

Status epilepticus: Using antioxidant agents as alternative therapies (Review)

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Abstract. The epileptic state, or status epilepticus (SE), is the most serious situation manifested by individuals with epilepsy, and SE events can lead to neuronal damage. An understanding of the molecular, biochemical and physiopathological mechanisms involved in this type of neurological disease will enable the identification of specific central targets, through which novel agents may act and be useful as SE therapies. Currently, studies have focused on the association between oxidative stress and SE, the most severe epileptic condition. A number of these studies have suggested the use of antioxidant compounds as alternative therapies or adjuvant treatments for the epileptic state.

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1. Overview of status epilepticus (SE)

Epilepsy generalities. Epilepsy is a group of different types of disorders that share an abnormally increased tendency to cause convulsive seizures (1). Epilepsy is a chronic neurological disorder characterized by abnormal organization of neuronal electrical activity leading to alterations in a neuronal population, which manifests in seizures, behavioral changes or impaired neuronal activity (1-4). The International League Against Epilepsy (ILAE) defines epilepsy as 'a pathological condition because of the presence of two or more recurrent seizures over a period longer than 24 h unprovoked' (5,6). The incidence of this neurological disease is high in children, stable in adults and increases in the final decades of life (7-11).

Classification of seizures. Based on their etiology, the seizures are classified as follows: i) Idiopathic (primary), associated with heredity; ii) symptomatic (secondary), associated with damage in the brain, including trauma, tumors, bleeding, infection, vascular malformations or metabolic abnormalities; and iii) cryptogenic, seizures with an unknown cause (12-14).

Seizures are focal or generalized, depending on the location of hypersynchronous activity (13-16). Focal seizures are caused by an electrical shock in a particular region of the brain, and can spread to the entire brain. Patients with focal seizures may or may not experience loss of consciousness (simple or complex seizures, respectively) (13-17). Generalized seizures are those in which the altered electrical activity occurs in the two cerebral hemispheres concurrently (3,9). In this type of seizure, a generalized motor impairment with or without autonomic disruption can occur, characterized by an electroencephalogram pattern that is bilateral, synchronous and symmetrical in the hemispheres (14-16).

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Generalities of status epilepticus (SE)

SE is a term used to describe a condition resulting from the failure of the mechanisms associated with seizure termination, or from the initiation of mechanisms that lead to prolonged seizures (18). According to the ILAE in 2015, a recent classification of SE has been proposed based on a clinical diagnosis, and on an investigation and therapeutic approaches for each patient (19). The following operational definition of SE has been proposed: In adults and children >5 years old was defined as ≥ 5 min of continuous seizure or ≥ 2 seizures during which there is incomplete recovery of consciousness (19,20). There are 3 principal factors that determine the risk of mortality and morbidity in SE: i) Etiology of seizure (principally infection in children; trauma, metabolic disruptions or intoxication in adults); ii) age ≥ 60 years old; and iii) duration and development of SE (the majority of patients with SE have no history of seizures, presenting a risk of development of chronic epilepsy) (21-25). Generalized convulsive SE is the most frequently observed type, however, non-convulsive SE is difficult to diagnose as it can be confused with other neurological and psychiatric disorders (26).

Etiology, initiation and propagation of SE. SE results from an alteration of the mechanisms that usually terminate a single and prolonged seizure (27). This alteration may result in constant neuronal excitation, or in failure of the inhibition mechanisms, and it has been suggested that reverberating seizure activity is induced in hippocampal structures and its progress is a sequence of distinct electrophysiological changes (28).

In temporal lobe epilepsy (TLE), an SE episode is generally considered a trigger that initiates epileptogenesis. It has been suggested that seizure initiation is produced by a dysregulation between the excitatory and inhibitory systems, leading to irregular neuronal activity (27). Furthermore, it has been suggested that protein phosphorylation, ion channel opening and closure, release of neurotransmitters and modulators and receptor desensitization occur during the first few seconds of a seizure. In addition, within seconds to minutes the movement of existing receptors to the synaptic membrane occurs. This process alters the activity of inhibitory and excitatory receptors available in the synaptic cleft (29). Furthermore, within minutes to hours, plastic changes in neuropeptide modulators occur, leading to a state of increased excitability (27).

When measured by *in vivo* intracerebral microdialysis, an increase in the levels of glutamate is the beginning of seizure activity in adults with TLE (30-32). The same mechanism may happen during the onset of generalized seizures. Inhibitory neurotransmitters increase in the seizure site and reestablish the balance between excitation and inhibition response (31).

Neurotoxicity and neuroprotection in SE. In SE, neuronal damage is the consequence of sustained N-methyl-D-aspartate receptor stimulation that leads to apoptosis. The cell destruction that is generated in this manner can be reversed if the SE is terminated within the first hour (27). The investigation for acute or chronic therapies should be based on the patient age, gender and genetic predisposition in addition to the SE etiology. In this manner, understanding the spectrum of SE may lead to the identification of neuroprotective treatments that are specific for the developing central nervous system, to diminish the consequences of SE.

Experimental models of SE. SE models are currently used to study the transition from a single SE episode to chronic epilepsy. Experimental models are used that comprise the seizure-initiating mechanisms, and that may facilitate the identification of novel therapeutic strategies for improving the treatment of SE (26). Systemic administration of pilocarpine (a muscarinic receptor agonist), systemic or local administration of kainic acid as a potent glutamate receptor agonist or protocols that electrically stimulate specific brain areas are the animal model most used for the study of SE (33-36).

Systemic or local convulsant chemicals. Systemic or intracerebral injection of pilocarpine induces seizures that originate in limbic regions. This results in structural damage and possible spontaneous recurrent seizures that resemble the etiology of human complex partial seizures, such as between human TLE and the pilocarpine model. Neurotrophins have been demonstrated to be altered in the hippocampus of patients with mesial TLE and in the hippocampus and neocortex of pilocarpine-treated rats (37,38). Furthermore, cognitive and memory deficits are commonly observed in TLE patients and are also present in pilocarpine-injected rats (26,39).

In addition, SE has been induced by intracerebral administration in the amygdala or hippocampal structures. Pilocarpine (intrahippocampal injection of 2.4 mg/ μ l; injected volume 1.0 μ l) induces SE and spontaneous recurrent seizures with low mortality (40).

Kainic acid was one of the first compounds used in the TLE rodent model (systemic or intracerebral administration). It induces neuronal depolarization, and often generalized seizures secondary to partial seizures, commonly begin in the hippocampus. Rodents exhibit remarkable hippocampal sclerosis as a consequence of the neurological damage induced by the seizures. Kainic acid has the advantage of causing injuries that are usually restricted to the hippocampus, in comparison with pilocarpine, which can also result in lesions in neocortical areas (26,39). Lower doses of kainic acid produce low mortality and seizures rates with relatively long latent periods (40).

SE induction by electrical stimulation. Perforant path stimulation (PPS) is widely used to produce continuous seizures in rats and was established by Sloviter in 1991 (41). In this model, anesthetized rats receive discontinuous PPS for one day, which is usually caused by a bipolar stimulating electrode implanted into the angular bundle of the perforant pathway resulting in brain lesions based on the stimulated area, time and intensity of the stimulus (26). The histopathological findings are similar to the kainic acid and pilocarpine model although with less neurodegeneration.

The self-sustained limbic SE model by Lothman *et al* (42) is provoked by continuous and localized electrical stimulation of the hippocampus. In this model, a normalized electrical stimulus is determined by each rat and in adequate conditions (length and side of stimuli or kindling application), the SE persists for hours after ceasing the stimulus. This model induces SE without producing the excitotoxic effect observed in the kainic acid or pilocarpine models.

SE models in immature animals. Clinical studies have noted that a broad range of children have suffered an episode of convulsive SE, and that incidence varies widely globally (13-74%). Thus, animal models of SE are important for investigating whether long-lasting seizures in the developing

brain can result in neuronal disorganization, epileptogenesis or cognitive impairment (22,43,44).

Pentylenetetrazol [a non-competitive γ -aminobutyric acid (GABA) antagonist] also leads to SE in immature animals when administered systemically at postnatal day 10 or 21 (45), similar to the models of kainic acid, lithium-pilocarpine and electrical stimulation protocols but with lower doses. In these models, seizure manifestation increases with age and induces neuronal loss in the hippocampus, amygdala and mediodorsal nucleus of the thalamus of a developing brain. However, the exact mechanisms have not been fully characterized. Nevertheless, young rats do not display the clear neuronal reorganization that is frequently observed in adults (26,46-51).

Recently, Mareš *et al* (52) demonstrated that SE induced by pilocarpine at P12 and P25 produced cognitive damage that increased with age and is correlated with the portion of the injured brain, but not with seizure parameters.

2. Oxidative stress in status epilepticus

Oxidative stress in epilepsy. The study of different illnesses of the nervous system has focused on the imbalance between the oxidant and antioxidant system since 1990 (53,54). The first experimental evidence describing an association between oxidative stress and epilepsy was presented by Armstead *et al* (55) in 1989. The authors demonstrated that the enzyme superoxide dismutase (SOD) was increased in newborn pigs that were subject to seizure with bicuculline (a competitive antagonist of GABA), compared with control pigs and those pretreated with indomethacin. The authors concluded that superoxide reactive species formed by the newborn pig brain during seizures induced by bicuculline and cyclooxygenase metabolism of arachidonic acid may be generating this radical (55). Other reports have demonstrated the relevance of oxidative stress in different experimental models (55-62) and patients (60-68) with epilepsy. Currently, there is particular attention paid to clarifying the role and relevance of oxidative stress in epilepsy, particularly in severe cases, such as SE or other epileptic states.

In the early 2000s, oxidative stress was studied in the epileptic state. The evidence suggested that oxidative stress was important in this neurological pathology. In particular, SE induced by lithium-pilocarpine, pilocarpine, kainic acid, pilocarpine and sleep deprivation or cocaine in animal models (mouse and chick) causes an increase in reactive oxygen species, nitrite levels and lipid peroxidation production. It can also cause a reduction in antioxidant activity of certain enzymes such as nitric oxide synthases (NOS), catalase (CAT), SOD, glutathione peroxidase and glutathione reductase, in addition to reduced glutathione (GSH) levels in the hippocampus, striatum, thalamus, cortex or the whole brain. On the other hand, pretreatment with rosiglitazone (peroxisome proliferator-activated receptor γ agonist), tempol (SOD mimetic), muscimol (GABA agonist), FK506 (immunosuppressive agent) or buspirone (partial agonist of the 5-HT_{1A} receptor) diminished the oxidative status while stimulating the antioxidant system (69-81). The complete information is available upon request.

Different antioxidants for the treatment of SE. Although the use of antioxidants as a therapy against epilepsy has been described since 1970s, extensive studies on the use of

antioxidants for treatment of SE have been reported since 2000. Different studies have demonstrated the use of antioxidants in SE, for the treatment of SE, indicating that pretreatment with vitamin E, vitamin C, coenzyme Q10, N-acetyl-cysteine, 7-nitroindazole, melatonin and various plant extracts or flavonoids reduces lipid oxidation and restores the activities of SOD, CAT and NOS and the levels of GSH in the rat hippocampus, striatum or cortex (82-100). The complete information is available upon request.

3. Physiological and therapeutic relevance

These results will increase the understanding of the close connection between oxidative stress and epileptic state, and provide direct evidence of this association in the experimental models of epilepsy.

Oxidative stress in the epileptic state is a potential condition that requires recognition and management in clinical studies. Therefore, further studies dissecting physiological processes are required in order to establish the most effective and beneficial actions for clinical practice. The comprehension of these processes may lead to novel therapies and treatments that prevent or reduce brain injuries. Furthermore, anti-epileptic drugs are beneficial to the regulation, prevention or inhibition of seizures, although it has been demonstrated that long-term use increases oxidative stress in experimental models and in humans (101). The present study suggests that the use of antioxidants with conventional therapies may provide a beneficial treatment for SE, by diminishing brain oxidative stress induced by these seizures. However, further evidence is required to validate this hypothesis.

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