J Bioenerg Biomembr (2010) 42:457–459
DOI 10.1007/s10863-010-9317-4

Mitochondrial matters of the brain: mitochondrial dysfunction and oxidative status in epilepsy

Sue-Joan Chang · Bu-Chin Yu

Published online: 18 November 2010

Abstract Epilepsy is a neurological disorder characterized by spontaneous, recurrent and paroxysmal cerebral discharge, clinically leading to persistent alterations in function and morphology of neurons. Oxidative stress is one of possible mechanisms in the pathogenesis of epilepsy. Oxidative stress resulting from mitochondrial dysfunction gradually disrupts the intracellular calcium homeostasis, which modulates neuronal excitability and synaptic transmission making neurons more vulnerable to additional stress, and leads to neuronal loss in epilepsy. In addition, the high oxidative status is associated with the severity and recurrence of epileptic seizure. Hence, treatment with antioxidants is critically important in epileptic patients through scavenging the excessive free radicals to protect the neuronal loss. In this review, we reviewed the recent findings that focus on the role for antioxidants in prevention of mitochondrial dysfunction and the correlation between oxidative status and disease prognosis in patients with epilepsy.

Keywords Epilepsy · Mitochondrial dysfunction · Oxidative stress · Antioxidative system

Introduction

Epilepsy is an etiologically and clinically diverse group of neurological disorders characterized by spontaneous, recurrent, paroxysmal cerebral discharges, resulting clinically in permanent alterations of normal function and morphology of neuronal cells, and even cell death (Treiman 1995). Oxidative stress is one of possible mechanisms in the pathogenesis of epilepsy. Oxidative stress caused the peroxidation of cellular protein, membrane lipid, and nuclear DNA and led to the loss of mitochondrial structure and functions (Floyd 1990). It impaired mitochondrial oxidative phosphorylation, resulted in excessive free radical generation and a deficient antioxidant system (Fillano et al. 2002; Peternel et al. 2009), thus a vicious circle was initiated. Further, mitochondrial dysfunction disrupted the intracellular calcium homeostasis and mitochondrial membrane depolarization that led to severe neuronal loss in epilepsy (Waldbaum and Patel 2010). Both excessive free radical generation and a deficient antioxidant system are associated with an increased risk of seizure recurrence (Jesberger and Richardson 1991; Kürekçi et al. 1995). Human and animal studies have demonstrated that antioxidant supplementation prevented the progressive deterioration of epilepsy (Gupta et al. 2004; Sumanont et al. 2006; Wu et al. 2009). Hence, antioxidant therapy is beneficial for epileptic patients according to the brain oxidative status.

In this review, we focus on the improvements by antioxidant in the mitochondrial dysfunction and on the evaluation of prognosis by the detection of oxidative status in epilepsy.

Mitochondrial dysfunction and oxidative status in epilepsy

Mitochondrial dysfunction has been identified as a potential cause of epileptic seizure. Myoclonus epilepsy is the most

S.-J. Chang (✉) · B.-C. Yu
Department of Life Sciences, College of Bioscience and Biotechnology, National Cheng Kung University, No.1, University Road, Tainan 701 Taiwan, Republic of China
e-mail: sjchang@mail.ncku.edu.tw

well known mitochondrial disorder with an epileptic phenotype. An A to G transition mutation (A8344G mutation) at nucleotide pair 8344 in human mitochondrial DNA (mtDNA) has been identified as the cause of myoclonus epilepsy. The mutation alters the TψC loop of the $tRNA^{Lys}$ gene and creates a CviJI restriction site which affects the biosynthesis of mitochondrial oxidative phosphorylation protein (Shoffner et al. 1990; Zeviani et al. 1993). In addition, Wu et al. (2010) indicated that the mtDNA mutation results in not only excessive production of reactive oxygen species (ROS) but also a deficient antioxidant system in cultured cells harboring the A8344G mutation of mtDNA. Thus, oxidative stress is involved in the mtDNA mutation-induced epilepsy. Kudin et al. (2009) also showed a list of mitochondrial DNA mutation associated with epileptic phenotypes. The majority of these mutations are located in the mitochondrial tRNA genes and nuclear genes that affect the mitochondrial respiratory chain or adenosine triphosphate (ATP) synthesis. The severity of genetic mitochondrial dysfunction increases with time, eventually leading to intracellular calcium dyshomeostasis and results in neuron excitotoxicity and neuronal loss (Wojda et al. 2008).

Oxidative stress is the initiator in the pathogenesis of epilepsy. The oxidative stress-induced impaired mitochondrial respiratory chain causes excess generation of free radicals and the deficient antioxidant system (SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase;GR, glutathione reductase; GSH/GSSG, glutathione/glutathione disulfide), resulting in a continuation of a vicious cycle and progressive cell death in the epileptic area of the brain (Frantseva et al. 2000; Milatovic et al. 2002; Peternel et al. 2009; Malinska et al. 2010). Chuang et al. (2009) demonstrated that NO^-, O_2^-, and peroxynitrite depressed the neuronal mitochondrial respiratory enzyme complex I activity in a time-dependent manner, induced cytosol-bound release of cytochrome c from the mitochondria, accompanied with activation of caspase 3 that leads to apoptotic cell death in the hippocampal CA3 subfield. The increased generation of ROS has been observed in status epilepticus induced by kainite or pilocarpine (PC) (Frantseva et al. 2000; Liang et al. 2000; Tsai et al. 2010) and in the low magnesium model of a seizure-like event (Schuchmann et al. 2002; Kovács et al. 2002). Liang and Patel (2006) have shown that hippocampus redox status was reduced following the kainate-induced seizure in a time-dependent manner. Using PC-induced different epileptic seizure, our previous study found that PC-treated with prolong seizure had excessive ROS production and decreased SOD, GPx and CAT activities compared to the control group. PC-treated with repeated seizure had lower activities of GPx and GSH compared to the control group (Tsai et al. 2010). Medication and brain surgery have been suggested for modulating the progression of epilepsy for most patients. Epileptic patients showed a correlation between advanced oxidation protein products and the developing time of the illness (López et al. 2007). In addition, some antiepileptic drugs, such as carbamazepine and phenobarbital decrease the antioxidant system and seriously increase membrane lipid peroxidation in neurons, leading to an increase in seizure recurrence (Hamed and Abdellah 2004; Aycicek and Iscan 2007). Thus, the antioxidant supply is considerable as an additional therapy with antiepileptic drugs for preventing the deterioration of epilepsy and seizure recurrence.

Hurd et al. (1996) indicated that N-acetylcysteine (NAC) is a sulfhydryl antioxidant that increases cellular glutathione and the activity levels of several antioxidant enzymes. NAC has additional actions that contribute to its efficacy in preventing or decreasing oxidative damage in progressive myoclonus epilepsy. Gupta et al. (2001) indicated that the brain malondialdehyde (MDA) levels were significantly elevated in the $FeCl_3$-induced posttraumatic seizures model of rats, while resveratrol delayed the onset of the appearance of epileptiform EEG changes by reducing the brain MDA level. Other antioxidants such as melatonin and curcumin prevent the oxidative stress-induced mitochondrial dysfunction, neuronal damage and increase the antioxidant activity in epileptic human and experimental animals (Gupta et al. 2004; Wu et al. 2009; Sumanont et al. 2006). Our study showed that the methioine-induced oxidative stress in the brain of chicks was decreased by the supplementation with vitamin E (Lin et al. 2005). In addition, we also collected and analyzed the indicators of oxidative stress (ROS, homocystein, MDA), and antioxidant activities (SOD, CAT, GPx, GR and GSH/GSSG) in the hippocampus of postoperative epileptic patients for predicting the outcome of epileptic surgery (Chang et al. 2005a, b). Our results suggested that the lower oxidative stress (ROS and MDA) and high antioxidant activity (SOD) are the predictors for a better outcome of epileptic surgery. Hence, antioxidant therapy plays a crucial role in the prevention of oxidative damage in mitochondrial dysfunction and recurrence of epileptic seizure. In addition, the detection of brain oxidative stress is essential for evaluating the prognosis of epileptic patients.

Brief overview of contribution to this minireview series

This review summarized the findings that focus on the mitochondria dysfunction and oxidative status in epilepsy. Mitochondrial dysfunction has been identified as a potential cause of epileptic seizure and therapy-resistant forms of severe epilepsy. Experimental and human studies have suggested that excessive free radical generation and a deficient antioxidant system are directly or indirectly implicated as taking part in the pathogenesis of epilepsy, resulting in seizure recurrence and resistance to treatment

with antiepileptic drugs (Hamed and Abdellah 2004). Antiepileptic drugs alter the neuronal oxidative status and increase membrane lipid peroxidation, leading to the increased risk of seizure recurrence (Hamed and Abdellah 2004). Epileptic patients and experimental animals with the antioxidant supplementations, such as vitamin E, melatonin and resveratrol, improve the oxidative damage in mitochondrial dysfunction. Hence, the antioxidant supply is beneficial for the prevention of mitochondrial dysfunction and recurrence of epilepsy. In addition, the detection of brain oxidative status is important for predicting the prognosis of patients with medication or surgery.

References

Aycicek A, Iscan A (2007) Eur Neurol 57:65–69

Chang SJ, Lee YC, Chang CN (2005a) The 26th International Epilepsy Congress, Paris, France. Epilepsia 46(suppl6):317–318

Chang CN, Chang SL, Lee YC, Hsue JC (2005b) The 26th International Epilepsy Congress, Paris, France. Epilepsia 46(suppl6):158–159

Chuang YC, Chen SD, Liou CW, Lin TK, Chang WN, Chan SH, Chang AY (2009) Epilepsia 50:731–746

Fillano JJ, Goldenthal MJ, Rhodes CH, Marín-García J (2002) J Child Neurol 17:435–439

Floyd RA (1990) FASEB J 4:2587–2597

Frantseva MV, Perez Velazquez JL, Tsoraklidis G, Mendonca AJ, Adamchik Y, Mills LR, Carlen PL, Burnham MW (2000) Neuroscience 97:431–435

Gupta YK, Chaudhary G, Sinha K, Srivastava AK (2001) Methods Find Exp Clin Pharmacol 23:241–244

Gupta M, Gupta YK, Agarwal S, Aneja S, Kalaivani M, Kohli K (2004) Epilepsia 45:1636–1639

Hamed SA, Abdellah MM (2004) J Pharmacol Sci 96:349–359

Hurd RW, Wilder BJ, Helveston WR, Uthman BM (1996) Neurology 47:1264–1268

Jesberger JA, Richardson JS (1991) Int J Neurosci 57:1–17

Kovács R, Schuchmann S, Gabriel S, Kann O, Kardos J, Heinemann U (2002) J Neurophysiol 88:2909–2918

Kürekçi AE, Alpay F, Tanindi S, Gökçay E, Ozcan O, Akin R, Işimer A, Sayal A (1995) Epilepsia 36:600–604

Kudin AP, Zsurka G, Elger CE, Kunz WS (2009) Exp Neurol 218:326–332

Liang LP, Patel M (2006) Free Radic Biol Med 40:316–322

Liang LP, Ho YS, Patel M (2000) Neuroscience 101:563–570

Lin YF, Tsai HL, Lee YC, Chang SJ (2005) J Nutr 135:2457–2461

López J, González ME, Lorigados L, Morales L, Riverón G, Bauzá JY (2007) Clin Biochem 40:292–298

Malinska D, Kulawiak B, Kudin AP, Kovacs R, Huchzermeyer C, Kann O, Szewczyk A, Kunz WS (2010) Biochim Biophys Acta 1797:1163–1170

Milatovic D, Gupta RC, Dettbarn WD (2002) Brain Res 957:330–337

Peternel S, Pilipovic K, Zupan G (2009) Prog Neuro-Psychopharmacol Biol Psychiatry 33:456–462

Schuchmann S, Albrecht D, Heinemann U, von Bohlen und Halbach O (2002) Neurobiol Dis 11:96–105

Shoffner JM, Lott MT, Lezza AM, Seibel P, Ballinger SW, Wallace DC (1990) Cell 61:931–937

Sumanont Y, Murakami Y, Tohda M, Vajragupta O, Watanabe H, Matsumoto K (2006) Life Sci 78:1884–1891

Treiman DM (1995) J Clin Neurophysiol 12:343–362

Tsai HL, Chang CN, Chang SJ (2010) Brain Dev 32:25–31

Waldbaum S, Patel M (2010) Epilepsy Res 88:23–45

Wojda U, Salinska E, Kuznicki J (2008) IUBMB Life 60:575–590

Wu Z, Xu Q, Zhang L, Kong D, Ma R, Wang L (2009) Neurochem Res 34:1393–1400

Wu SB, Ma YS, Wu YT, Chen YC, Wei YH (2010) Mol Neurobiol 41:256–266

Zeviani M, Muntoni F, Savarese N, Serra G, Tiranti V, Carrara F, Mariotti C, DiDonato S (1993) Eur J Hum Genet 1:80–87