REVIEW ARTICLE

POST TRAUMATIC EPILEPSY : A REVIEW OF SCIENTIFIC EVIDENCE

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Abstract : Post traumatic epilepsy is the development of recurrent seizures following head trauma and has a high clinical relevance. Several risk factors including some genetic factors increase the susceptibility of post traumatic epilepsy. The precise mechanisms of epileptogenesis in post-traumatic epilepsy are still poorly understood. Many structural, physiologic and biochemical changes in the brain may account for epileptogenesis. The reactive oxygen species (ROS), especially $\cdot OH$ and excitotoxicity are primarily involved. Antioxidants, like tocopherol, antiepileptic drug zonisamide, condensed tannins, melatonin, adenosine, trans-resveratrol, and some other agents have been proposed to prevent epileptogenic focus formation. The review also discusses various aspects of post traumatic epilepsy, mechanisms of epileptogenesis, and clinical implications.

Key words : epilepsy   trauma   posttraumatic
            seizure   oxidative stress

INTRODUCTION

Epilepsy is one of the most common neurological disorders affecting nearly 0.5 percent of the world population (1). Traumatic brain injury, which is a major cause of morbidity and mortality world wide, has been reported to be one of the major risk factor for epileptic seizures. Post-traumatic epilepsy occurs following severe head injury and is characterized by recurrent epileptic seizures due to brain damage (2). It complicates the management of the head injuries patients by increasing the intracranial pressure and altering the level of unconsciousness. Among the long term complications of traumatic brain injury, post traumatic epilepsy remains one of the most troubling and in the long term. PTE can have a negative effect on patients functioning. The more severe the injury the more the likelihood

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that posttraumatic seizure will occur.

Epidemiology of PTE

The reported incidence of post-traumatic epilepsy varies from 5% for head injury in general to 25 to 30% for severe closed head injury with hematoma, and up to 51% in survivors of military penetrating head injury (3). In the United States, the annual incidence of head injury is about 200/100,000 population, and men are more often affected than women. All studies show a peak incidence of brain injury in young adults 15 to 24 years of age. Next most affected are young children and the elderly. About 10% of the brain injuries are fatal. Early seizures occur in 2–5% of all patients with head injuries, being more common in children than adults (4). The frequency of early seizures after severe head injuries is even higher 10–15% for adults and 30–35% for children. Early seizures are followed by late seizures in 25–35% of adults (5). Late seizures, is a major residual complication and an event that is difficult to predict. Annegers calculated the relative risk of late post traumatic epilepsy and found it to be 12.7% in the first year, 4.4% during the next four years, and 1.4% thereafter in the follow up (6).

Nature and Course of PTE

Depending on the time interval following head trauma the epilepsy can be classified into three major types, i.e. (i) impact seizures, (ii) early seizures and (iii) late seizures. Impact seizures are sometimes considered as subgroup of early seizures and occur immediately after or within 24 hours after injury.

Early seizures are acute symptomatic seizures and appear within one week after injury. Late seizures might have a chronic course and occur after the recovery from the acute effects of the injury. Late seizures may be single or multiple. Only recurrent late seizures are referred as post-traumatic epilepsy (7). Although trauma accounts for only about 5% of all epilepsy cases, this is still a problem of considerable magnitude. More importantly because it is a potentially preventable cause of epilepsy.

What are the risk factors for post-traumatic epilepsy ?

Several risk factors complicate the posttraumatic epilepsy, for example neural location, agent of injury, severity, missile injuries, loss of consciousness, intracerebral hemorrhage, diffuse cerebral contusions, presence of focal neurological deficits and prolonged (> 3days) post traumatic amnesia.

Do Genetic factors affect susceptibility to post traumatic epilepsy ?

Genetic susceptibility may also increase the risk for epilepsy in patients of head injury. Some investigators have reported that a family history of epilepsy is more common in subjects in whom epilepsy develops following head injury than those in whom it does not (8, 9). Specific brain genetic factors that cause a liability to develop post traumatic epilepsy remains unknown. However, a possible genetic predisposition has been observed with detection of decreased levels of serum haptoglobin in familial epilepsy (10).

Haptoglobins are acute phase glycoprotiens in the alpha I -globulin fraction of serum that forms stable complexes with hemoglobin. Sequestration of free hemoglobin with haptoglobin is one of the mechanisms against oxidative stress. Impairment in the synthesis of these glycoproteins may identify an inherent susceptibility to development of epilepsy after head trauma.

What are the mechanisms underlying post-traumatic epilepsy ?

The precise mechanisms of epileptogenesis in post-traumatic epilepsy are still poorly understood. However many structural, physiologic and biochemical changes take place in the brain following head trauma which may account for epileptogenesis. Early posttraumatic seizures are thought to be due to mechanical damage to the neurons, caused by extravasated blood. Head trauma initiates a sequence of responses that includes altered blood flow and vasoregulation, disruption of blood brain barrier, increase in intracranial pressure, focal or diffuse ischemic hemorrhage, inflammation, necrosis, and disruption of fiber tract and blood vessels (11). The reports have also suggested that iron (hemorrhage) induced neuronal lipid peroxidation and excitotoxicity could be the probable mechanisms, involved in the post traumatic epilepsy. Red blood cells which lyse into hemin and iron may lead to epileptogenesis by affecting synaptic transmission.in the ferric chloride model of epilepsy in rats. The epileptogenic action of ferric chloride is due to free radicals generation leading to cell death (12).
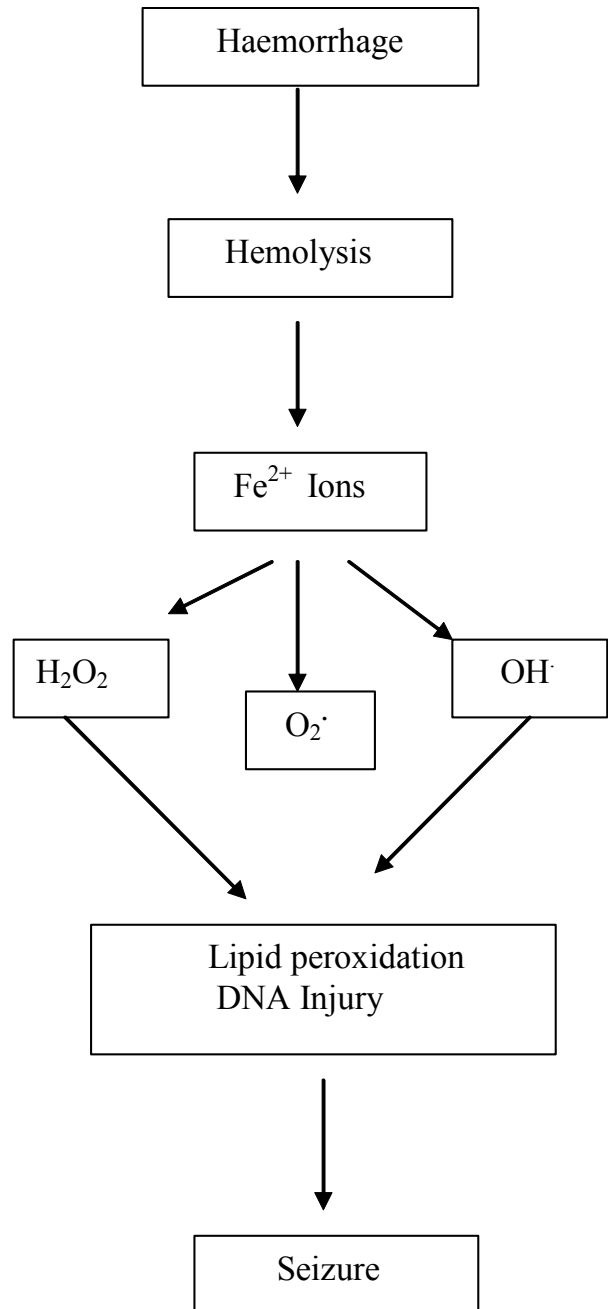

Fig. 1 : Free radical mechanism underlying posttraumatic epilepsy.

Excitotoxicity as a mechanism

Both clinical and experimental studies

have demonstrated immediate and marked increased in the extracellular level of excitatory amino acids following brain injury (13). In rats, seizures occurring immediately or shortly after traumatic injury are accompanied by increased glutamate and aspartate levels, postulated to be responsible for epileptogenesis. Release of excitatory amino acids may also be responsible for the large calcium - dependent increase in extra cellular potassium seen after experimental brain injury. Increased extra cellular potassium further increases neuronal excitability and may contribute to epileptogenesis (14).

Oxidative stress mechanism

It has been proposed that reactive oxygen species (ROS), especially ·OH, are involved in the mechanism responsible for PTE. In 1978, Willmore et al reported an animal model of post traumatic epilepsy. They showed that epileptic seizure discharge in electrocorticogram (ECOG) was induced 15 minutes after a single injection of $FeCl_3$ solution into the rat cerebral cortex (15). In 1979, it was shown that convulsive seizures are induced by intracortical hemoglobin (Hb) injection with a few days latency (16). Willmore and Rubin suggested that after intracranial hemorrhage, red blood cells break down and release iron ions from hemoglobin, which then generate ROS in brain tissue by iron or Hb mediated reaction. These free radicals react with methylene group, adjacent to double bond of polyunsaturated fatty acids and lipids, causing hydrogen abstractions and subsequent propagation of peroxidation reaction.
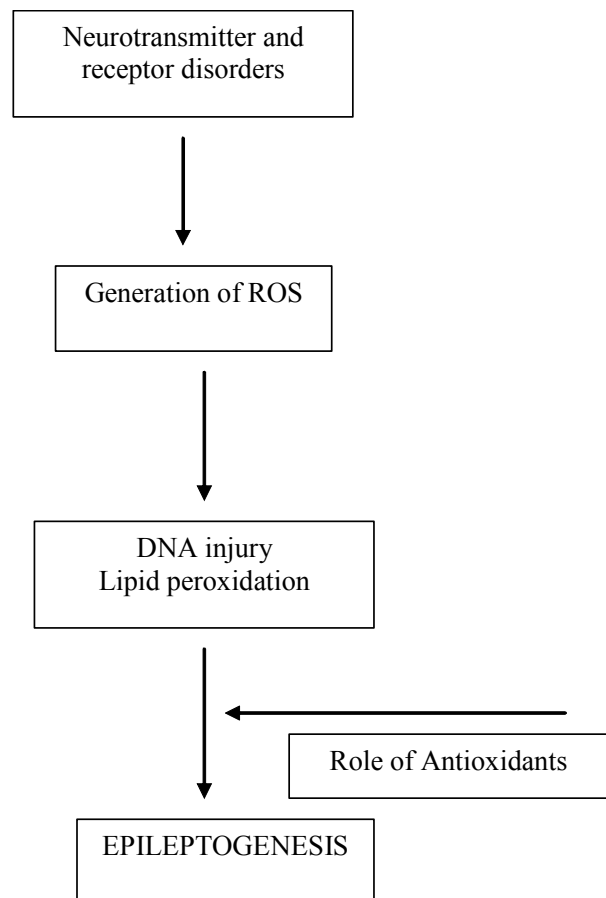

Fig. 2 : Mechanism of Epileptogenesis.

The non enzymatic initiation and propagation of lipid peroxidation causes disruption of membranes and subcellular organelles. Injury to membranes impairs Na^+-K^+ ATPase activity. As Na^+ K^+ ATPase in neuronal membranes maintains ionic gradients of neuron, a decrease in its activity decreases the convulsive threshold. Injury to the membrane also leads to neurotransmitter disorders. The release of aspartic acid, an excitatory neurotransmitter increases, and the release of GABA, which is an inhibitory neurotransmitter decreases (17). Apart from this ·OH accelerates the

production of methylguanidine a known endogenous convulsant from creatinine (18). These findings suggest that oxidation by ROS specially hydroxyl radicals is involved in the mechanism involved in posttraumatic epilepsy.

What are the conventional treatments and prophylaxis for posttraumatic epilepsy ?

Evidence demonstrate that following head injury early seizure activity may increase the associated risk of PTE, and the administration of anticonvulsant drugs immediately after head injury is commonly implemented as prophylactic measure. For anticonvulsant prophylaxis, phenytoin is considered as the drug of choice because of its demonstrated efficacy and the availability of a formulation for intravenous administration. The patients with head injuries are often medically unstable and especially vulnerable to such physiologic consequences of seizures such as metabolic acidosis, sudden increase in cerebral blood flow and intracranial pressure. For these reasons, phenytoin is administered soon after brain injury in an effort to prevent seizure activity and to minimize complications from seizures occurring during acute management (19).

Standard treatment for patients with moderate to severe head injuries is i.v. phenytoin or fosphenytoin in a dose equivalent to 20 mg/kg. Carbamazepine and valproate are also useful in treating the early seizures. A large number of studies have shown that the early use of anticonvulsants is effective in preventing early PTE . However other studies failed to demonstrate the efficacy of anticonvulsants in preventing early seizures (20). In experimental model of post-traumatic epilepsy, though phenytoin inhibited the occurrence of epileptiform EEG discharges, could not affect the biochemical mechanism of PTE i.e. lipid peroxidation. Thus an uninhibited lipid peroxidation might be responsible for ineffectiveness of phenytoin in patients of post traumatic epilepsy. However the suppression of EEG discharges by phenytoin could be attributed to its neuronal membrane stabilizing effect (21).

Several newer anticonvulsants have also been tried in PTE. These include gabapentin, lamotrigine, topiramate and vigabatrin, and most recently zonisamide (22). Vigabatrin has also been shown to induce some protective effects in an experimental model of PTE (23).

Need for effective and alternative pharmacological agents

The current anticonvulsant drugs are able to prevent PTE only to a limited extent, thus there is a need for alternative treatment strategies. This is particularly important because the currently used anticonvulsants possess a high potential for side effects, which can be complicated further by the presence of brain injury. Preventive measures, however appear to be ineffective at preventing the development of PTE, and may therefore unnecessarily expose brain injured patient to anticonvulsant drugs. Moreover, the anticonvulsant agents administered are not effective against cognitive impairment after posttraumatic epilepsy and may themselves cause deleterious effects on cognition.

Since posttraumatic epilepsy involves ROS in its pathogenesis, treatment designed to prevent peroxidation may be more effective in epilepsy prophylaxis, than the administration of anticonvulsant drugs that prevent convulsive seizures, while bio-chemical brain injury continues. Anti-epileptic drugs with antioxidant properties may be one of the promising agents as they have the potential to alter the basic pathology of the disease. Many antioxidants have been examined in experimental models of PTE (22).

Can natural antioxidants prevent post traumatic epilepsy ?

Levy et al in 1990 have reported that tocopherol (Vit. E) administration significantly reduced the onset of EEG seizures induced by intracerebral $FeCl_2$ (24). Tocopherol prevented both peroxidation and epilepsy caused by iron injection into hippocampus in rats as did phenobarbital (25, 26). Free radicals scavengers, such as polyethylene glycol (PEG) monomer with SOD or PEG-catalase have also demonstrated beneficial activity in animal models (27). An antiepileptic effect of combination of Vit C, E, and L-ascorbic acid has also been observed (28). TJ 960, a Japanese herbal medicine has been found to have scavenging activity for free radicals generated within an iron induced epileptogenic region of rat brain (29). Recently, zonisamide has been reported to exert free radical scavenging actions by scavenging NO and ·OH ions, along with stabilizing the neuronal membranes.

Adenosine :

Adenosine which is an endogenous neuromodulator, has been found to be an effective antiepileptic agent in different animals models (30). Adenosine has also been shown to have free radical scavenging activity and neuroprotective actions. Adenosine has been demonstrated to have an anticonvulsant action which is mediated predominantly by the adenosine A1 receptor subtype. When phenobarbitone/carbamazepine were coadministered with adenosine/N6-cyclopentyladenosine (CPA), a specific adenosine A1 receptor agonist, an enhancement in protection against PTZ-induced seizures was observed. The diversity of anticonvulsant mechanism of carbamazepine/phenobarbitone and that of adenosinergic agents could be responsible for this effect. (31, 32, 33). Yokoi et observed the scavenging effects of adenosine and 2-chloroadenosine on hydroxyl radicals and also their effect on ferric chloride induced cortical EEG discharge in an experimental model of post traumatic seizures (34).

Melatonin :

The neurohormone melatonin (5-methoxy-N-acetyltryptamine) was first successfully isolated and identified from bovine pineal. Melatonin is released in the blood stream with a circadian rhythm that peaks during the night. Pinealectomy has been shown to produce convulsions (35). On the basis of this it was hypothesized that melatonin or some other substance released has anticonvulsant properties. Melatonin has shown both antiepileptic (36–38) and free radical scavenging activity. Numerous in vitro, in vivo and clinical studies have shown potent antioxidant actions with melatonin (39, 40). As a direct scavenger, melatonin inactivates free radicals by electron

donation. However, its ability to resist oxidative damage seems not exclusively attributable to this process. Pharmacological levels of melatonin have been reported to stimulate the activity of glutathione peroxidase (GSH-Px) in the brain, a major antioxidant defensive mechanism in the central nervous system. Melatonin, crosses the blood brain barrier with ease and enters both neurons and glia. It has been seen that after peripheral administration of melatonin, its brain concentration rises quickly. Another feature that has generated interest to melatonin is its possible neuroprotective actions. Melatonin has been shown to alter the neuronal and behavioral changes inflicted by kainic acid in both in vitro and in vivo studies (41). The antiexcitotoxic action of melatonin has been related to its capability to scavenge free radicals (42). Recently, melatonin has shown in vivo inhibition of lipid peroxidation in intracortical ferric chloride model of post traumatic epilepsy (43).

Transresveratrol :

After the realization of reduced cardiac risk by red wine popularly referred as French paradox, much interest has emerged in resveratrol, which is the active constituent of red wine. Resveratrol (3, 4, 5 tri hydroxy stilbene) is a naturally occurring phytoalexin present in high concentration in skin of grapes and wine (44). It has been shown to have a potent free radical scavenging activity proven in various invitro and in vivo studies. Resveratrol has also shown the protective effects against ferric chloride model of post traumatic epilepsy in rats. Resveratrol (20 and 40 mg/kg ip.) administered 30 min before FeCl3 injection

delayed the onset of the appearance of epileptiform EEG changes. The brain MDA levels were also significantly reduced in the trans-resveratrol-treated animals as compared to the vehicle-treated FeCl3-injected rats. Recently transresveratrol has shown its effectiveness in neurological disorders including stroke and epilepsy, wherein it was reported that transresveratrol is protective against middle cerebral artery occlusion model of stroke. Protective effect of transresveratrol against kainic acid induced seizures and oxidative stress has also been reported. Pretreatment (5 min) of single dose of trans-resveratrol (40 mg/kg i.p.) could not inhibit the convulsions though the latency was significantly increased. When multiple doses of trans-resveratrol were injected in two-dose schedules in different animals (20 and 40 mg/kg ip, 5 min prior and repeated 30 and 90 min after kainic acid), there was significant reduction in incidence of convulsions in both treatment schedules. The brain MDA levels were found to be significantly attenuated in the trans-resveratrol-treated groups (multiple doses of 20 and 40 mg/kg) as compared to the kainic acid alone. The protective effect of trans-resveratrol against kainic acid-induced convulsions and the attenuation of raised MDA level suggest the potential use of antioxidants in the prevention of posttraumatic epilepsy (45, 46, 47,48).

Calcium channel blockers

Experimental studies have shown that the total brain tissue calcium level is increased in injury areas, a sustained increase in intracellular calcium levels initiates a series of damaging events (49). The calcium antagonist nimodipine, a

strongly lipophilic agent has been tried with limited benefit (50).

Excitatory Amino Acid Antagonists

Excitatory amino acids have been shown to play a major role in neuronal damage after experimental brain trauma (51). Both clinical and experimental studies demonstrated an immediate and marked increase in the extra cellular level of excitatory amino acids following injury (52). Various glutamate antagonists, acting at different sites have been developed, of which 4 were carried forward into phase III trials. These are eliprodil, selfotel, D-3 (2- carooxy-piperazine-4-yl) propenyl -1 phosphonic acid (D-) and aptigonel (53).

Miscellaneous   agents :

Condensed tannins, fermented papaya, Uyaku, Gastrodia elata, Guilingji are some of the herbal plant products exerting significant antioxidant and free radical scavenging effects. These agents may be potential agents for prevention of post traumatic epilepsy or attenuation of epileptic seizures (22).

Conclusions :

The conventional antiepileptic drugs have not been fully effective in the control and prevention of posttraumatic epilepsy. Further their adverse side effects limit their use for prophylaxis. The new pharmacotherapeutic options discussed above may represent future pharmacological interventions, aimed at limiting damage caused by reactions underlying epileptogenesis (54). Some of them may be employed in clinical practice, but up to date there is no controlled study in human beings. Moreover, partial effectiveness of anticonvulsant drugs, refractoriness of epilepsies and adverse effects associated with the use of conventional antiepileptic drugs, advocate the necessity of newer antiepileptic drugs with antioxidant and neuroprotective properties, to combat the oxidative stress implicated in posttarumatic epilepsy.

REFERENCES

1. Sander JW AS Shrovan SO: Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry* 1996; 61: 433–443.

2. Yokoi I, Toma J, Liu J et at. Adenosine scavenged hydroxy radicals and prevented post traumatic epilepsy. *Free Radic Biol Med* 1995; 19: 473–479.

3. Caveness WF, Walker AE, Ascroft PB. Incidence of post traumatic epilepsy in Korean veterans as compared with those from World war 1 and world war II. *J Neurosurg* 1962; 19: 122–129.

4. Frey LC. Epidemiology of posttraumatic epilepsy: a critical review. *Epilepsia* 2003; 44: 11–7.

5. De Santis A, Sganzerela E, Spagnoli D, Bello L, Tiberio F. Risk factors for late post traumatic epilepsy. *Acta Neurochir* 1992; 55: 64–67.

6. Annegers JF, Grabow JD, Groover RV, Laws ER, EJeveback LR, Kurland LT. Seizure after head trauma a population study. *Neurology* 1980; 30: 683–689.

7. Kollevold T. Immediate and early seizures after head injuries. *J Oslo City Hospital* 1976; 26: 99–114.

8. Caveness WF. Onset and cessation of fits following craniocerebral trauma. *J Neurosurg* 1963; 10: 570–582.

9. Schaumann BA, Annegers JF, Johnson SB, Moore KJ, Lubozynski MF, Salinsky MC. Family history of seizures in post traumatic and alcohal associated seizure disorders. *Epilepsia* 1994; 35: 48–52.

10. Panter S S, Sadrzadesh SM, Hallaway PE, Haines JL, Anderson VE, Eaton JW. Hypohaptoglobinemia associated with familial epilepsy. *J Exp Med* 1985; 161: 748–754.

11. Gannarelli TA, Thiabault LE, Adams JH, Graham DI, Thompson CJ, Marcinin RP. Diffuse axonal injury and traumatic coma in the primate. *Ann Neurol* 1982; 12: 564–574.

12. Bullock R. Zauner A Woodward JJ Myseros J, Choi SC, Ward JD, Marmarou A, Young HF. Factor affecting excitatory aminoacid release following severe human head injury. *J Neurosurg* 1998; 89: 507–518.

13. Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increase in extracellular potassium and indiscriminate release of glumate following concussive brain injury. *J Neurosurg* 1990; 73: 889–900.

14. Nilson P, Ronne- Engstrom E, Flink R Ungerstedt U, Carlson H, Hillered L. Epileptic seizure activity in the acute phase following cortical impact trauma in rat. *Brain Res* 1994; 637: 227–232.

15. Willmore LJ, Sypert GW, Munson JB. Recurrent seizures induced by cortical iron injection; A model of post traumatic epilepsy. *Ann Neurol* 1978; 4: 329–336.

16. Rosen AD. Frumin NY. Focal epileptogenesis after intracortical haemoglobin injection. *Exp Neurol* 1979; 66: 277–284.

17. Zhang, ZH, Zoo QH, Wu XR. Effect of lipid peroxidation on GABA uptake and release in iron induced seizures. *Chinese Med J* 1989; 102: 24–27.

18. Matsumoto M, Koabyoshi K, Kishikawa H, Mori A. A convulsive activity of methyl guanidine in cats and rabbits. *IRCS Med Sci* 1976; 4: 65.

19. Pagni CA, Zenga F. Posttraumatic epilepsy with special emphasis on prophylaxis and prevention. *Acta Neurochir Suppl* 2005; 93: 27–34.

20. Young B, Rapp RP, Normn JA, Haack D, Tibbs PA, Bean JR. Failure of prophylactically administered phenytoin to prevent the late post traumatic seizures. *J Neurosurgery* 1983; 58: 236–241.

21. Willmore LJ, Tiggs WJ. Effect of phenytoin and corticosteroids on seizures and lipid peroxidation in experimental post traumatic epilepsy. *J Neurosurg* 1984; 60: 467–472.

22. Mori A, Yokoi I, Noda Y, Willmore LJ. Natural antioxidants may prevent posttraumatic epilepsy: a proposal based on experimental animal studies. *Acta Med Okayama* 2004 June; 58(3): 111–118.

23. Shin C, Rigsbee LC, Mc Namara JO. Antiseizure and antiepileptogenic effect of gamma- vinyl gamma- aminobutyric acid in amygdaloid kindling. *Brain Res* 1986; 398: 310–314.

24. Levy SL, Burnham M, Hwang PA. An evaluation of the anticonvulsant effects of vitamin E. *Epilepsy Res* 1990; 6: 12–17.

25. Demopoulos HB, Flamm ES, Seligman ML, Jorgensen E, Ransohoff J. Antioxidant effects of barbiturates in model membranes undergoing free radical damage. *Acta Neurol Scand* 1977; 64: 152–53.

26. D'Ambrosio R, Perruca E. Epilepsy after head injury. *Curr Opin Neurol* 2004; 17(6): 731–735.

27. Muizelaar JP, Marmarou A. Young HF, Choi SC, Wolf A, Schneider RL, Kontos HA. Improving the out come of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase. a phase II trial. *J Neurosurg* 1993; 78(3): 375–382.

28. Yokoi I, Kabuto H, Yamamoto, M, Mori A. Effect of ferric iron and active oxygen scavenger on monoamine release in the striatum of the rat. *Jpn J Psychiatry Neurol* 1990; 44: 440–441.

29. Komatsu M, Hiramatsu M, Yokoyama H, Willmore LJ. Effect of TJ- 960 (a Japanese herbal medicine) on free radical changes within an iron induced focal epileptogenic region in rat brain measured by in vivo L band electron spin resonance. *Neurosci Lett* 1996; 205: 189–192.

30. Malhotra J, Gupta YK. Effect of adenosine receptor modulation on pentylenetetrazole-induced seizures in rats. *Br J Pharmacol* 1997; 120: 282–288.

31. Srivastava AK, Malhotra J, Gupta YK. Adenosine receptors do not mediate the melatonin protection against pentylenetetrazole induced seizures in rats. *Neurobiology* 2001; 9(3–4): 147–152.

32. Malhotra J, Gupta YK. Effect of adenosinergic modulation on the anticonvulsant effect of phenobarbitone and carbamazepine. *Methods Find Exp Clin Pharmacol* 1999; 21(2): 79–83.

33. Gupta YK, Malhotra J. Adenosinergic system as an endogenous anticonvulsant mechanism. *Indian J Physiol Pharmacol* 199; 41: 329–343.

34. Yokoi I, Toma J, Liu J, Kabuto H, Mori A. Adenosines scavenged hydroxyl radicals and prevented posttraumatic epilepsy. *Free Radic Biol Med* 1995; 19(4): 473–479.

35. Philo R and Reiter RJ. Characterization of pinealectomy-induced convulsions in the Mongolian gerbil (Merioner-unguicalabes). *Epilepsia* 1978; 19: 485–492.

36. Gupta YK, Gupta M, Kohli K. Neuroprotective role of melatonin in oxidative stress vulnerable brain. *Indian J Physiol Pharmacol* 2003; 47(4): 373–386.

37. Gupta YK, Gupta M, Chaudhary G, Kohli K. Modulation of antiepileptic effect of phenytoin and carbamazepine by melatonin in mice. *Methods Find Exp Clin Pharmacol* 2004; 26: 99–102.

38. Srivastava AK, Gupta SK, Jain S, Gupta YK. Effect of melatonin and phenytoin on an intracortical ferric chloride model of posttraumatic seizures in rats. *Methods Find Exp Clin Pharmacol* 2002; 24: 145–149.

39. Gupta M, Gupta YK, Agarwal S, Aneja S, Kalaivani M, Kohli K. Effects of add-on melatonin administration on antioxidant enzymes in children with epilepsy taking carbamazepine monotherapy: a randomized, double-blind, placebo-controlled trial. *Epilepsia* 2004; 45: 1636–1639.

40. Gupta M, Gupta YK, Agarwal S, Aneja S, Kohli K. A randomized, double-blind, placebo controlled trial of melatonin add-on therapy in epileptic children on valproate monotherapy: effect on glutathione peroxidase and glutathione reductase enzymes. *Br J Clin Pharmacol* 2004; 58: 542–547.

41. Reiter RJ, Tang L, Garcia JJ, Munoz-Hoyos A. Pharmacological actions of melatonin in oxygen radical pathophysiology. *Life Sci* 1997; 60: 2255–2271.

42. Giusti P, Lipartiti M, Gusella M, Floreani M, Manev H. In vitro and in vivo protective effects of melatonin against glutamate oxidative stress and neurotoxicity. *Ann NY Acad Sci* 1997; 825: 79–84.

43. Srivastava A.K, Gupta Y.K. Role of melatonin in experimental model of posttraumatic epilepsy in rats. *Indian J Pharmacol* 2000; 32: 76.

44. Fremont L. Biological effects of resveratrol. *Life Sci* 1999; 66: 663–673.

45. Virgili M., Contestabile A. Partial neuroprotection of in vivo excitotoxic brain damage by chronic administration of the red wine antioxidant agents, trans resveratrol in rats. *Neurosci Lett* 2000, 281: 123–126.

46. Sinha K, Chaudhary G and Gupta YK Protective effect of resveratrol against oxidative stress middle cerebral artery occlusion model of stroke in rats. *Life Sci* 2002; 71: 655–665.

47. Gupta YK, Chaudhary G, Sinha K, Srivastava AK. Protective effect of resveratrol against intracortical FeCl3-induced model of posttraumatic seizures in rats. *Methods Find Exp Clin Pharmacol* 2001; 23: 241–244.

48. Gupta YK, Briyal S, Chaudhary G. Protective effect of trans-resveratrol against kainic acid-induced seizures and oxidative stress in rats. *Pharmacol Biochem Behav* 2002; 71: 245–249.

49. Fineman I, Hovda DA, Smith M, Yoshino A, Becker DP. Concussive brain injury is associated with prolonged accumulation of calcium: a 45 Ca autoradiographic study. *Brain Res* 1993; 624: 94–102.

50. Robinson MJ, Teasdale OM. Calcium antagonists in the management of subarrachnoid haemorrhage. *Cerebrovascular Brain Metabolism Review* 1990; 2: 205–226.

51. Benveniste H. The excitotoxic hypothesis in relation to cerebral ischemia. *Cerebrovascular Brain Metabolism Review* 1991; 3: 213–245.

52. Faden AI, Demediuk P, Panter SS, Vink R. The role of excitatory amino acid on NMDA receptors in traumatic brain injury. *Science* 1989; 244: 798–800.

53. Bullock R. Zauner A, Woodward JJ, Myseros J, Choi SC, Ward JD, Marmarou A, Young HF. Factor affecting excitatory aminoacid release following severe human head injury. *J Neurosurg* 1998; 89: 507–518.

54. Bernardo LS. Prevention of epilepsy after head trauma: do we need new drugs or a new approach? *Epilepsia* 2003; 44: 27–33.