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

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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.

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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 (Aβ) 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. Aβ 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 PKCε can improve synaptogenesis [7]. PKCγ 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 3β (p-GSK3β) [10]. Restoration of the PKCε cytosol-to-cell membrane translocation and activity decrease both NFTs and Aβ 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 PKCε 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. PKCα has an organized linear configuration consisting of N-terminal pseudosubstrate domains, a kinase domain, targeting domains, and inhibitory regulatory domains [23]. PKCα provides biochemical and structural support for synaptic architecture through activation of protein synthesis and has been associated with memory capacity [24, 25]. PKCβ has a distinct active site with a Cα 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 PKCδ are a catalytic domain and a highly reactive regulatory domain, C1B, which interacts with diacylglycerol [28]. PKCδ plays important roles in the regulation of apoptosis [29]. PKCε has a catalytic domain and two C1 domains that help direct translocation from the plasma membrane to nuclear membrane [30]. PKCε contributes to recognition memory and wound healing [31, 32]. PKCγ has a flexible C1B domain that can be phosphorylated at serine 109 [33]. PKCγ plays a vital role in pain regulation and reward seeking behavior [34, 35]. PKCζ has a series of N-terminal PB1 domains that have important roles in cellular processes [36]. PKCζ 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]. AKAP7α 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 PKCα can also lead to an increase in matrix metalloproteinases within the aged brain [59]. In contrast, PKCγ levels are maintained at a constant level in the aged hippocampus, but translocation of this isoform is impaired. Such deficits in PKCγ 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]. PKCδ 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]. PKCβ 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]. PKCα has been linked to increased risk for hemorrhagic transformation following ischemic stroke [69]. PKCδ contributes to a release of reactive oxygen species and apoptosis following ischemia [70, 71]. PKCδ likewise contributes to increased BBB permeability via activation of matrix metalloproteinase-9 and phosphorylation of occludin [72, 73]. PKCε is downregulated leaving neuronal mitochondria susceptible to injury [74]. PKCζ and PKCβ 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]. PKCβ, 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]. PKCζ 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 PKCε is increased, however, scavenging molecules that protect cells from reactive oxygen species are elevated [86]. The level of PKCε activity is inversely correlated with infarct volume [87]. PKCε exerts its protective effects through mitochondrial stabilization [88].

If the brain is reperfused by thrombolytics, PKCδ 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 PKCδ allowing for more extensive BBB disruption following stroke [91]. Obesity increases PKCζ, 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 PKCε and decreases PKCδ, which has been shown to decrease infarct volume in animal models of stroke [95, 96]. PKCε 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 (NFκB) [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.

PKCα is linked to the formation of aversive and high-impact memories, whereas PKCε is important in spatial memory formation and object recognition [25, 31]. Additionally, PKCζ 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 PKCβ 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 PKCβ is essential in normal amygdala synaptic plasticity, limbic driven memory, and learning. Transgenic animals with a PKCζ 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).

PKCα is known to upregulate α-secretase, an enzyme important in non-pathogenic amyloid processing. Activation of α-secretase degrades amyloid-β protein precursor (AβPP), promotes the formation of soluble AβPP α (sAβPPα), and prevents Aβ accumulation. α-secretase is believed to be activated directly by PKCα and PKCε, and indirectly through the mitogen-activated protein kinase (MAPK) pathway [115]. Dysfunctional PKCα is deficient in activating α-secretase leading to disrupted AβPP processing and subsequent Aβ accumulation. It is important to note that sAβPPα, formed by the α-secretase cleavage of AβPP, also promotes translocation of PKCβ to the plasma membrane by RACK1 [116]. If PKCβ 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, PKCε, when fully functional reduces Aβ accumulation. PKCε knockout mice display poor reward seeking behavior and have severe cognitive decline on memory tasks indicating the importance of this isoform [119]. PKCε induces the endothelin-converting enzyme to degrade $A\beta_{40}$ and $A\beta_{42}$ to small fragments [120], and facilitates the clearance of the Aβ fragments [115]. Aβ fragment clearance is associated with improved histological findings as well as potential neurological and cognitive benefits. In PKCε transgenic knock-in mice, the amyloid plaque burden is significantly reduced as well as a reduction in neuritic dystrophy, reactive astrocytosis, 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. Aβ is known to downregulate PKC activity [112, 122]. Aβ decreases PKC in a dose-dependent manner by binding to the PKC pseudosubstrate domain and inhibiting activation [123]. Aβ also disrupts cytosol to membrane translocation of PKCα and PKCε. The disrupted translocation prevents the clearance of Aβ [122]. Improving RACK1 translocation can drastically decrease the Aβ burden by allowing protective PKC isoforms to stimulate the degradation and reduction of Aβ. Novel PKC isoforms, including PKCδ and PKCθ, are heavily involved in mediating $A\beta_{42}$ processing. $A\beta_{42}$ 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 Aβ are widely known, the study into the evolutionary benefit of Aβ as an antioxidant is in its infancy [127]. PKC isoforms also serve as potent regulators of tau phosphorylation at serine 199–202 [9]. Importantly, PKCα regulates tau binding to tubulin within axons. If PKCα activity is dysfunctional, tau readily dissociates from tubulin leading to increased tau pathology [6]. Another well-known tau kinase, GSK3β, downregulates the neuroprotective isoform PKCε 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 Aβ [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 PKCδ 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-born 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. PKCε 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 PKCδ 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 PKCε 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 PKCε and improves function after stroke [149]. Another approach is to deliver HSP90 or the PKCε 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 Aβ. For instance, bryostatin-1, a potent modulator of classic and novel PKC isoforms, effectively reduces $A\beta_{40}$ and $A\beta_{42}$ 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 PKCε [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 Aβ model [154]. Yessotoxin, a PKC activator, also decreases both hyperphosphorylated tau and Aβ accumulation [10]. It works by inhibiting the tau kinase, GSK3β [155]. GSK3β 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 Aβ accumulation. Increased Aβ 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 PKCε is properly translocated, it can provide neuroprotection. Often, however, pre-existing comorbidities lead to disrupted PKC translocation and worse outcome following ischemic infarction. PKCε is also protective against memory decline in AD, but toxic Aβ 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.

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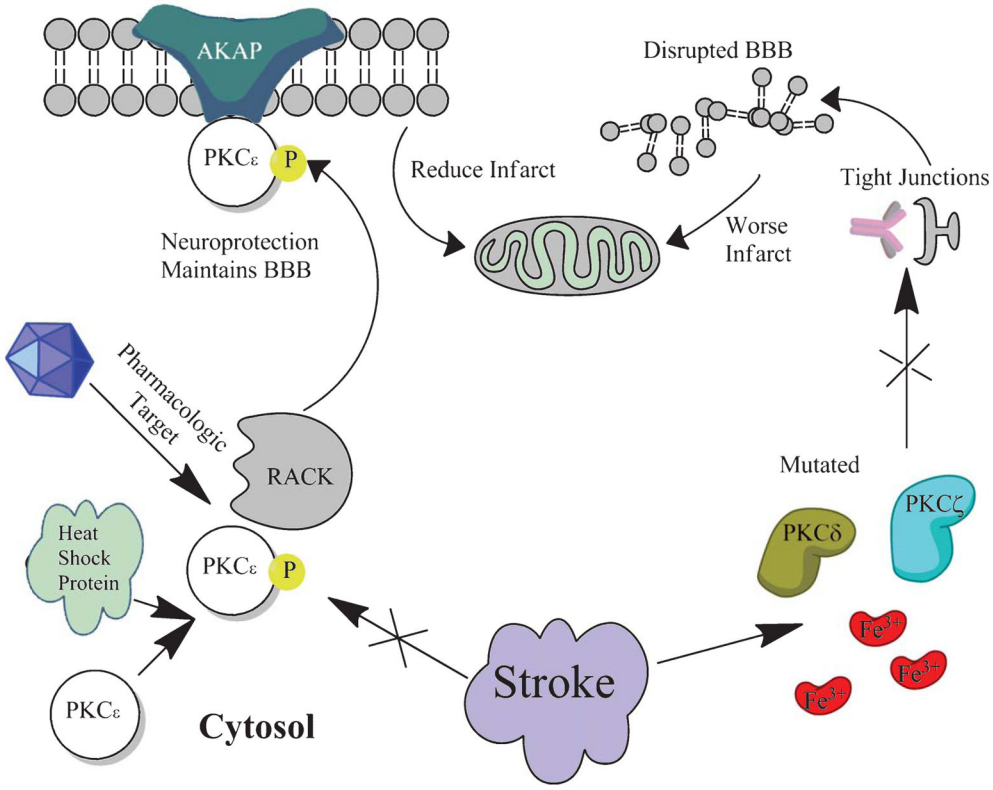

Fig. 1.

Following stroke, PKCδ and PKCζ become dysfunctional and are increased. The result is an increase in BBB disruption and worse ischemic infarct. If PKCε is targeted pharmacologically in order to enhance translocation to the membrane, the BBB is maintained and ischemic infarct is reduced.

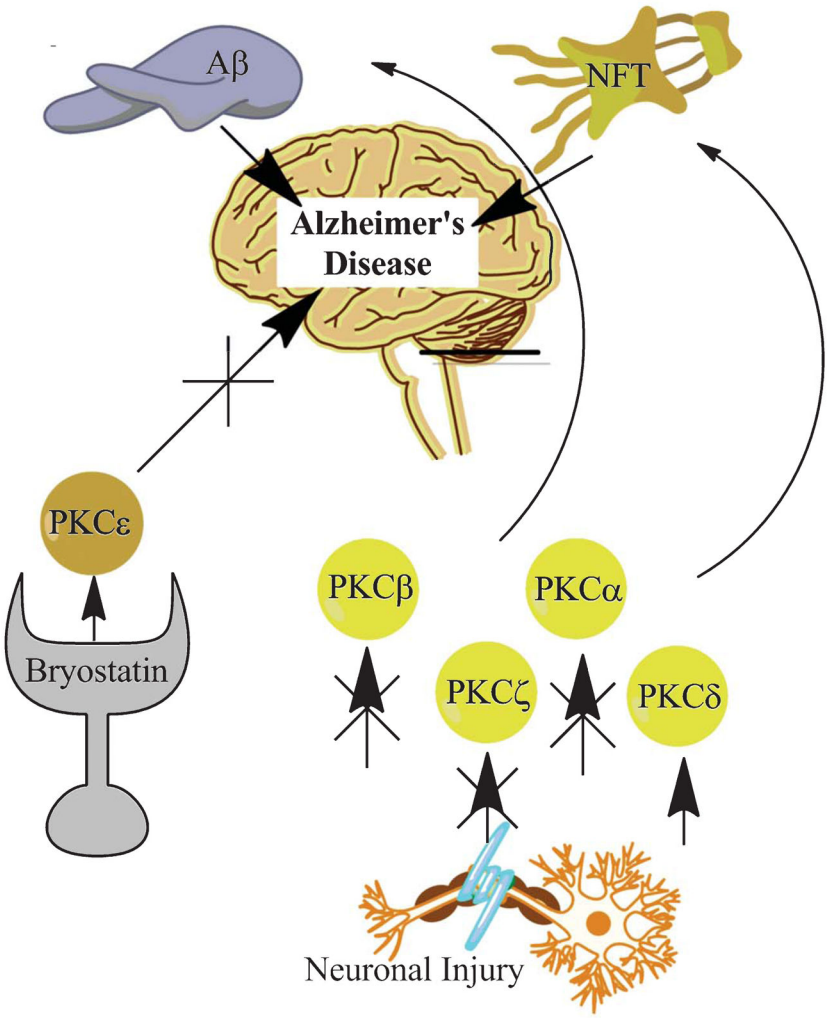

Fig. 2.

Neuronal injury causes dysregulation of PKC β, ζ, and α as well as an increase in PKCδ. These changes contribute to the development and progression of Aβ 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 Aβ pathology will be slowed.

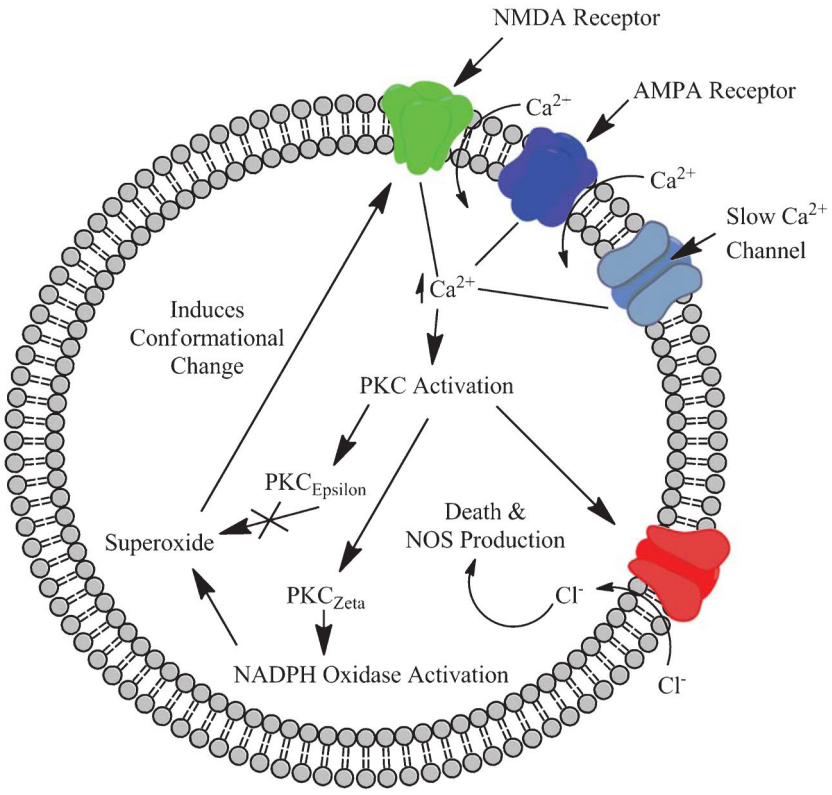

Fig. 3.

Glutamate activation of NMDA and AMPA receptors causes an increase in intracellular calcium. The calcium surge triggers an increase in PKCζ 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 PKCε 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
PKCα	Hippocampus Vasculature	↓ Hongpaisan et al. [7]	↑ Ladage et al. [159]	↓ Sozio et al. [160]
PKCβ	Cortex Hippocampus Vasculature	↓ Shelton et al. [161]	↑ Gerschutz et al. [162]	↑ Srivastava et al. [80]
PKCδ	Cortex Hippocampus Vasculature	=Pascale et al. [163]	↓ Bright et al., [164]	=Yi et al. [153]
PKCε	Hippocampus Vasculature	↓ Hongpaisan et al. [7]	↓ Bright et al. [165]	↓ Yi et al. [153]
PKCζ	Cortex Hippocampus Vasculature	↓ Galve-Roperh et al. [166]	↑ Willis et al. [14]	↓ Moore et al. [167]