The Mechanisms of Medically Refractory Temporal Lobe Epilepsy

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Abstract- The mechanisms underlying the refractory temporal lobe epilepsy (TLE) are not well understood. Several explanations for refractory TLE are (1) an overexpression of P-glycoprotein (P-gp) encoded by multiple drug resistance 1 (MDR1) gene and other efflux transporters such as multidrug resistance protein (MRP) in the cerebrovascular endothelium in or around the region of the epileptic focus may lead to drug resistance in epilepsy; (2) the loss of antiepileptic drug sensitivity at certain target sites in the brain, including the sodium ion channel and the gamma aminobutyric acid (GABA)A receptor; and (3) seizures beget seizures by means of a cascade of events that include various types of neuronal damage, sprouting of neuronal axons and new synapse formations that establish aberrant glutamatergic synapses.

TLE may be a progressive neurological disorder that requires early and effective treatment. Early recognition of refractory TLE and referral for epilepsy surgery may prevent years of unnecessary seizure activity and its consequences.

Key Words: Temporal lobe epilepsy, Hippocampal sclerosis, Antiepileptic drugs

Acta Neurol Taiwan 2009;18:155-160

The definition of refractory epilepsy is controversy. A patient is considered to have refractory epilepsy if any seizures occur while the person is documented as having an antiepileptic drug (AED) concentration of at least one standard medication in the usually effective range, and the definition holds until the patient has been seizure free for at least one year[1]. Refractory epilepsy can also be defined as a chronic disorder requiring treatment with AEDs over the course of many years[1]. The US National Association of Epilepsy Centers defines AED resistance as continuing seizures despite 12 months of care in an epilepsy center[2]. There is also common agreement that failure of two monotherapy trials is the minimum criterion for declaring that someone has refractory epilepsy[3].

Besides, correct identification of the patient and the epilepsy syndrome is very important for proper selection of AEDs. In temporal lobe epilepsy (TLE), certain AEDs such as carbamazepine, lamotrigine, topiramate, oxcarbazepine, levetiracetam and zonisamide, become the drugs of choice. To date, none of the new AEDs has demonstrated a superior effectiveness over the older AEDs in the head to head monotherapy trials[4-7]. There is no statistically significant difference in efficacy

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Received May 21, 2009. Revised June 1, 2009.
Accepted July 17, 2009.
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among the new AEDs by head to head or meta-analyses[8-10]. Despite new AED therapy, epilepsy remains uncontrolled in a significant proportion of patients[11-14], particularly refractory TLE.

In regard to the cause of refractory TLE, initial precipitating injury (IPI) of seizures may play a role in refractory TLE. IPI is defined as any significant medical event prior to seizure onset[15]. They include febrile seizures, status epilepticus, central nervous system infection, head trauma, or birth trauma. However, previous prospective epidemiologic studies of children experiencing either one seizure or status epilepticus and population studies of children with febrile seizures suggest that the majority of these children will not develop refractory TLE[16]. This suggests that IPI alone may not be the cause of refractory TLE. A large study found that patients with IPI related to either status epilepticus or febrile seizures were found to have hippocampal sclerosis (HS). It explained that prolonged febrile seizures might produce hippocampal injury and thereby increase hippocampal excitability leading to the gradual development of HS and TLE[15]. In addition, HS constituted the most frequent neuropathologic finding in adult patients with medically refractory TLE[17], but this does not mean that all patients with HS have refractory TLE. A study used a 3D volumetric sequence, T_2 relaxation times and proton MR spectroscopy to predict seizure intractability. It was found that refractory TLE had HS associated with signal change in the anterior temporal white matter and the reduction of N-acetylaspartate in the ipsilateral temporal lobe[18]. Additionally, HS patients with refractory TLE often have extrahippocampal structural abnormalities[19-22]. Recent study provides a unique quantitative assessment in patients with TLE and indicates that regions of the brain remote from the temporal lobe of seizure onset may be adversely affected with significant changes in cerebral cortical structure[23]. It is concluded that refractory TLE may not be related simply to the presence of HS.

It was also found that hippocampal atrophy might be seen immediately after episodes of status epilepticus, febrile seizure and other severe IPI[24,25]. Additionally, progressive hippocampal atrophy was correlated with durations of TLE[26]. Hippocampal atrophy was associated with a substantially higher risk of relapse after AED withdrawal[27]. Other lesion etiologies in the temporal lobe may be additional risk factors in refractory TLE. Stroke, vascular malformation or tumor seem to be much more treatment responsive than those associated with cortical dysplasia, hippocampal sclerosis or dual pathologies[28]. Cortical dysplasia is frequently associated with medically refractory epilepsy[29,30]. A Sprague-Dawley rat embryo model that mimics human focal cortical dysplasia shows early development of hippocampal kindling. Cortical dysplasia is therefore associated with vulnerability to epilepsy[31].

The mechanisms underlying the refractory TLE are not known. One explanation for refractory TLE is impairment of drug penetration into the brain by efflux transporters[32]. One of the members of efflux transporters is P-glycoprotein (P-gp). P-gp is believed to act as an active efflux pump by reducing intracellular drug accumulation. P-gp belongs to a highly conserved protein superfamily, the adenosine triphosphate (ATP)-binding cassette (ABC) proteins which has more than 100 members and can be found in all kinds of organisms[33]. Human P-gp is encoded by a small gene family comprising two genes, designated ABCB1 or multiple drug resistance 1 (MDR1) and ABCB4 or multiple drug resistance 2 (MDR2), located near each other on chromosome 7q21.1[34]. But only human MDR1 genes encode the drug transporter associated with multidrug resistance[35]. This is supported by another study that overexpression of MDR1 gene in brain of some patients with medically refractory epilepsy contributed to their lack of response to AED treatment[36]. The role of P-gp in drug resistance in epilepsy is further complicated by the presence of other efflux transporters in the brain such as multidrug resistance protein (MRP) with at least 9 members identified in humans[37,38]. Some 20 other efflux transporters belonging to protein families such as organic anion transporter and organic cation transporter and monocarboxylic acid transporter also have been found in a variety of tissues including the brain[38-40]. Whether these transporters contribute to the blood-brain barrier and drug resistance is largely unknown. The role

of P-gp and other efflux transporters in drug resistance of refractory epilepsy is assessed in different studies. MDRs are upregulated in the hippocampus of patients with refractory TLE[41]. P-gp and multiple drug resistance protein (MRP) are found in temporal lobe pathologies of patients with refractory temporal epilepsy who underwent temporal lobectomy[36,41-43]. Current evidence suggests that an overexpression of P-glycoprotein (P-gp) encoded by MDR1 and other efflux transporters such as MRP in the cerebrovascular endothelium in or around the region of the epileptic focus may lead to drug resistance in epilepsy[32].

Another major theory for refractory TLE is the loss of antiepileptic drug sensitivity at certain target sites in the brain. Cumulative evidence suggested that there was reduced pharmacosensitivity to sodium channel-acting drugs in both epileptic rats and patients with refractory TLE[44]. Carbamazepine produced a use-dependent blockade of sodium channel activity in normal rodent brain, characterized by a progressive increase in inhibition with higher frequencies of stimulation, but use-dependent block of sodium channel activity was absent in epileptic brain tissue. Loss of sodium channel sensitivity to carbamazepine was shown in tissue from temporal lobe surgery patients resistant to carbamazepine[44].

The sodium channel is just one of many possible AED targets that may be altered in refractory TLE. Alterations in gamma aminobutyric acid (GABA)A receptor activity may be another target mechanism of pharmacoresistance to certain AEDs. Using an experimental model of TLE, the pharmacosensitivity of (GABA)A receptor subunits was reduced in single dentate granule cells harvested from epileptic rats. Reorganization of (GABA)A-receptor subtypes was demonstrated in the hippocampus of human temporal lobe epilepsy, reducing potency of AEDs that enhanced GABAergic inhibition via (GABA)A receptor[45].

Frequency, duration and severity of seizures may contribute to refractory TLE. Gowers first postulated the seizures beget seizures[46]. In TLE, hippocampal volume as measured by MRI is inversely correlated with seizure frequency[47]. Other studies found no relationship between frequency or duration and ipsilateral hippocampal volume, but rather a correlation between seizure frequency and contralateral hippocampal volume[24,48]. The total estimated number of seizures, partial or generalized, as calculated from reported frequency times duration of epilepsy, also correlated with hippocampal atrophy[49]. The above studies show that hippocampal and extrahippocampal neuronal damage or dysfunction increases with duration of TLE in patients who become intractable.

Recent extensive experimental data have provided sufficiently convincing evidence to suggest that seizures indeed do beget seizures by means of a cascade of events that include various types of neuronal damage, sprouting of neuronal axons and new synapse formations that establish aberrant glutamatergic synapses[50]. Experimental studies showed that mossy fiber synapses, instrumental in TLE and enriched in kainate excitatory receptors, sprout in humans and in animal models; the mossy fiber synapses also establish novel functional synapses, including aberrant ones[51,52]. The formation of aberrant kainate receptor-mediated synapses further contributes to the generation of additional seizures[53].

Additional studies showed that in some brain regions, there is a direct link between the severity of seizures and neuronal loss. The extent of the CA3 lesion is directly correlated with the severity of the seizures i.e., duration of the postictal depressions; duration and severity of the ictal events[53]; lesions of the mossy fibers that innervate CA3 neurons reduce both the initial seizures triggered by kainate and the extent and the severity of the subsequent lesions[54]; and neuronal damage is not seen at an early developmental stage when mossy fibers are not fully operative[55]. It is concluded that seizure frequency and intensity is critical to epilepsy progression in refractory TLE[56].

Recent study showed that TLE may be a progressive neurological disorder that requires early and effective treatment[57-59]. MRI study revealed that progressive neocortical atrophy occurred in patients with refractory TLE and was correlated with epilepsy duration[23]. The prolonged period of refractory epilepsy may be associated with progressive psychosocial deprivation, and cognitive impairment[60]. It is also evident that patients with med-

ically refractory TLE are physically and socially disabled[60]. Since epilepsy surgery is the most effective "curative" management for patients with refractory TLE[61,62], early recognition of refractory TLE and referral for epilepsy surgery may prevent years of unnecessary seizure activity and its consequences[63] and is recommended for refractory TLE under American Academy of Neurology practice guidelines[64].

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