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Breakdown of Membrane Phospholipids in Alzheimer Disease

Involvement of Excitatory Amino Acid Receptors

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ABSTRACT

Membrane phospholipids are not only essential membrane constituents but also determine many membrane functions and integrity. Normal receptor function, signal transduction, and transport of essential substrates depend strongly on normal membrane phospholipid metabolism. Studies of plasma membrane phospholipid composition have indicated that ethanolamine glycerophospholipids decrease, whereas serine glycerophospholipids increase significantly, in Alzheimer disease (AD). The release of arachidonate from the *sn-2* position of glycerophospholipids is catalyzed by phospholipases and lipases. These enzymes are coupled to EAA receptors. Overstimulation of these receptors may be involved in abnormal calcium homeostasis, degradation of membrane phospholipids, and the accumulation of free fatty acids, prostaglandins, and lipid peroxides. Accumulation of the mentioned metabolites, as well as abnormalities in signal transduction owing to stimulation of lipases and phospholipases, may be involved in the pathogenesis of the neurodegeneration in AD.

Index Entries: Glutamate; excitatory amino acids; membrane phospholipids; calcium ions; free fatty acids; lipid peroxidation; neurodegeneration; Alzheimer disease.

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Abbreviations: Excitatory amino acid (EAA); *N*-methyl-D-aspartate (NMDA); kainate (KA); 2-amino-3-hydroxy-5-methylisoxazole propionic acid (AMPA); L-2-aminophosphonobutyrate (AP4); (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (1S,3R-ACPD); apolipoprotein E (ApoE); Alzheimer disease (AD); β-amyloid (Aβ).

INTRODUCTION

AD is a progressive neurodegenerative disease occurring in middle or late life. It is the most common cause of dementia in elderly subjects, affecting 20–25% of the population over 80 y old. Numerous theories have been proposed to explain the degeneration of neurons in AD (Katzman et al., 1988; Katzman and Saitoh, 1991) including

1. Selective vulnerability of cholinergic neurons in the basal forebrain;
2. A viral agent;
3. Aluminum deposits;
4. Lack of trophic factors; and
5. Overstimulation of excitatory amino acid (EAA) receptors.

Recent evidence suggests that altered membrane phospholipid metabolism may be an important component of the neurodegeneration observed in AD (Farooqui et al., 1988b; Nitsch et al., 1991; Farooqui and Horrocks, 1994). This work examines the enzymic mechanisms involved in the breakdown of membrane phospholipids and their relationship to EAA receptors. It is hoped that this discussion will stimulate further studies on receptor-mediated changes in membrane phospholipid composition that may be involved in cellular membrane dysfunction and neurodegeneration.

STRUCTURE AND PROPERTIES OF NEURAL MEMBRANES

Neural membranes are composed of arrays of phospholipid molecules organized in bilayers and held together by hydrophobic, coulombic, and van der Waal forces and hydrogen bonding. Neural membranes perform two major functions. They insulate cell contents from the exterior environment and they catalyze the transport of specific compounds, such as nutrients and ions. Phospholipids provide the membrane with suitable fluidity and permeability. The distribution of phospholipids is normally asymmetric across the plane of the plasma membrane, with ethanolamine glycerophospholipids and phosphatidylserine concentrated in the inner leaflet, and choline glycerophospholipids and sphingomyelin concentrated in the outer leaflet. The motion and orientation of phospholipid molecules

from one membrane leaflet to another is called "flip-flop." Normal membrane phospholipid homeostasis is based on a balance between phospholipid catabolism and resynthesis by reacylation and *de novo* synthesis pathways (Porcellati, 1983).

The phospholipid bilayer is penetrated to varying degrees by receptors, enzymes, and ion channels that protrude differentially through the membrane or are localized predominantly on the intracellular or extracellular membrane surface. Functioning of neural membranes depends on a number of factors, including protein and lipid composition, membrane potential, receptor occupancy, and phosphorylation-dependent intermolecular associations. Neural membranes are highly interactive and dynamic. They respond to both internal and external changes and integrate enzymic responses and functions as well as sensitivities to other stimuli by rearrangement of membrane configuration and also by altered composition. Depending on the nature and duration of perturbation and the initial state of the membrane at the time the stimulus is applied, different responses may be obtained (Chapman, 1983).

In neural membranes, lipid and protein molecules move about rapidly in the plane of their own bilayer (Cullis et al., 1983; Bergelson, 1992). The fatty acid side chains of the phospholipids contain even numbers of carbon atoms, mostly in the range of 14–24. The fatty acid in the 2-position is usually polyunsaturated, such as arachidonic, adrenic, or docosahexaenoic acid. Membrane fluidity is closely related to the presence of unsaturated and polyunsaturated side chains because the melting point of a fatty acid is inversely proportional to chain length and number of double bonds (Chapman, 1983; Bergelson, 1992). A *cis*-double bond in the carbon chain enhances rotation and thereby flexibility of the fatty acyl chain. The cell spends a considerable amount of metabolic energy inserting double bonds into fatty acyl chains of membrane lipids and contains several mechanisms to protect unsaturated lipids from degradation (Chow, 1991).

MECHANISMS FOR THE RELEASE OF ARACHIDONIC ACID

The interaction of ligand with receptor markedly affects membrane phospholipid metabolism (Farooqui and Horrocks, 1991; Fowler et al., 1992) and results in the release of arachidonate by several direct and indirect enzymic pathways (Fig. 1). The direct pathway involves the stimulation of Ca^{2+}-dependent and/or Ca^{2+}-independent phospholipases A_2 (Farooqui et al., 1992; Piomelli, 1993). One indirect pathway requires the activation of phospholipase C, followed by diacylglycerol and monoacylglycerol lipases. A second indirect pathway releases arachidonate by utilizing a lysophospholipase preceded by phospholipase A_1. The hydrolysis of phospholipids by phospholipase D produces phosphatidic acid, which

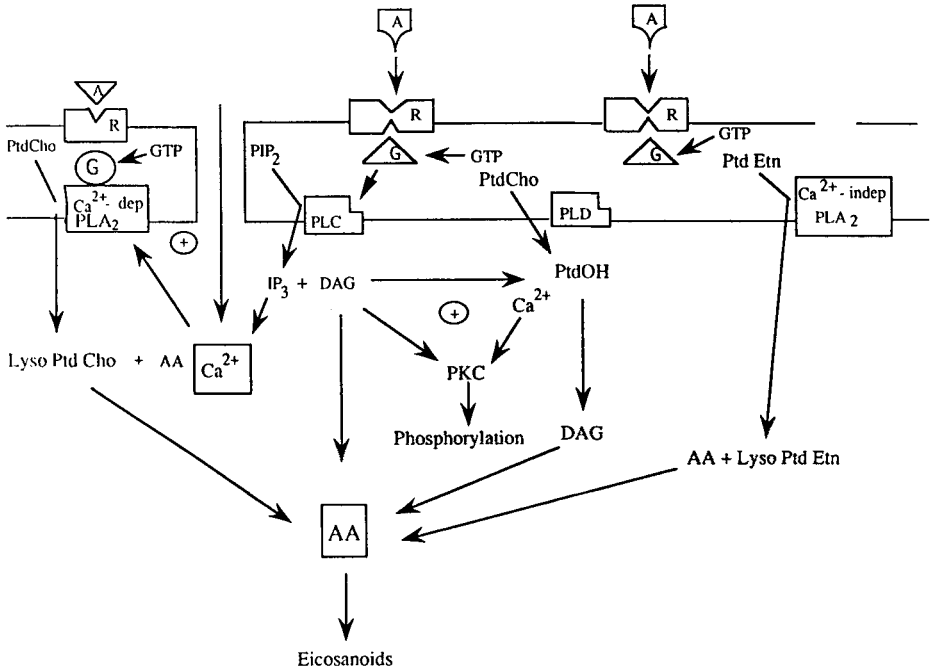

Fig. 1. Hypothetical diagram showing the breakdown of phospholipids by phospholipases. A, Agonist; R, Receptor; G, GTP-binding protein; PtdCho, phosphatidylcholine; PIP_2, phosphatidylinositol 4,5-bisphosphate; PtdEtn, phosphatidylethanolamine; Ca^{2+}-dep PLA_2, Ca^{2+}-dependent phospholipase A_2; PLC, phospholipase C; PLD, phospholipase D; Ca^{2+}-indep PLA_2, Ca^{2+}-independent phospholipase A_2; LysoPtdCho, lysophosphatidylcholine; AA, arachidonic acid; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PtdOH, phosphatidic acid; PKC, protein kinase C; LysoPtdEtn, lysophosphatidylethanolamine.

can then be hydrolyzed by a phosphatidic acid-specific phospholipase A_2. The action of a phosphatase on phosphatidic acid generates diacylglycerol, which can be hydrolyzed by diacylglycerol and monacylglycerol lipases.

Although the relative contributions of these pathways to the release of arachidonate are still obscure, the importance of the direct deacylation of phospholipids by phospholipase A_2 and the actions of diacylglycerol and monoacylglycerol lipases preceded by phospholipase C has been clearly established (Farooqui et al., 1992; Piomelli, 1993).

INVOLVEMENT OF EXCITATORY AMINO ACID (EAA) RECEPTORS IN THE RELEASE OF ARACHIDONIC ACID

Glutamate and its analogs exert their effects on the nerve cell by interacting with at least five EAA receptor subtypes that have been defined by

their selective agonists: *N*-methyl-D-aspartate (NMDA), kainate (KA), 2-amino-3-hydroxy-5-methylisoxazole propionic acid (AMPA), L-2-amino-phosphonobutyrate (AP4) and (1S,3R)-1-aminocyclopentyl-1,3-dicarboxylate (1S,3R-ACPD) (Farooqui and Horrocks, 1991). Of these, the NMDA receptor is of particular interest because it is involved in long-term potentiation (Monaghan et al., 1989; Nakanishi, 1992), a persistent increase in synaptic efficacy following brief, high-frequency stimulation of monosynaptic pathways, particularly in the hippocampus (Bliss and Lomo, 1973). This phenomenon serves as a good model of memory formation (Colley and Routtenberg, 1993). The NMDA receptor also is associated with the degeneration of neurons found in a variety of chronic neurological disorders, including AD (Farooqui and Horrocks, 1994).

The NMDA Receptor and Phospholipase A_2

The interactions of glutamate and NMDA with EAA receptors produce a marked increase in the release of arachidonic acid from the membrane phospholipids of the striatal, hippocampal, and hypothalamic neurons and cerebellar granule cells (Dumuis et al., 1988; Lazarewicz et al., 1988, 1990; Patel et al., 1990; Sanfeliu et al., 1990; Rage et al., 1991). This elevation can be blocked in a dose-related manner by the NMDA receptor antagonist 2-amino-5-phosphovalerate (Sanfeliu et al., 1990; Sucher et al., 1991). The enzymatic mechanisms responsible for the liberation of arachidonate are not fully understood. However, based on the effect of mepacrine, a nonspecific inhibitor of phospholipase A_2, it has been suggested that the stimulation of phospholipase A_2 may be involved in this process. This finding should be treated with caution because higher doses of mepacrine also inhibit phospholipase C and cyclooxygenases. Unlike the α-adrenergic receptor, where phospholipase A_2 is coupled to the receptor complex through a G-protein (Axelrod, 1990), in cerebellar granule cells the coupling of the NMDA receptor to phospholipase A_2 (arachidonic acid release) is not mediated by a G-protein (Lazarewicz et al., 1990). Thus it seems likely that the elevated intracellular concentration of Ca^{2+}, triggered by the opening of NMDA receptor channels, may serve a second messenger function in activating phospholipases A_2 directly or through some other signal transduction mechanism.

Our studies with neuron-enriched cultures from fetal mouse spinal cord have indicated that glutamate and NMDA stimulate the activities of diacylglycerol and monoacylglycerol lipases in a dose- and time-dependent manner (Fig. 2), and this increase can be blocked by dextrorphan or MK-801 (Farooqui et al., 1993). At present it is not clear how the NMDA receptor is coupled to diacylglycerol and monoacylglycerol lipases. However, marked enrichment of polyphosphoinositide turnover is observed in striatal neurons after NMDA treatment (Dumuis et al., 1990). This suggests the involvement of phospholipase C. Diacylglycerol lipase probably

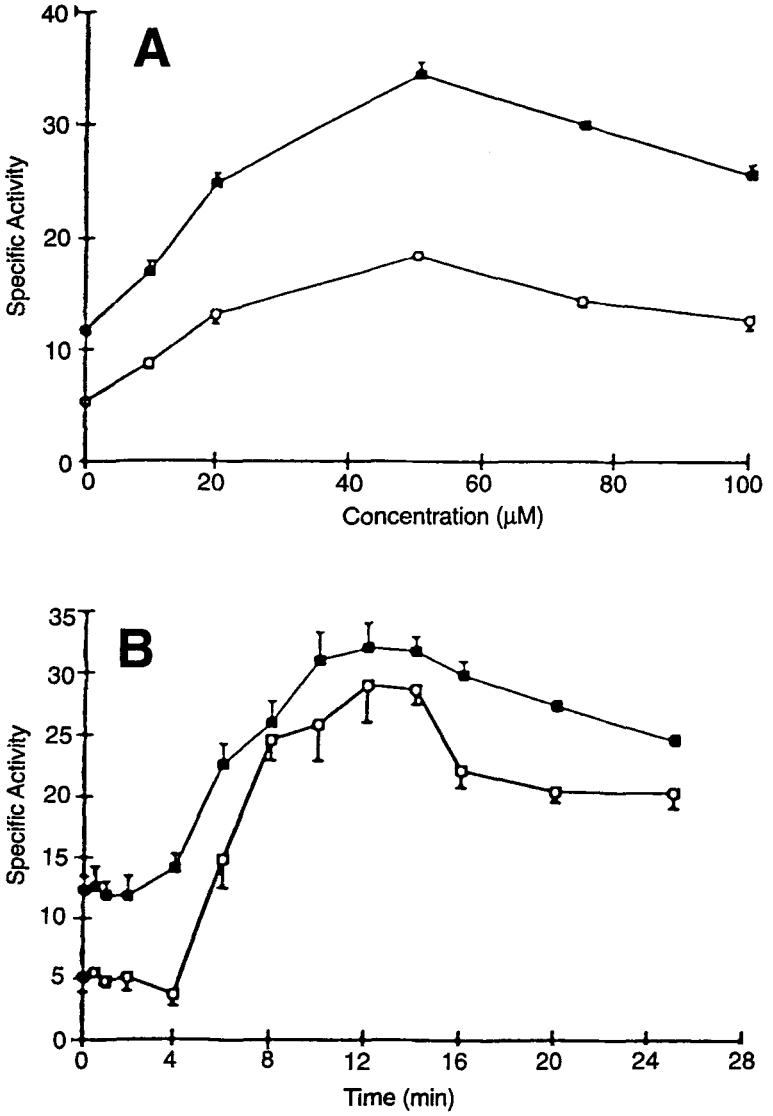

Fig. 2. (**A**) Dose- and (**B**) time-dependence of the effects of glutamate on the activities of diacylglycerol (□) and monoacylglycerol (■) lipases in neuron-enriched cultures from fetal mouse spinal cord. Dose-dependence was studied at 15 min; time-dependence at 50 μM. Each point is the mean of three experiments with the SEM indicated by the bar. Specific activity is expressed as nmol/min/mg protein. (Taken from Farooqui et al., 1993.)

hydrolyzes much of the diacylglycerol released by the action of phospholipase C. Thus, both phospholipase A_2 and diacylglycerol lipase and monoacylglycerol lipase pathways participate in the release of arachidonate in response to glutamate and its analogs (Fig. 1). However, the relative contributions of these pathways are still obscure.

The (1S,3R)-ACPD Receptor and Phospholipase C

Stimulation of membrane phospholipid degradation by EAA agonists has been reported in a variety of neuronal preparations. These include mouse striatal cultures (Sladeczek et al., 1988), cerebellar granule cell cultures (Nicoletti et al., 1986), and rat brain synaptoneurosomes (Récasens et al., 1987). It is known that the (1S,3R)-ACPD receptor is linked to polyphosphoinositide turnover through the activation of phospholipase C. Interestingly, several laboratories have reported that polyphosphoinositide hydrolysis is also increased by NMDA in primary striatal neurons (Sladeczek et al., 1988), cerebellar granule cells (Nicoletti et al., 1987), and in rat brain synaptoneurosomes (Récasens et al., 1987). However, these effects are not observed in slices from rat hippocampus or cerebral cortex (Schoepp and Johnson, 1988; Gonzales and Moerschbaecher, 1989). At present it is not known how NMDA receptors are coupled to phospholipase C. Because both Ca^{2+} and a G-protein stimulate phospholipase C, Ca^{2+} ions entering through the NMDA channel may be responsible for direct phospholipase C stimulation (Baird and Nahorski, 1991). Astrocytes from mouse (Stella et al., 1994) brain possess ionotropic and metabotropic glutamatergic receptors that are involved in the release of arachidonic acid.

STATUS OF NEURAL MEMBRANES AND PHOSPHOLIPIDS IN AD

The pathogenesis of AD remains unknown. However, receptor function, membrane integrity, and membrane-dependent processes are altered in AD (Stokes and Hawthorne, 1987; Bertoni-Freddari, 1988; Raber and Bast, 1989; Fowler et al., 1992; Bothmer and Jolles, 1994). Thus, those membrane lipids whose metabolism is linked to membrane receptors may play an important role in the pathogenesis of AD. These lipids are polyphosphoinositides (Stokes and Hawthorne, 1987), plasmalogens (Horrocks et al., 1986), phosphatidylcholine (Wurtman et al., 1985), and gangliosides (Svennerholm and Gottfries, 1994). Marked increases have been reported in levels of prostaglandins and lipid peroxides in AD (Iwamoto et al., 1989; Subbarao et al., 1990). These metabolites may be derived from increased degradation of membrane phospholipids.

Several studies have indicated that the degradation of neural membrane phospholipids is markedly increased in AD brain as choline and ethanolamine glycerophospholipid levels, and the levels of their precursors, choline and ethanolamine, are decreased in contrast to the levels of their deacylation products, which are increased (Nitsch et al. 1992). The authors have determined the phospholipid composition of synaptosomal plasma membrane (SPM) and plasma membrane (PM) fractions from the hippocampus and three areas of the cerebral cortex of control and AD brain (Wells et al., unpublished). We found significantly lower levels of

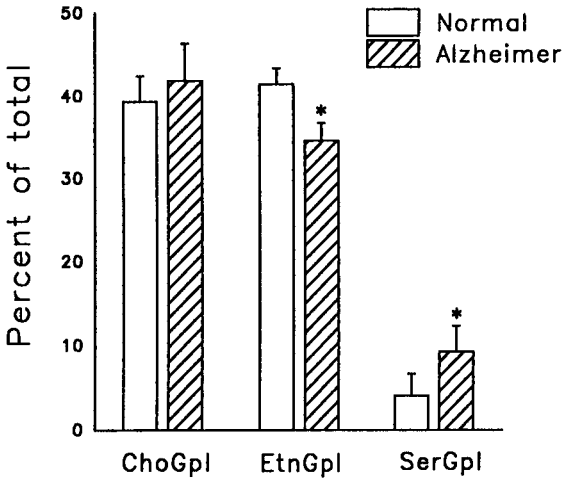

Fig. 3. Proportions of choline, ethanolamine, and serine glycerophospholipids in synaptosomal plasma membrane (SPM) fractions from cerebral cortex of control and AD patients. EtnGpl (p = 0.0001) and SerGpl (p = 0.0001) values differed significantly.

ethanolamine glycerophospholipids and significantly higher levels of serine glycerophospholipids compared to corresponding fractions from age-matched control brain (Figs. 3 and 4). This may be owing to:

1. A decrease in ethanolamine glycerophospholipid synthesis;
2. An increase in ethanolamine glycerophospholipid degradation; or
3. Conversion of ethanolamine glycerophospholipid to phosphatidylserine by base-exchange.

Finally, these results may also be caused by different mixtures of membranes that have been used for phospholipid determination. None of these possibilities have been investigated in brain tissue from AD patients. Phospholipid breakdown from neuronal membranes in AD can activate microglia that secrete a number of cytokines including tumor necrosis factor α (TNF-α) and interleukin 1α and β. These cytokines may amplify inflammatory processes, neuronal and synaptic losses, and induce abnormal processing of β-amyloid protein (Dickson et al., 1993).

The decrease in levels of glycerophospholipids in AD brain is accompanied by a marked elevation in glycerophosphocholine, phosphocholine, and phosphoethanolamine (Pettegrew, 1989). It is interesting to note that levels of phosphomonoesters correlate inversely to the number of senile plaques, whereas levels of phosphodiesters correlate positively to the number of senile plaques (Pettegrew et al., 1988b; Pettegrew, 1989). Further, the decrease in ethanolamine glycerophospholipid level may be related to the loss of synapses in AD (Allain et al., 1993) and the activation of lipolytic enzymes (Farooqui et al., 1990).

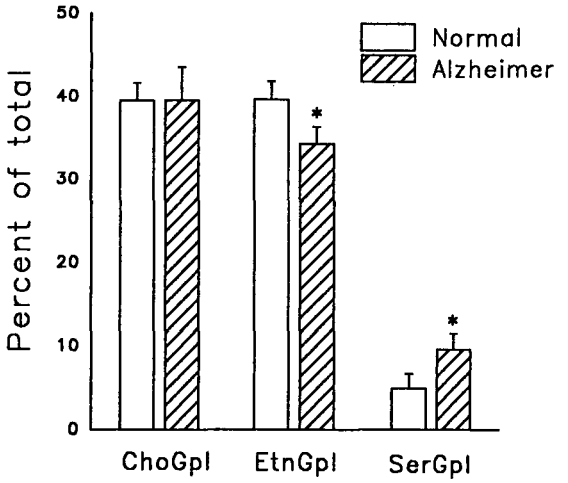

Fig. 4. Proportions of choline, ethanolamine and serine glycerophospholipids in plasma membrane (PM) fractions from cerebral cortex of control and AD patients. EtnGpl (p = 0.0001) and SerGpl (p = 0.0001) values differed significantly.

The increase in phosphatidylserine may reflect attempts of the degenerating brain tissue to restore memory function. Phosphatidylserine has been shown to improve memory function and learning ability of aged animals and humans by partially restoring NMDA receptor density and function (Cohen and Müller, 1992). Phosphatidylserine stimulates protein kinase C, an enzyme that plays an important role in signal transduction, cell differentiation and cell division (Farooqui et al., 1988a). In spite of the increase in phosphatidylserine in AD, protein kinase C activity is markedly decreased in AD brain homogenates (Cole et al., 1988). This may be a result of the unavailability of diacylglycerol, which is hydrolyzed by the high level of diacylglycerol lipase in AD tissues (Farooqui et al., 1990).

In AD brain the fatty acid composition of the glycerophospholipids differs considerably from age-matched normal human brain. The choline glycerophospholipids in AD brain contain mostly saturated and 18:1 fatty acids. The ethanolamine glycerophospholipids also contain increased amounts of saturated fatty acids (14:0, 16:0, and 18:0) and significantly decreased amounts of polyunsaturated fatty acids (20:4, 22:4, and 22:6) (Söderberg et al., 1991). The causes of these changes are not known. However, abnormalities in Δ6-desaturase have been proposed (Nakada et al., 1990). At present it is not clear whether these changes are specific to AD or found in other neurodegenerative diseases.

Thus, phospholipid degradation may be closely related to the abnormalities of signal transduction in AD (Fowler et al., 1992). Phospholipid composition studies have also indicated that the phospholipid:protein mass ratio is unchanged but the unesterified cholesterol:phospholipid mole ratio is decreased by 30% in the AD temporal gyrus compared to age-matched controls (Mason et al., 1992). By contrast, the cholesterol:

phospholipid ratio in the cerebellum does not change significantly in AD. X-ray diffraction analysis of a cholesterol-enriched AD sample showed a virtual restoration of the normal membrane bilayer width and electron density profile, suggesting that the cholesterol deficit also plays an important role in the perturbation of the plasma membrane structure in AD (Mason et al., 1992). Membrane abnormalities affecting cells within and outside the central nervous system are known to occur in AD. Zubenko (Zubenko et al., 1987; Zubenko, 1986, 1990) was the first to report that membrane fluidity is markedly increased in platelets and hippocampal membranes from AD patients. These changes in membrane fluidity can be attributed to the proliferation of the internal membrane system (Zubenko, 1990; Scott, 1993) that induce a lowering of the cholesterol to phospholipid ratio. It is now accepted that the fluidity of biological membranes can have a marked effect on their properties, modulating the activities of membrane-bound enzymes and other membrane components such as ion channels and receptors (Monaghan et al., 1989). A number of factors can influence membrane fluidity, such as chain length and degree of unsaturation of the acyl groups of phospholipids, peroxidation of fatty acids, and membrane cholesterol content. It must be understood at this stage that abnormalities in membrane fluidity may not be specific to AD; rather, they may reflect lipid changes secondary to lipids released from the CNS (Scott, 1993).

ROLE OF EAA-INDUCED PHOSPHOLIPID BREAKDOWN IN NEURODEGENERATION

The overstimulation of EAA receptors produces increased Ca^{2+} influx and activation of lipases and phospholipases (Dumuis et al., 1990; Lazarewicz et al., 1990); with accumulation of free fatty acids, diacyglycerol, and lipid peroxides (*see*, for review, Bazan, 1989; Farooqui and Horrocks, 1991, 1994). High levels of these lipid metabolites are cytotoxic and may contribute to neuronal injury.

Free radicals can disrupt membrane integrity by reacting with proteins and unsaturated lipids in the plasma membrane. These reactions lead to a chemical crosslinking of membrane proteins and lipids and a reduction in unsaturated membrane lipids. This depletion of unsaturated lipids may alter membrane fluidity (Bruch and Thayer, 1983; Ginsberg et al., 1993) and the activities of membrane-bound enzymes and receptors (Heikkila, 1983). Elevated intracellular Ca^{2+} and free radicals may act in concert to induce neuronal injury (Pellegrini-Giampietro et al., 1990). Also, lipid peoxidation stimulates the activities of phospholipases A_2 and C (Sevanian and Kim, 1986; Beckman et al., 1987). This process may further damage membrane integrity.

In chronic neurodegenerative diseases such as AD, there is not an excessive release of glutamate. However, the number of NMDA and other EAA receptors is decreased in the neocortex and hippocampal regions compared to age-matched controls (Greenamyre and Young, 1989; Geddes et al., 1992). AD patients have high levels of cytosolic calcium in the brain (Sang et al., 1993), and intracellular calcium is known to be an important regulator of neuronal cytoarchitecture (Mattson, 1990). Because the NMDA receptor is linked to lipases and phospholipases (Dumuis et al., 1988; Sanfeliu et al., 1990), abnormalities in phospholipid metabolism are expected with AD (Farooqui et al., 1988b). Indeed, the authors have observed a marked elevation of diacylglycerol and monoacylglycerol lipase activities in neural membrane fractions prepared from nucleus basalis and hippocampal regions of 23 AD patients (Farooqui et al., 1988c, 1990), and others have reported abnormal phospholipid metabolism in AD patients (Pettegrew et al., 1988a; Farooqui et al., 1988b; Klunk et al., 1991; Nitsch et al., 1992). A marked increase in phospholipase C immunoreactivity is also found in the brains of AD patients (Shimohama et al., 1991). However, increased immunoreactivity does not correlate with phosphatidylinositol-specific phospholipase C activity, which is not altered in AD (Shimohama et al., 1992). The abnormal accumulation of phospholipase C-δ has also been reported in Pick's disease, progressive supranuclear palsy, and diffuse Lewy body disease (Shimohama et al., 1993). Furthermore, AD is characterized by a decrease in the activities of phospholipase D and protein kinase C (Kanfer et al., 1986; Huynh et al., 1989). These observations suggest that there is a relationship in AD among EAA receptors, stimulation of lipolytic enzymes, abnormal calcium homeostasis, and abnormal phospholipid metabolism.

Thus, excitotoxin-induced abnormal phospholipid metabolism may be a common mechanism involved in acute neural trauma and neurodegenerative diseases. EAA-induced degeneration may occur in those neurons that have an intrinsic vulnerability to excitotoxic injury. One factor that is important in the transition of EAA from neurotransmitter to excitotoxin is the energy status within the neuron (Novelli et al., 1988). A low-energy state within certain neurons may potentiate or induce excitotoxic properties of EAA. Another possible factor is the accumulation of β-amyloid protein, following the observation that the treatment of neuronal cultures with this protein increases EAA cytotoxicity in vitro (Koh et al., 1990). Furthermore, cysteine has been reported to show extensive excitotoxic damage through its effects on EAA receptors (Klingman and Choi, 1989). This suggestion is supported by the observation that elevated plasma cysteine-to-sulfate ratios have been found in AD patients (Heafield et al., 1990).

In ischemia and spinal cord trauma, the excitotoxin-induced neurodegeneration may be rapid (days) because of the sudden lack of oxygen,

decrease in ATP levels, and the sudden collapse of ion gradients. In neurodegenerative diseases, oxygen, nutrients, and ATP are available to the nerve cells, and ionic homeostasis is maintained to a limited extent, resulting in neurodegeneration that takes several years to develop (Beal, 1992; Farooqui and Horrocks, 1992; Hoyer, 1992). At present it cannot be decided whether the stimulation of lipases and phospholipases (release of arachidonate) and alterations in the number of EAA receptors in AD brain are primary or secondary in nature. Even if these changes are secondary, they may be useful for monitoring therapeutic responses or developing diagnostic tests (Farooqui and Horrocks, 1991).

APOLIPOPROTEIN E AND AD

Apolipoprotein E (ApoE) is a component of low-density lipoproteins (LDL) circulating in the blood. LDL receptors bind ApoE so that the associated lipids can be taken up into cells. The gene for ApoE is located on chromosome 19 q 13.2. At least three different isoforms, coded by alleles 2, 3, and 4, are known. In late-onset familial AD, the allele frequency is significantly higher for allele 4 than in controls (Strittmatter et al., 1993). These isoforms have different binding properties, including the binding of Aβ peptide, a primary component of senile plaques. ApoE is also found in the senile plaques (Strittmatter et al., 1993).

LDL receptors and ApoE are plentiful in the central nervous system (DeWille and Horrocks, 1991). Their function is inferred to be in cholesterol and lipid transport, particularly from astrocytes to neurons. The ApoE in the CNS is synthesized by astrocytes and differs by glycosylation from that made in the liver. ApoE levels in the CSF are about 20-fold higher than other plasma proteins and lipoproteins because of the synthesis within the CNS. ApoE may also be involved in the repair response to tissue injury, immunoregulation, and modulation of cell growth and cell differentiation. It interacts with heparin and heparan sulfate and promotes increased adhesion of neurons to the matrix and stimulates axon extension (Mahley, 1988).

Several mechanisms can be postulated for the participation of ApoE in the pathogenesis of AD. ApoE may be involved in amyloid deposition in AD directly through interaction with Aβ. It may act as a pathologic "chaperone" by binding to heparan sulfate and Aβ. A faulty mechanism of clearance or sequestration of Aβ/ApoE complex in brain parenchyma and cerebral blood vessels may be involved in the development of AD (Peacock and Fink, 1994). Differences in the binding of allelic isoforms of ApoE, Aβ, and heparan sulfate may also contribute to a variable tendency for Aβ accumulation (Peacock and Fink, 1994). It is also likely that the enrichment of ApoE in senile plaques represents the excitatory amino acid induced astrocytic response to the disease process, and this may be

responsible for gliosis. Finally, the alterations in membrane phospholipid composition found in AD (Farooqui et al., 1988b; Nitsch et al., 1992; Wells and Horrocks, unpublished) may be related to the interactions of isoforms of ApoE with lipolytic enzymes. The activities of these enzymes are markedly increased in plasma membrane and synaptosomal plasma membrane preparations from hippocampal and nucleus basalis regions of AD autopsy brain and brain from a potential animal model of AD (Farooqui et al., 1988c, 1990, 1991).

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