Akhlaq A. Farooqui

Phytochemicals, Signal Transduction, and Neurological Disorders

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This monograph is dedicated to the memory of my late parents as a token of affection and respect! I am still walking through the doors they opened for me.

Akhlaq A. Farooqui

Preface

Phytochemicals are a heterogeneous non-nutritive group of chemical compounds with numerous biological effects in animals and men. They are derived from plants and form the backbone of traditional medicine, which uses plant preparations (seeds, fruits, leaves, stems and roots) as a source of drugs. Phytochemicals have been classified into five major families, carotinoids, alkaloids, nitrogen-containing phytochemicals, sulfur-containing phytochemicals and phenolics.

Phytochemicals have been used in various ancient medicinal systems (Indian, Chinese, Egyptian, Babylonian, and Greek), as potential drugs against numerous diseases. They exert specific medicinal actions without serving a nutritional role in the human diet and may be used in response to specific health problems over short- or long-term intervals. In recent years, research on phytochemicals has increased all over the world and new terms such as "functional food" and "nutraceutical" have been introduced. These terms illustrate the high expectations associated with current phytochemical research. However, the precise molecular mechanisms through which specific phytochemicals exert their beneficial biological effects still remain the subject of intense investigations. Health benefits of phytochemicals on visceral tissue and brain are due to their anti-inflammatory, antioxidant, anticarcinogenic, antiproliferative, hypocholesterolemic, and cellular repair properties. In addition, effects of phytochemicals are mediated through signal transduction processes, which not only involve various transcription factors, growth factors and inhibition of inflammatory cytokines expression, but also regulation of enzymes, such phospholipases, cyclooxygenases, protein kinases, and protein phosphatases. Phytochemicals also mediate their effects through the modulation of immune function. Regular consumption of phytochemicals from childhood to adulthood may be associated with reduced risks of neurotraumatic (stroke, traumatic brain injury, and spinal cord injury), neurodegenerative (Alzheimer disease, Parkinson disease, and cataracts), neuropsychiatric (depression, Schizophrenia, and bipolar disorders) diseases, osteoporosis, diabetes, and some of the functional decline associated with normal aging. Antioxidant and anti-inflammatory properties of phytochemicals mitigate the damaging effect of oxidative stress, neuroinflammation, and apoptosis. The chemical structures of phytochemicals are often used as "privileged structures"

for creating their synthetic analogs, which have improved pharmacological activities through optimized bioavailability and pharmacokinetic profiles. Recently, there have been considerable developments in defining the molecular mechanisms associated with beneficial effects of phytochemicals on neurological disorders. The effects of phytochemicals on visceral and brain tissues can be conductive, additive, synergistic, and antagonistic. Through these properties, phytochemicals regulate neuronal and glial cell differentiation, proliferation, and apoptosis. Among phytochemicals, polyphenols, phenolic acids, and flavonoids scavenge reactive oxygen species (ROS), singlet molecular oxygen, and peroxyl radicals generated during lipid peroxidation. In addition, the use of polyphenols and flavonoids may not only result in improvements of memory acquisition and consolidation, but also in storage and retrieval of memory. These phytochemicals are highly effective in reversing age-related declines in memory via their ability to interact with the cellular and molecular architecture of the brain responsible for memory related processes. Phytochemicals produce their effects through their ability to modulate signal transduction pathways critical in controlling synaptic plasticity, and inducing neurogenesis in the hippocampus. The ability of many phytochemicals to activate the extracellular signal-regulated kinase (ERK1/2) and the protein kinase B (PKB/Akt) signaling pathways, leading to the activation of the cAMP response element binding protein (CREB), a transcription factor responsible for increasing the expression of a number of growth factors (neurotrophins) important in defining memory, a process by which knowledge is encoded, stored, and later retrieved.

Although, many original papers, reviews, and edited books have been published on the effects of phytochemicals on visceral organs, but information on the effect of phytochemicals on brain is scattered throughout the literature in the form of original papers, and reviews. I have decided to provide readers with a comprehensive and cutting-edge description on metabolism and molecular mechanism associated with the beneficial effects of phytochemicals in neurological disorders in a manner that is useful not only to students and teachers but also to researchers and physicians. This monograph has 11 chapters. The first chapter describes the effect of lifestyle, aging, and phytochemicals on the onset of neurological disorders. Chapters 2 and 3 cover beneficial effects of extra virgin olive oil and flaxseed oil on signal transduction processes in neurological disorders. Chapter 4 provides information on the beneficial effects of flavonoids in neurological disorders. Chapter 5 describes beneficial effects of green tea catechins on neurological disorders. Chapters 6 and 7 present beneficial effects of curcumin and resveratrol in neurological disorders, respectively. Chapters 8 and 9 discuss the beneficial effects of Ginkgo biloba and garlic in neurological disorders. Chapter 10 describes beneficial effects of propolis in neurological disorders. Finally, Chapters 11 focuses on my view on the importance of phytochemicals in diet and direction for future research on neurological disorders. Studies on the effect of phytochemicals on brain fall in a fast-paced research area of neurological disorders. This monograph presents information on the metabolism, bioavailability, and proposed molecular mechanism of action in the brain, along with some pharmacokinetics. This monograph also provides information on delaying the onset and target-based treatment of neurological disorders by

using phytochemicals. This monograph can be used as supplemental text for a range of phytotherapeutics courses. Clinicians and pharmacologists will find this book useful for understanding molecular aspects of phytochemicals in neurological disorders.

I have tried to ensure uniformity in mode of presentation along with extensive bibliography. For the sake of simplicity and uniformity a large number of figures with chemical structures of phytochemicals that produce beneficial effects in neurological disorders and signal transduction diagrams showing the site of action of phytochemicals have also been included. I hope that my attempts to integrate and consolidate the knowledge on beneficial effects of phytochemicals on signal transduction processes associated with pathogenesis of neurological disorders will initiate more studies on molecular mechanisms associated with beneficial effects of phytochemicals in neurotraumatic, neurodegenerative, and neuropsychiatric diseases.

Columbus, OH, USA Akhlaq A. Farooqui

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Akhlaq A. Farooqui

About the Author

Akhlaq A. Farooqui is a leader in the field of signal transduction, brain phospholipases A_2, bioactive ether lipid metabolism, polyunsaturated fatty acid metabolism, glycerophospholipid-, sphingolipid-, and cholesterol-derived lipid mediators, glutamate-induced neurotoxicity, and modulation of signal transduction by phytochemicals. Akhlaq A. Farooqui has discovered the stimulation of plasmalogen-selective phospholipase A_2 (PlsEtn-PLA_2) and diacyl- and monoacylglycerol lipases in brains from patients with Alzheimer disease. Stimulation of PlsEtn-PLA_2 produces plasmalogen deficiency and increases levels of eicosanoids that may be related to the loss of synapses in brains of patients with Alzheimer disease. Akhlaq A. Farooqui has published cutting-edge research on the generation and identification of glycerophospholipid-, sphingolipid-, and cholesterol-derived lipid mediators in kainic acid-mediated neurotoxicity by lipidomics. Akhlaq A. Farooqui has authored seven monographs:

Glycerophospholipids in Brain: Phospholipase A_2 in Neurological Disorders (2007); Neurochemical Aspects of Excitotoxicity (2008); Metabolism and Functions of Bioactive Ether Lipids in Brain (2008); and Hot Topics in Neural Membrane Lipidology (2009); *Beneficial Effects of Fish Oil in Human Brain (2009); Neurochemical Aspects of Neurotraumatic and Neurodegenerative Diseases (2010)*; *and Lipid Mediators and their Metabolism in the Brain (2011). All monographs are published by Springer, New York. In addition, Akhlaq A. Farooqui has edited six books* (*Biogenic Amines: Pharmacological, Neurochemical and Molecular Aspects in the CNS Nova Science Publisher, Hauppauge, N.Y (2010), Molecular Aspects of Neurodegeneration and Neuroprotection, Bentham Science Publishers Ltd.* (*2011*); *Phytochemicals and Human Health: Molecular and pharmacological Aspects (2011), Nova Science Publisher, Hauppauge, N.Y.; Molecular Aspects of Oxidative Stress on Cell Signaling in Vertebrates Invertebrates (2012), Wiley Blackwell Publishing Company, New York, 2012*); *Beneficial effects of propolis on Human Health in Chronic Diseases (2012) Vol 1, Nova Science Publishers, Hauppaauge, New York (in press); and Beneficial effects of propolis on Human Health in Chronic Diseases (2012) Vol 2, Nova Science Publishers, Hauppaauge, New York (in press).*

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List of Abbreviations

AD	Alzheimer disease
AGE	Aged garlic extract
ALA	α-Linolenic acid
ALS	Amyotrophic lateral sclerosis
ARA	Arachidonic acid
BBB	Blood–brain barrier
CAPE	Caffeic acid phenethyl ester
COX	Cyclooxygenase
DADS	Diallyl disulfide
DAS	Diallyl sulfide
DHA	Docosahexaenoic acid
EGb761	Ginkgo. biloba leaves extract
EGCG	(-)-Epigallocatechin-3-gallate
EPA	Eicosapentaenoic acid
HD	Huntington disease
Ins-1,4,5-P_3	Inositol-1,4,5-trisphosphate
LA	Linoleic acid
LOX	Lipoxygenase
MS	Multiple sclerosis
PD	Parkinson disease
PKC	Protein kinase C
PLA_2	Phospholipase A_2
PLC	Phospholipase C
PlsCho	Choline plasmalogen
PlsEtn	Ethanolamine plasmalogen
PtdCho	Phosphatidylcholine

PtdEtn	Phosphatidylethanolamine
PtdIns	Phosphatidylinositol
PtdIns(4,5)P_2	Phosphatidylinositol 4,5-bisphosphate
PtdIns4*P*	Phoshatidylinositol 4-phosphate
SAC	*S*-Allylcysteine

Chapter 1
Effect of Lifestyle, Aging, and Phytochemicals on the Onset of Neurological Disorders

1.1 Introduction

Neurological disorders include neurotraumatic and neurodegenerative diseases. Common neurodegenerative diseases include Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), and multiple sclerosis (MS), whereas common neurotraumatic diseases include strokes, traumatic brain injury (TBI), and spinal cord injury (SCI) (Farooqui 2010). Among neurotraumatic diseases, stroke is a metabolic insult induced by severe reduction or blockade in cerebral blood flow. This blockade not only causes deficiency of oxygen and reduction in glucose metabolism, but also results in ATP depletion and accumulation of toxic products. TBI and SCI due to motor cycle and car accidents are major cases of disability among young people. Neurotraumatic and neurodegenerative diseases share excitotoxicity, oxidative stress, and neuroinflammation as a common mechanism of cell death. In addition to excitotoxicity, oxidative stress, and neuroinflammation, neurodegenerative diseases are accompanied by the accumulation of misfolded proteins, mitochondrial and proteasomal dysfunction, loss of synapses, and premature and slow death of certain neuronal populations in brain tissue (Graeber and Moran 2002). For example in AD, neuronal degeneration occurs in the nucleus basalis, whereas in PD, neurons die in the substantia nigra. The most severely affected neurons in HD are striatal medium spiny neurons (Farooqui 2010).

The most important risk factors for stroke and neurodegenerative diseases are old age, race/ethnicity, a positive family history, unhealthy lifestyle, and endogenous factors (Fig. 1.1). The onset of stroke and neurodegenerative diseases is often subtle and usually occurs in mid to late life and their progression depends not only on genetic, but also on environmental factors (Graeber and Moran 2002). The onset of neurological diseases may occur when neurons fail to respond adaptively to age-related increase in oxidative and nitrosative stress and neuroinflammation. Persistence presence of oxidative and nitrosative stress and neuroinflammation induces the accumulation of damaged proteins, DNA, and membrane fragments.

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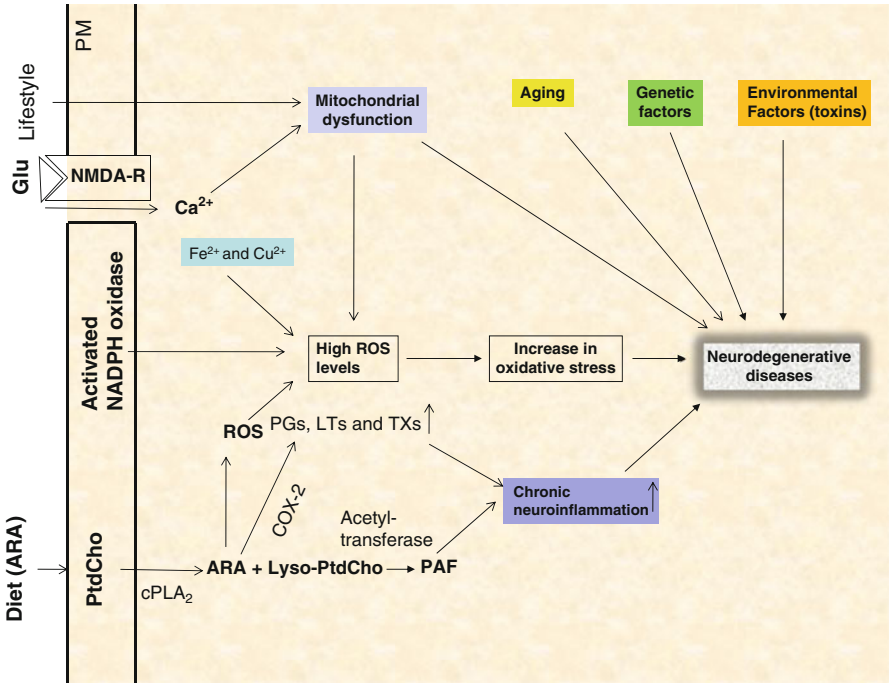

Fig. 1.1 Effect of diet, lifestyle, high oxidative stress, and environmental and genetic factors on the onset of neurodegenerative diseases. Plasma membrane (PM); glutamate (Glu); *N*-methyl D-aspartate receptor (NMDA-R); phospholipase A_2 (PLA_2); arachidonic acid (ARA); phosphatidylcholine (PtdCho); lysophosphatidylcholine (lyso-PtdCho); reactive oxygen species (ROS); prostaglandins (PGs); leukotrienes (LTs); and thromboxanes (TXs)

In addition, neurodegenerative diseases are accompanied by the accumulation of disease-specific proteins, such as accumulation of Aβ and its aggregates in the cerebral cortex and hippocampal region in AD, α-synuclein in the brain stem in PD, and huntingtin in striatal medium spiny neurons in HD. Furthermore, abnormalities in signal transduction processes along with elevated levels of lipid mediators and disturbance in stress resistance mechanisms have also been reported in both types of neurological disorders (Farooqui and Horrocks 2007; Farooqui and Farooqui 2011, 2012). Both stroke and neurodegenerative diseases lead to progressive cognitive and motor disabilities with devastating consequences to patients. In older individuals and animals, age-related alterations in interplay (cross-talk) among excitotoxicity, oxidative stress, and neuroinflammation may cause abnormalities in motor and cognitive performance. An enhanced rate (upregulation) of interplay among excitotoxicity, oxidative stress, and neuroinflammation may be a common mechanism of brain damage in stroke and neurodegenerative diseases (Farooqui and Horrocks 2007; Farooqui et al. 2007; Farooqui 2010). In addition, diet, genetic, lifestyle, and environmental factors may also be associated with the increased vulnerability of neurons in stroke and neurodegenerative diseases (Kidd 2005; Farooqui 2010).

1.2 Factors Influencing the Onset of Stroke and Neurodegenerative Diseases

As stated earlier, the most important risk factors for stroke and neurodegenerative diseases are old age and a positive family history. The pathogenesis of age-related diseases is complex and it is often difficult to identify causal risk factors, especially if their relative effects are weak. Stroke and neurodegenerative diseases are multifactorial illnesses caused by complex interactions among genetic factors, environmental factors, aging, and lifestyle (an expression of individual choices and their interaction with the environment). Environmental and dietary risk factors, such as heavy metals, hormones, cholesterol, high-fat diet, high alcohol intake, diet deficient in n-3 fatty acids, antioxidants and vitamins, and reduced levels of physical activity (exercise) may promote the onset and progression of stroke and neurodegenerative diseases (Fig. 1.1). Other factors, such as too much cigarette smoking, exposure to secondhand smoke, midlife high blood pressure, and chronic diseases (e.g., obesity, diabetes, traumatic brain injury, and cerebrovascular lesions) may also promote the early onset of stroke and neurodegenerative diseases. Stroke prevention guidelines developed and endorsed by the American Heart Association and American Stroke Association emphasize the benefits of adopting healthy lifestyle choices—such as quitting smoking; eating a low-fat diet, which is enriched in n-3 fatty acids, fruits, and vegetables; drinking in moderation; exercising regularly; and maintaining a normal body weight—to reduce the risk of stroke (Mitka 2011) (Fig. 1.2). The risk

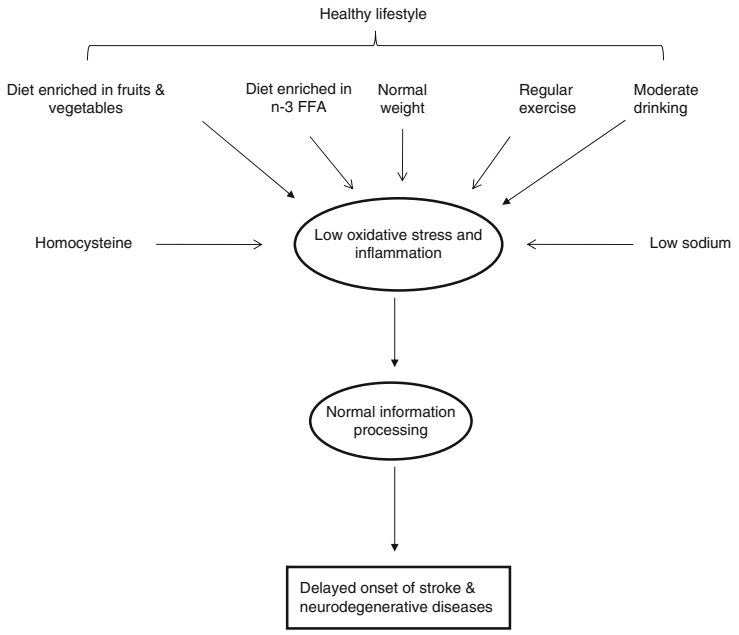

Fig. 1.2 Effect of healthy lifestyle on stroke and neurodegenerative diseases

factors for neurodegenerative diseases also include diet deficient in n-3 fatty acids, environmental factors, and lifestyle (consumption of processed food and lack of exercise) (Santana-Sosa et al. 2008; Pasinetti and Eberstein 2008). Thus, humans consuming fatty fish twice per week have lower risk of developing neurodegenerative diseases compared with those who consumed fatty fish less than once per month. Modest alcohol intake (1–6 drinks per week) provides in the fewest subclinical cerebrovascular abnormalities. Compared with little activity, moderate and high leisure-time activity results in 28 % and 44 % lower mortality, respectively, while compared with nonexercisers, low, moderate, and high exercise intensity predicted 30 %, 37 %, and 53 % more years of healthy life, respectively. Former and current smokers have 25 % and 44 % fewer years of healthy life than those who never smoked; lifetime smoking (pack-years) predicts higher mortality (Boden-Albala and Sacco 2000; Mozaffarian et al. 2004; King et al. 2009).

A healthy lifestyle keeps interplay among excitotoxicity, oxidative stress, and neuroinflammation to a level, which is necessary for optimal health (Farooqui 2009). This lifestyle must be maintained throughout the life (from childhood to old age) to delay or prevent stroke and neurodegenerative diseases. Changes in lifestyle after the onset of stroke or neurodegenerative disease may not have any effect on the disease process. This is tempting to speculate that adherence to a healthy lifestyle may either directly protect against stroke and neurodegenerative diseases or may delay these neurological diseases (Fratiglioni and Qiu 2009).

1.2.1 Effect of Natural and Processed Food on Human Health

Fresh natural food contains a higher proportion of naturally occurring vitamins, fibers, and minerals than processed food. Many constituents of natural fresh food are destroyed during food processing (Griep et al. 2011). For example, vitamin C is destroyed by heat and therefore canned fruits have a lower content of vitamin C than fresh ones. Often nutrients are deliberately removed or added to the processed food for improving its "shelf-life," appearance, and taste (Levenstein 2003). This process is widespread in foods such as bread, pasta, and premade meals. Processed foods contain many additives, such as sugar, salt, flavorings, and texture-enhancing agents (Pollan 2008). As a result, eating large amounts of processed foods can lead to excessive intake of these substances, which can then lead to a variety of health complications including high blood pressure, weight gain, and diabetes. Preservatives added to extend the "shelf-life" of commercially available products, such as nitrites or sulfites, may cause adverse health effects. In vivo chemical reactions between nitrites and secondary amines or proteins can generate nitrosamine, which may exert their toxic effects by alkylating N-7 of guanine, leading to increased DNA damage (Swann and Magee 1968) and generation of reactive oxygen species such as superoxide (O_2-) and hydrogen peroxide (H_2O_2). Consequences include increased lipid peroxidation, protein adduct formation, and pro-inflammatory cytokine activation (Espey et al. 2002). These molecular and biochemical pathogenic cascades

have been proposed for the induction of human insulin-resistance diseases, such as type 2 diabetes, nonalcoholic steatohepatitis, and AD (Pasquier et al. 2006; Nicolls 2004; Yeh and Brunt 2007; de la Monte et al. 2009). Additionally, processed food has higher calories than fresh natural food (Levenstein 2003; Pollan 2008). Studies on the effect of raw and processed vegetables and fruits on humans indicate that high intake of raw fruit and vegetables may protect against stroke (Griep et al. 2011). High salt and sugars, which are present in processed food, are also major risk factors for stroke, heart disease, diabetes, and renal diseases. Salt intake is not the only determinant of high blood pressure associated with cerebrovascular, cardiovascular, and renal diseases, but other modifiable risk factors include relative mass, physical activity, overall dietary quality, and alcohol consumption. Consumption of processed meats, but not red meats, is not only associated with higher incidence of coronary heart disease, diabetes mellitus, and stroke, but also several types of cancers. These results highlight the need for better understanding of potential mechanisms of effects and for particular focus on processed meats for dietary intake (Linseisen et al. 2006). Presence of added sugar in processed food raises blood pressure (Nguyen et al. 2009; Bremer et al. 2009). Animal studies in rats and human studies, such as the Framingham Heart Study, indicate that consumption of ≥1 soft drink per day significantly increased the odds of developing high blood pressure (Rebello et al. 1983). Processed food is stored and sold in iron, tin, aluminum, and plastic containers. Storage of processed food in metal and plastic containers may result in toxicity due to leakage of chemicals and metal ions (Borchers et al. 2010).

1.2.2 Effect of Soft Drinks on Human Health

Soft drinks contain large amounts of high-fructose corn syrup (55 % fructose and 45 % glucose), which is enriched in fructose. Consumption of a high-fructose diet for 4 weeks in rats not only produces systemic insulin resistance and reduces tyrosine phosphorylation of the insulin receptor in liver, but also impairs insulin receptor substrate-1 (IRS-1) phosphorylation and IRS-1 association with phosphoinositol-3-kinase in both liver and skeletal muscle (Bezerra et al. 2000), supporting the view that specific points in the insulin signal transduction pathway that are affected by dietary fructose. These processes may lead to hepatic insulin resistance, increased total and visceral fat mass, and accumulation of ectopic fat in the liver and skeletal muscle. Thus, in humans, monkeys, and rodents, diet containing high fructose may lead to the development of obesity, diabetes, high blood pressure, and high triglyceride levels (Malik et al. 2006; Havel 2005; Stanhope and Havel 2008). Insulin resistance along with visceral obesity, dyslipidemia, and hypertension is a major component of the metabolic syndrome (Fig. 1.3) which is strongly associated with an increased risk for cardiovascular disease. Unhealthy lifestyle (a lack of regular physical activity and consumption of processed food rich in highly saturated fats, sugars, and salt) results in higher levels of risk factors (hypertension, dyslipidemia, diabetes, and obesity that act independently and synergistically) and are