PubMed: 19996389]
93. Salamanca DA, Khalil RA. Protein kinase C isoforms as specific targets for modulation of vascular smooth muscle function in hypertension. *Biochem Pharmacol*. 2005; 70:1537–1547. [PubMed: 16139252]

94. Howard VJ, Woolson RF, Egan BM, Nicholas JS, Adams RJ, Howard G, Lackland DT. Prevalence of hypertension by duration and age at exposure to the stroke belt. *J Am Soc Hypertens.* 2010; 4:32–41. [PubMed: 20374949]
95. Gao X, Zhang H, Takahashi T, Hsieh J, Liao J, Steinberg GK, Zhao H. The Akt signaling pathway contributes to postconditioning's protection against stroke; the protection is associated with the MAPK and PKC pathways. *J Neurochem.* 2008; 105:943–955. [PubMed: 18182053]
96. Yeung J, Apopa PL, Vesci J, Kenyon V, Rai G, Jadhav A, Simeonov A, Holman TR, Maloney DJ, Boutaud O, Holinstat M. Protein kinase C regulation of 12-lipoxygenase-mediated human platelet activation. *Mol Pharmacol.* 2012; 81:420–430. [PubMed: 22155783]
97. Faisal A, Saurin A, Gregory B, Foxwell B, Parker PJ. The scaffold MyD88 acts to couple protein kinase Cepsilon to Toll-like receptors. *J Biol Chem.* 2008; 283:18591–18600. [PubMed: 18458086]
98. Simpkins JW, Dykens JA. Mitochondrial mechanisms of estrogen neuroprotection. *Brain Res Rev.* 2008; 57:421–430. [PubMed: 17512984]
99. Simpkins JW, Yi KD, Yang SH, Dykens JA. Mitochondrial mechanisms of estrogen neuroprotection. *Biochim Biophys Acta.* 2010; 1800:1113–1120. [PubMed: 19931595]
100. Amadoro G, Corsetti V, Florenzano F, Atlante A, Ciotti MT, Mongiardi MP, Bussani R, Nicolini V, Nori SL, Campanella M, Calissano P. AD-linked, toxic NH2 human tau affects the quality control of mitochondria in neurons. *Neurobiol Dis.* 2014; 62:489–507. [PubMed: 24411077]
101. Hasham MI, Pelech SL, Krieger C. Glutamate-mediated activation of protein kinase C in hippocampal neurons. *Neurosci Lett.* 1997; 228:115–118. [PubMed: 9209112]
102. Maurice N, Tkatch T, Meisler M, Sprunger LK, Surmeier DJ. D1/D5 dopamine receptor activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons. *J Neurosci.* 2001; 21:2268–2277. [PubMed: 11264302]
103. Vicente-Torres MA, Davila D, Bartolome MV, Carricondo F, Gil-Loyzaga P. Biochemical evidence for the presence of serotonin transporters in the rat cochlea. *Hear Res.* 2003; 182:43–47. [PubMed: 12948600]
104. Chen XK, Wang LC, Zhou Y, Cai Q, Prakriya M, Duan KL, Sheng ZH, Lingle C, Zhou Z. Activation of GPCRs modulates quantal size in chromaffin cells through G(betagamma) and PKC. *Nat Neurosci.* 2005; 8:1160–1168. [PubMed: 16116443]
105. Shema R, Hazvi S, Sacktor TC, Dudai Y. Boundary conditions for the maintenance of memory by PKMzeta in neocortex. *Learn Mem.* 2009; 16:122–128. [PubMed: 19181618]
106. Weeber EJ, Atkins CM, Selcher JC, Varga AW, Mirnikjoo B, Paylor R, Leitges M, Sweatt JD. A role for the beta isoform of protein kinase C in fear conditioning. *J Neurosci.* 2000; 20:5906–5914. [PubMed: 10934237]
107. Favata MF, Horiuchi KY, Manos EJ, Daulerio AJ, Stradley DA, Feeser WS, Van Dyk DE, Pitts WJ, Earl RA, Hobbs F, Copeland RA, Magolda RL, Scherle PA, Trzaskos JM. Identification of a novel inhibitor of mitogen-activated protein kinase kinase. *J Biol Chem.* 1998; 273:18623–18632. [PubMed: 9660836]
108. Bordi F, Marcon C, Chiamulera C, Reggiani A. Effects of the metabotropic glutamate receptor antagonist MCPG on spatial and context-specific learning. *Neuropharmacology.* 1996; 35:1557–1565. [PubMed: 9025103]
109. Hargreaves EL, Cain DP. Hyperactivity, hyper-reactivity, and sensorimotor deficits induced by low doses of the N-methyl-D-aspartate non-competitive channel blocker MK801. *Behav Brain Res.* 1992; 47:23–33. [PubMed: 1315138]
110. Shema R, Haramati S, Ron S, Hazvi S, Chen A, Sacktor TC, Dudai Y. Enhancement of consolidated long-term memory by overexpression of protein kinase Mzeta in the neocortex. *Science.* 2011; 331:1207–1210. [PubMed: 21385716]
111. Govoni S, Bergamaschi S, Racchi M, Battaini F, Binetti G, Bianchetti A, Trabucchi M. Cytosol protein kinase C downregulation in fibroblasts from Alzheimer's disease patients. *Neurology.* 1993; 43:2581–2586. [PubMed: 8255461]
112. Masliah E, Cole GM, Hansen LA, Mallory M, Albright T, Terry RD, Saitoh T. Protein kinase C alteration is an early biochemical marker in Alzheimer's disease. *J Neurosci.* 1991; 11:2759–2767. [PubMed: 1880547]

113. Corsini E, Battaini F, Lucchi L, Marinovich M, Racchi M, Govoni S, Galli CL. A defective protein kinase C anchoring system underlying age-associated impairment in TNF-alpha production in rat macrophages. *J Immunol.* 1999; 163:3468–3473. [PubMed: 10477619]
114. McKee AC, Kosik KS, Kennedy MB, Kowall NW. Hippocampal neurons predisposed to neurofibrillary tangle formation are enriched in type II calcium/calmodulin-dependent protein kinase. *J Neuropathol Exp Neurol.* 1990; 49:49–63. [PubMed: 2153760]
115. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. *Biochim Biophys Acta.* 2010; 1802:396–405. [PubMed: 20079433]
116. Buoso E, Biundo F, Lanni C, Aiello S, Grossi S, Schettini G, Govoni S, Racchi M. Modulation of Rack-1/PKCbetaII signalling by soluble AbetaPPalpha in SH-SY5Y cells. *Curr Alzheimer Res.* 2013; 10:697–705. [PubMed: 23905995]
117. Gerschutz A, Heinsen H, Grunblatt E, Wagner AK, Bartl J, Meissner C, Fallgatter AJ, Al-Sarraj S, Troakes C, Ferrer I, Arzberger T, Deckert J, Riederer P, Fischer M, Tatschner T, Monoranu CM. Neuron-specific mitochondrial DNA deletion levels in sporadic Alzheimer's disease. *Curr Alzheimer Res.* 2013; 10:1041–1046. [PubMed: 24156256]
118. de Barry J, Liegeois CM, Janoshazi A. Protein kinase C as a peripheral biomarker for Alzheimer's disease. *Exp Gerontol.* 2010; 45:64–69. [PubMed: 19895879]
119. Kumar S, Sieghart W, Morrow AL. Association of protein kinase C with GABA(A) receptors containing alpha1 and alpha4 subunits in the cerebral cortex: Selective effects of chronic ethanol consumption. *J Neurochem.* 2002; 82:110–117. [PubMed: 12091471]
120. Pacheco-Quinto J, Eckman EA. Endothelin-converting enzymes degrade intracellular beta-amyloid produced within the endosomal/lysosomal pathway and autophagosomes. *J Biol Chem.* 2013; 288:5606–5615. [PubMed: 23283972]
121. Sementchenko VI, Watson DK. Ets target genes: Past, present and future. *Oncogene.* 2000; 19:6533–6548. [PubMed: 11175369]
122. Pakaski M, Papp H, Rakonczay Z, Fakla I, Kasa P. Effects of acetylcholinesterase inhibitors on the metabolism of amyloid precursor protein *in vitro*. *Neurobiology (Bp).* 2001; 9:55–57. [PubMed: 11558939]
123. Chauhan A, Chauhan VP, Brockerhoff H, Wisniewski HM. Action of amyloid beta-protein on protein kinase C activity. *Life Sci.* 1991; 49:1555–1562. [PubMed: 1943460]
124. Manterola L, Hernando-Rodriguez M, Ruiz A, Apraiz A, Arrizabalaga O, Vellon L, Alberdi E, Cavaliere F, Lacerda HM, Jimenez S, Parada LA, Matute C, Zugaza JL. 1-42 beta-amyloid peptide requires PDK1/nPKC/Rac 1 pathway to induce neuronal death. *Transl Psychiatry.* 2013; 3:e219. [PubMed: 23340502]
125. Rigor RR, Beard RS Jr, Litovka OP, Yuan SY. Interleukin-1beta-induced barrier dysfunction is signaled through PKC-theta in human brain microvascular endothelium. *Am J Physiol Cell Physiol.* 2012; 302:C1513–C1522. [PubMed: 22403784]
126. Lee MC, Wei SC, Tsai-Wu JJ, Wu CH, Tsao PN. Novel PKC signaling is required for LPS-induced soluble Flt-1 expression in macrophages. *J Leukoc Biol.* 2008; 84:835–841. [PubMed: 18511573]
127. Luna S, Cameron DJ, Ethell DW. Amyloid-beta and APP deficiencies cause severe cerebrovascular defects: Important work for an old villain. *PLoS One.* 2013; 8:e75052. [PubMed: 24040383]
128. Cai Z, Zhao Y, Zhao B. Roles of glycogen synthase kinase 3 in Alzheimer's disease. *Curr Alzheimer Res.* 2012; 9:864–879. [PubMed: 22272620]
129. Sun MK, Hongpaisan J, Nelson TJ, Alkon DL. Post-stroke neuronal rescue and synaptogenesis mediated *in vivo* by protein kinase C in adult brains. *Proc Natl Acad Sci U S A.* 2008; 105:13620–13625. [PubMed: 18768786]
130. Hongpaisan J, Sun MK, Alkon DL. PKC epsilon activation prevents synaptic loss, Abeta elevation, and cognitive deficits in Alzheimer's disease transgenic mice. *J Neurosci.* 2011; 31:630–643. [PubMed: 21228172]
131. Sun MK, Hongpaisan J, Alkon DL. Postischemic PKC activation rescues retrograde and anterograde long-term memory. *Proc Natl Acad Sci U S A.* 2009; 106:14676–14680. [PubMed: 19667190]

132. Heikkinen R, Malm T, Heikkilä J, Muona A, Tanila H, Koistinaho M, Koistinaho J. Susceptibility to focal and global brain ischemia of Alzheimer mice displaying abeta deposits: Effect of immunoglobulin. *Aging Dis.* 2014; 5:76–87. [PubMed: 24729933]
133. Pretorius E, Kell DB. Diagnostic morphology: Biophysical indicators for iron-driven inflammatory diseases. *Integr Biol (Camb).* 2014; 6:486–510. [PubMed: 24714688]
134. Yavuz BB, Cankurtaran M, Haznedaroglu IC, Halil M, Ulger Z, Altun B, Ariogul S. Iron deficiency can cause cognitive impairment in geriatric patients. *J Nutr Health Aging.* 2012; 16:220–224. [PubMed: 22456776]
135. De Reuck JL, Deramecourt V, Auger F, Durieux N, Cordonnier C, Devos D, Defebvre L, Moreau C, Caparros-Lefebvre D, Leys D, Maurage CA, Pasquier F, Bordet R. Iron deposits in post-mortem brains of patients with neurodegenerative and cerebrovascular diseases: A semi-quantitative 7.0 T magnetic resonance imaging study. *Eur J Neurol.* 2014; 21:1026–1031. [PubMed: 24698410]
136. Bandyopadhyay S, Rogers JT. Alzheimer's disease therapeutics targeted to the control of amyloid precursor protein translation: Maintenance of brain iron homeostasis. *Biochem Pharmacol.* 2014; 88:486–494. [PubMed: 24513321]
137. Gamez A, Carbonell T, Rama R. Does nitric oxide contribute to iron-dependent brain injury after experimental cerebral ischaemia? *J Physiol Biochem.* 2003; 59:249–254. [PubMed: 15164943]
138. Okun E, Griffioen KJ, Mattson MP. Toll-like receptor signaling in neural plasticity and disease. *Trends Neurosci.* 2011; 34:269–281. [PubMed: 21419501]
139. Buchanan MM, Hutchinson M, Watkins LR, Yin H. Toll-like receptor 4 in CNS pathologies. *J Neurochem.* 2010; 114:13–27. [PubMed: 20402965]
140. Burguillos MA, Deierborg T, Kavanagh E, Persson A, Hajji N, Garcia-Quintanilla A, Cano J, Brundin P, Englund E, Venero JL, Joseph B. Caspase signalling controls microglia activation and neurotoxicity. *Nature.* 2011; 472:319–324. [PubMed: 21389984]
141. Elali A, Theriault P, Rivest S. The role of pericytes in neurovascular unit remodeling in brain disorders. *Int J Mol Sci.* 2014; 15:6453–6474. [PubMed: 24743889]
142. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: Is Alzheimer's a vascular disorder? *Am J Cardiovasc Dis.* 2013; 3:197–226. [PubMed: 24224133]
143. Kook SY, Seok Hong H, Moon M, Mook-Jung I. Disruption of blood-brain barrier in Alzheimer disease pathogenesis. *Tissue Barriers.* 2013; 1:e23993. [PubMed: 24665385]
144. Kim E, Zhang J, Hong K, Benoit NE, Pathak AP. Vascular phenotyping of brain tumors using magnetic resonance microscopy (muMRI). *J Cereb Blood Flow Metab.* 2011; 31:1623–1636. [PubMed: 21386855]
145. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry.* 2010; 67:505–512. [PubMed: 19358976]
146. Bhattacharya P, Pandey AK, Paul S, Patnaik R. Melatonin renders neuroprotection by protein kinase C mediated aquaporin-4 inhibition in animal model of focal cerebral ischemia. *Life Sci.* 2014; 100:97–109. [PubMed: 24530291]
147. Yang Z, Zhao T, Zhang JH, Feng H. Curcumin inhibits microglia inflammation and confers neuroprotection in intracerebral hemorrhage. *Immunol Lett.* 2014; 160:89–95. [PubMed: 24680995]
148. Tan Z, Turner RC, Leon RL, Li X, Hongpaisan J, Zheng W, Logsdon AF, Naser ZJ, Alkon DL, Rosen CL, Huber JD. Bryostatin improves survival and reduces ischemic brain injury in aged rats after acute ischemic stroke. *Stroke.* 2013; 44:3490–3497. [PubMed: 24172582]
149. Wang XF, Hu WW, Yan HJ, Tan L, Gao JQ, Tian YY, Shi XJ, Hou WW, Li J, Shen Y, Chen Z. Modulation of astrocytic glutamine synthetase expression and cell viability by histamine in cultured cortical astrocytes exposed to OGD insults. *Neurosci Lett.* 2013; 549:69–73. [PubMed: 23791924]
150. Elvers M, Grenegard M, Khoshjabinzadeh H, Munzer P, Borst O, Tian H, Di Paolo G, Lang F, Gawaz M, Lindahl TL, Falker K. A novel role for phospholipase D as an endogenous negative regulator of platelet sensitivity. *Cell Signal.* 2012; 24:1743–1752. [PubMed: 22579635]

151. Sridhar J, Wei ZL, Nowak I, Lewin NE, Ayres JA, Pearce LV, Blumberg PM, Kozikowski AP. New bivalent PKC ligands linked by a carbon spacer: Enhancement in binding affinity. *J Med Chem.* 2003; 46:4196–4204. [PubMed: 12954072]
152. Etcheberrigaray R, Tan M, Dewachter I, Kuiperi C, Van der Auwera I, Wera S, Qiao L, Bank B, Nelson TJ, Kozikowski AP, Van Leuven F, Alkon DL. Therapeutic effects of PKC activators in Alzheimer's disease transgenic mice. *Proc Natl Acad Sci U S A.* 2004; 101:11141–11146. [PubMed: 15263077]
153. Yi P, Schrott L, Castor TP, Alexander JS. Bryostatin-1 vs. TPPB: Dose-dependent APP processing and PKC- α , - δ , and - ϵ isoform activation in SH-SY5Y neuronal cells. *J Mol Neurosci.* 2012; 48:234–244. [PubMed: 22700373]
154. Hammamieh R, Chakraborty N, Gautam A, Miller SA, Muhie S, Meyerhoff J, Jett M. Transcriptomic analysis of the effects of a fish oil enriched diet on murine brains. *PLoS One.* 2014; 9:e90425. [PubMed: 24632812]
155. Fang X, Yu S, Tanyi JL, Lu Y, Woodgett JR, Mills GB. 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. *Mol Cell Biol.* 2002; 22:2099–2110. [PubMed: 11884598]
156. Ferrer I, Gomez-Isla T, Puig B, Freixes M, Ribe E, Dalfo E, Avila J. Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. *Curr Alzheimer Res.* 2005; 2:3–18. [PubMed: 15977985]
157. Pei JJ, Braak E, Braak H, Grundke-Iqbal I, Iqbal K, Winblad B, Cowburn RF. Distribution of active glycogen synthase kinase 3 β (GSK-3 β) in brains staged for Alzheimer disease neurofibrillary changes. *J Neuropathol Exp Neurol.* 1999; 58:1010–1019. [PubMed: 10499443]
158. Wang DS, Dickson DW, Malter JS. β -Amyloid degradation and Alzheimer's disease. *J Biomed Biotechnol.* 2006; 2006:58406. [PubMed: 17047308]
159. Ladage D, Tilemann L, Ishikawa K, Correll RN, Kawase Y, Houser SR, Molkentin JD, Hajjar RJ. Inhibition of PKC α / β with ruboxistaurin antagonizes heart failure in pigs after myocardial infarction injury. *Circ Res.* 2011; 109:1396–1400. [PubMed: 21998327]
160. Sozio P, Rapino M, Di Valerio V, Laserra S, Pacella S, Di Stefano A, Cataldi A. pPKC α -mediated effect on *in vitro* A β production in response to gamma secretase inhibitor LY411575 in rat CTXTNA2 astrocytes. *J Biol Regul Homeost Agents.* 2012; 26:245–251. [PubMed: 22824752]
161. Shelton RC, Sanders-Bush E, Manier DH, Lewis DA. Elevated 5-HT 2A receptors in postmortem prefrontal cortex in major depression is associated with reduced activity of protein kinase A. *Neuroscience.* 2009; 158:1406–1415. [PubMed: 19111907]
162. Gerschutz A, Heinsen H, Grunblatt E, Wagner AK, Bartl J, Meissner C, Fallgatter AJ, Al-Sarraj S, Troakes C, Ferrer I, Arzberger T, Deckert J, Riederer P, Fischer M, Tatschner T, Monoranu CM. Neuron-specific alterations in signal transduction pathways associated with Alzheimer's disease. *J Alzheimers Dis.* 2014; 40:135–142. [PubMed: 24334724]
163. Pascale A, Fortino I, Govoni S, Trabucchi M, Wetsel WC, Battaini F. Functional impairment in protein kinase C by RACK1 (receptor for activated C kinase 1) deficiency in aged rat brain cortex. *J Neurochem.* 1996; 67:2471–2477. [PubMed: 8931480]
164. Bright R, Steinberg GK, Mochly-Rosen D. DeltaPKC mediates microcerebrovascular dysfunction in acute ischemia and in chronic hypertensive stress *in vivo*. *Brain Res.* 2007; 1144:146–155. [PubMed: 17350602]
165. Bright R, Sun GH, Yenari MA, Steinberg GK, Mochly-Rosen D. epsilonPKC confers acute tolerance to cerebral ischemic reperfusion injury. *Neurosci Lett.* 2008; 441:120–124. [PubMed: 18586397]
166. Galve-Roperh I, Malpartida JM, Garcia-Barreno P, Haro A, Laviada ID. Levels and activity of brain protein kinase C α and ζ during the aging of the medfly. *Mech Ageing Dev.* 1996; 92:21–29. [PubMed: 9032752]
167. Moore P, White J, Christiansen V, Grammas P. Protein kinase C- ζ activity but not level is decreased in Alzheimer's disease microvessels. *Neurosci Lett.* 1998; 254:29–32. [PubMed: 9780084]

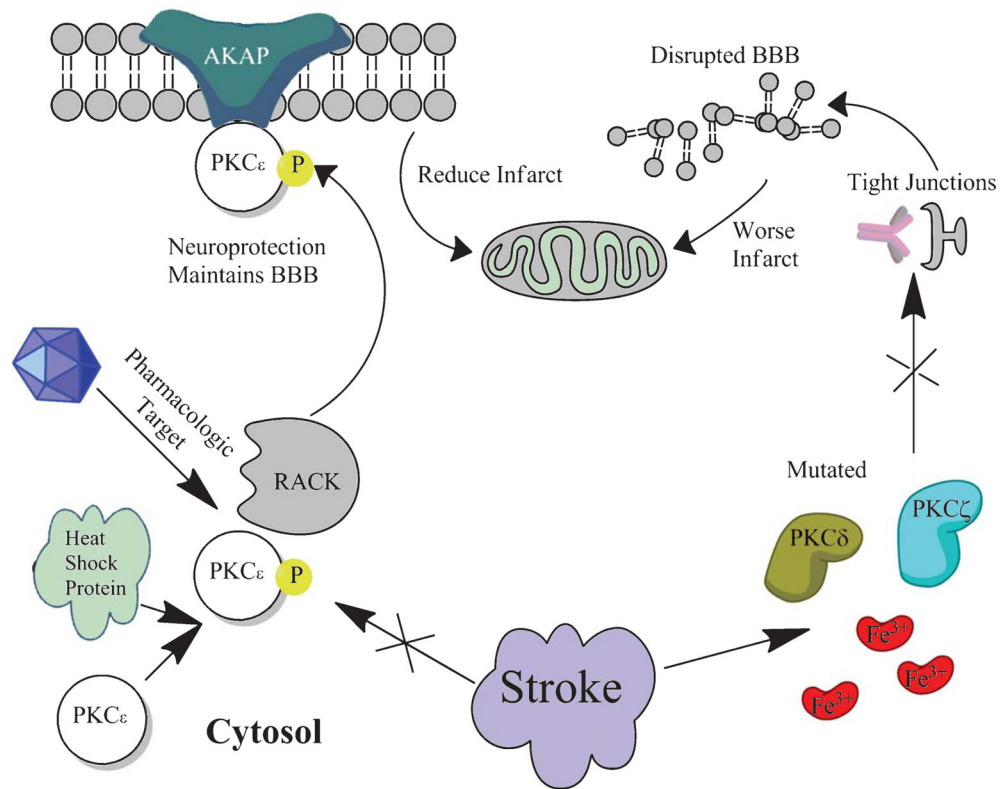


Fig. 1. Following stroke, PKC δ and PKC ζ become dysfunctional and are increased. The result is an increase in BBB disruption and worse ischemic infarct. If PKC ϵ is targeted pharmacologically in order to enhance translocation to the membrane, the BBB is maintained and ischemic infarct is reduced.

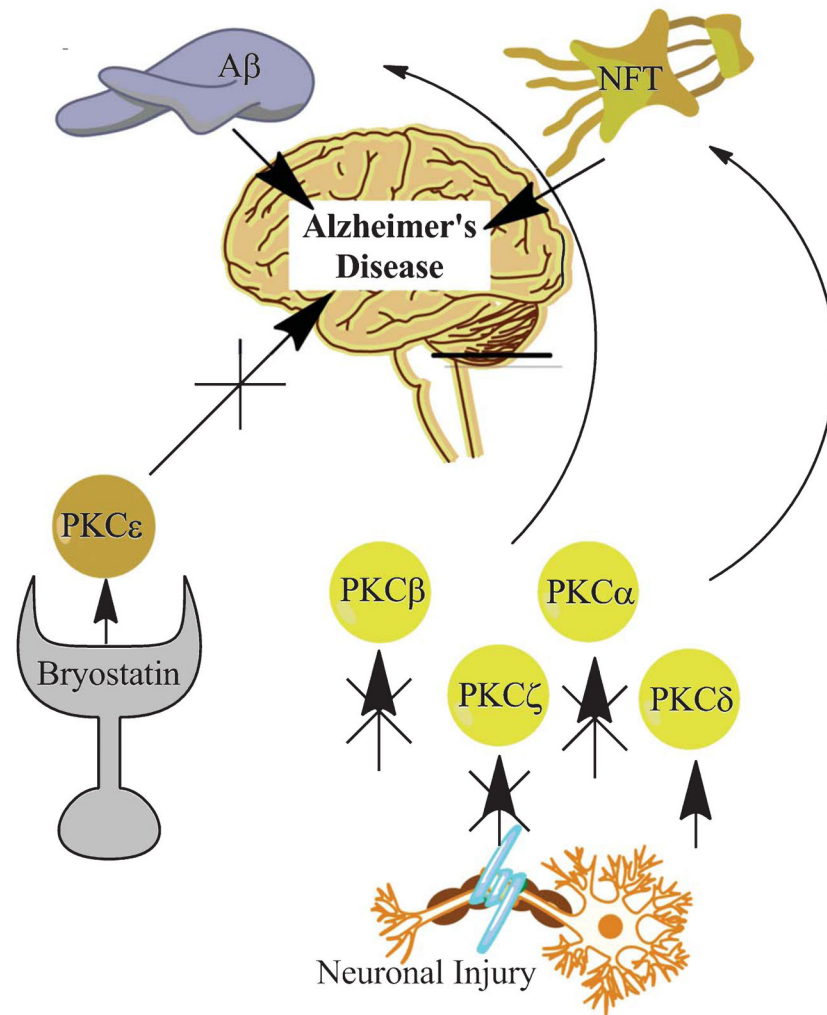


Fig. 2. Neuronal injury causes dysregulation of PKC β , ζ , and α as well as an increase in PKC δ . These changes contribute to the development and progression of A β pathology and NFTs. Targeting PKC ϵ with the pharmacologic agent Bryostatin may prove beneficial in protecting the brain against harmful PKC changes. By increasing PKC ϵ , the progression of NFTs and A β pathology will be slowed.

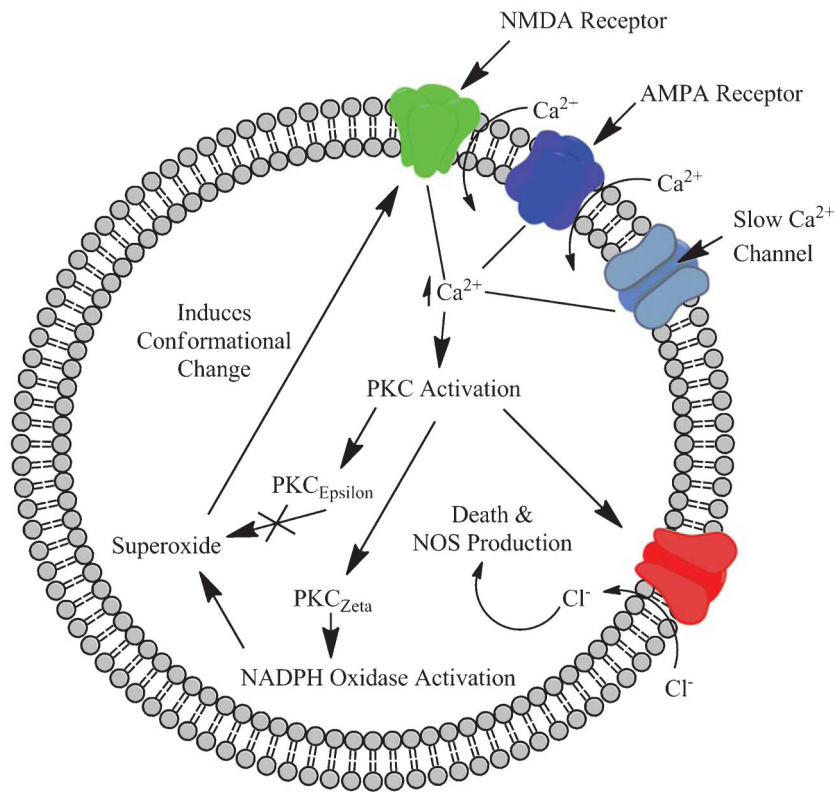


Fig. 3. Glutamate activation of NMDA and AMPA receptors causes an increase in intracellular calcium. The calcium surge triggers an increase in PKC ζ that subsequently leads to superoxide formation. PKC activation also contributes to the formation of nitric oxide synthase (NOS) and associated cell death. An increase in PKC ϵ can mitigate the detrimental effects of oxidative stress and prevent conformational changes at the membrane.

Table 1

PKC isoform changes within the brain for aging, stroke, and AD organized by brain region

PKC Isoforms	Brain region	Aging	Stroke	AD
PKC α	Hippocampus Vasculature	↓ Hongpaisan et al. [7]	↑ Ladage et al. [159]	↓ Sozio et al. [160]
PKC β	Cortex Hippocampus Vasculature	↓ Shelton et al. [161]	↑ Gerschutz et al. [162]	↑ Srivastava et al. [80]
PKC δ	Cortex Hippocampus Vasculature	=Pascale et al. [163]	↓ Bright et al., [164]	=Yi et al. [153]
PKC ϵ	Hippocampus Vasculature	↓ Hongpaisan et al. [7]	↓ Bright et al. [165]	↓ Yi et al. [153]
PKC ζ	Cortex Hippocampus Vasculature	↓ Galve-Roperh et al. [166]	↑ Willis et al. [14]	↓ Moore et al. [167]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript