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Ethosuximide: From Bench to Bedside

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ABSTRACT

Ethosuximide, 2-ethyl-2-methylsuccinimide, has been used extensively for "petit mal" seizures and it is a valuable agent in studies of absence epilepsy. In the treatment of epilepsy, ethosuximide has a narrow therapeutic profile. It is the drug of choice in the monotherapy or combination therapy of children with generalized absence (petit mal) epilepsy. Commonly observed side effects of ethosuximide are dose dependent and involve the gastrointestinal tract and central nervous system. Ethosuximide has been associated with a wide variety of idiosyncratic reactions and with hematopoietic adverse effects. Typical absence seizures are generated as a result of complex interactions between the thalamus and the cerebral cortex. This thalamocortical circuitry is under the control of several specific inhibitory and excitatory systems arising from the forebrain and brainstem. Corticothalamic rhythms are believed to be involved in the generation of spike-and-wave discharges that are the characteristic electroencephalographic signs of absence seizures. The spontaneous pacemaker oscillatory activity of thalamocortical circuitry involves low threshold T-type Ca^{2+} currents in the thalamus, and ethosuximide is presumed to reduce these low threshold T-type Ca^{2+} currents in thalamic neurons. Ethosuximide also decreases the persistent Na^+ and Ca^{2+}-activated K^+ currents in thalamic and layer V cortical pyramidal neurons. In addition, there is evidence that in a genetic absence epilepsy rat model ethosuximide reduces cortical γ-aminobutyric acid (GABA) levels. Also, elevated glutamate levels in the primary motor cortex of rats with absence epilepsy (but not in normal animals) are reduced by ethosuximide.

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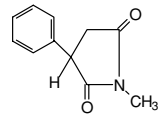
INTRODUCTION

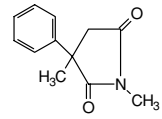
Ethosuximide, 2-ethyl-2-methylsuccinimide, is one of the succinimides that is being used extensively in the treatment of "petit mal" seizures. It is also a valuable compound in studies of absence seizures (Zimmerman and Burgmeister 1958; Mares et al. 1994). Ethosuximide controls absence seizures in almost 50% of patients; it also decreases the frequency of seizures in 40–45% of patients (Browne et al. 1975; Berkovic et al. 1987). Epileptic negative myoclonus can also be prevented by ethosuximide (Rubboli and Tassinari 2006; Grunewald and Panayiotopoulos 1993). However, the drug fails to control generalized tonic–clonic seizures. In addition to its activity in epilepsy, evidence has been accumulating that ethosuximide affects sensory transmission and is efficacious in the treatment of pain (Matthews and Dickenson 2001; McGivern 2006).

The action of ethosuximide has produced a mixture of intriguing results since its discovery in the 1950s. Therefore, multiple mechanisms have been proposed to explain its anticonvulsant efficacy. This review focuses on the mechanism(s) related to the reduction of low-threshold Ca^{2+} currents in thalamic neurons and also on neurotransmitter-related mechanisms in corticothalamocortical seizures. In addition, this review provides basic information about ethosuximide's pharmacology, animal toxicology, clinical use, and adverse effects in humans.

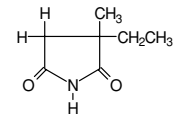
Ethosuximide is one of three succinimides used as anticonvulsants (Edwardson and Dean 1992; Zhang et al. 1996) The other two are: methsuximide (*N*-2-dimethyl-2-phenylsuccinimide) and phensuximide (*N*-methyl-2-phenylsuccinimide) (Browne 1983). The chemical structures of succinimide anticonvulsants are presented in Figure 1. The structure of ethosuximide contains a five-membered ring with two negatively charged carbonyl



Phensuximide



Methsuximide



Ethosuximide

FIG. 1. The chemical structures of succinimide antiepileptics.

oxygen atoms. The anticonvulsant effect of the drug is attributed to the "ring nitrogen" situated between the two groups (Edwardson and Dean 1992). The drug exists as a racemic mixture of two separate enantiomers because of a chiral carbon at position two of the succinimide ring.

PHARMACOKINETICS

Ethosuximide is clinically available for oral administration in the form of syrup or capsules. It is rapidly and almost completely absorbed when given orally to either children or adults; the syrup is absorbed at a faster rate (Buchanan et al. 1973). The bioavailability of ethosuximide is 95–100%. The volume of its distribution has been reported as 0.7 L/kg in either children or adults (Buchanan et al. 1969, 1973). Ethosuximide is not bound to plasma proteins and its levels in cerebrospinal fluid, saliva, or tears are similar to those in plasma (Piredda and Monaco 1981). Ethosuximide is uniformly distributed in the cerebral cortex, midbrain, cerebellum, pons, and medulla of rats (Patel et al. 1977). It passes the placenta barrier, and its plasma levels in neonates are similar to those in the mother. The ratio of its levels in breast milk to those in plasma was reported to be (Koup et al. 1978). In another report involving 10 epileptic mothers treated with ethosuximide and their newborns, the ratios of the fetal/maternal serum levels and milk/maternal serum levels were 0.97 $\pm$0.02 and 0.86 $\pm$0.08, respectively (Kuhnz et al. 1984).

In healthy adult males, the peak plasma levels of ethosuximide reached 15 μg/mL at 3–5 hours after a single 750 mg oral dose of the drug and remained at this level for 24 hours (Hansen and Feldberg 1974). Ethosuximide is clinically effective at plasma levels ranging from 40 to 100 mg/L (300–700 μmol/L), but in some patients levels of up to 150 mg/L (1000 mmol/L) are required and tolerated if achieved by slow titration (Sherwin 2002). In nursing infants, serum levels are maintained between 15 and 40 mg/L. Due to its linear kinetics, the plasma levels of ethosuximide increase in proportion to increasing doses (Patsalos 2005). Seven to 12 days are required to reach steady-state plasma levels of ethosuximide (Buchanan et al. 1969; Browne et al. 1975).

Approximately 80% of ethosuximide undergoes hepatic metabolism, which is mediated primarily by cytochrome P450 isoenzymes, with a major contribution from CYP3A and, to a lesser extent, from CYP2E and CYP2C/B. The remainder, around 20% of an administered dose of ethosuximide, is excreted unchanged in the urine. The hydroxyethyl derivative known as the major metabolite of ethosuximide is inactive and is excreted as glucuronide in the urine (Millership et al. 1993). The metabolic pathways and the metabolites of ethosuximide are presented in Figure 2. Because ethosuximide is a racemic mixture of two enantiomers, the plasma levels and the ratio of enantiomers in plasma of patients on long-term therapy was studied. There was no stereoselectivity, and the metabolism and elimination rates of two enantiomers of ethosuximide were similar (Villen et al. 1990; Mifsud et al. 2001). The elimination half-life of ethosuximide ranged from 30 to 60 hours in adults and from 30 to 40 hours in neonates or children (Buchanan et al. 1969; Kuhnz et al. 1984). The clearance of ethosuximide is increased in epileptic patients who are co-medicated with enzyme-inducing anticonvulsant drugs, resulting in lower plasma levels of ethosuximide. Giaccone et al. (1996) have shown that the rate of ethosuximide metabolism in patients receiving phenobarbital, phenytoin, or carbamazepine is higher than that in control subjects. In order to evaluate the combination of ethosuximide and valproate experimentally, this

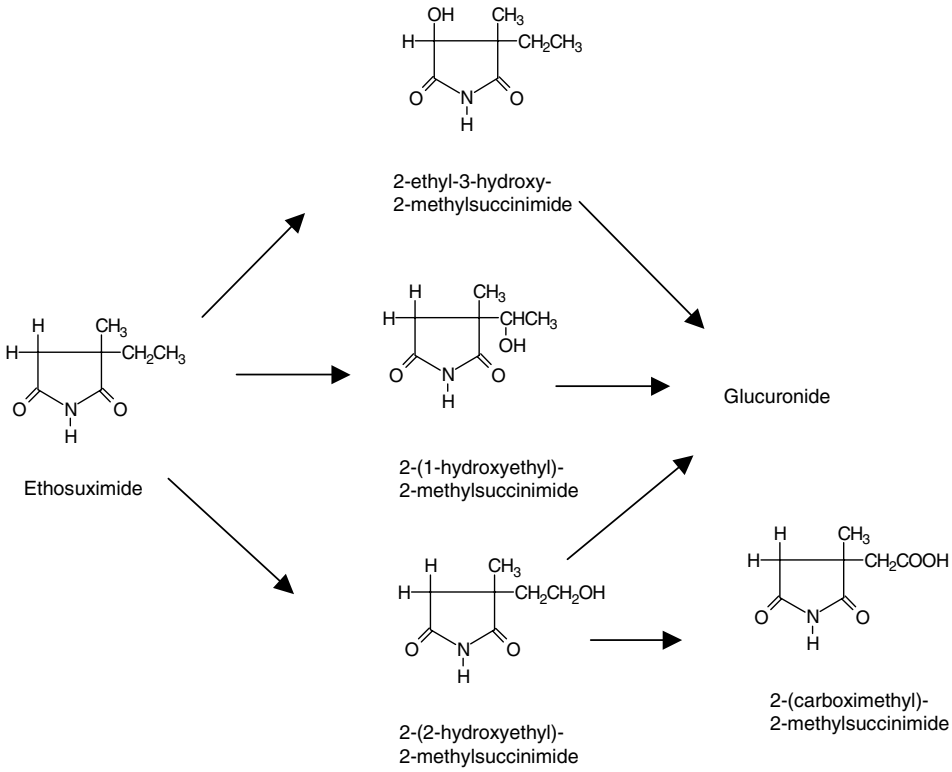


FIG. 2. The metabolites and the metabolic pathways of ethosuximide.

combination has been studied in mice to define their pharmacodynamic interactions and the efficacy–toxicity ratio. Their anticonvulsant effects were purely additive and a combination had a better therapeutic index than either drug alone (Bourgeois 1988). There was, however, a discrepancy in the published studies related to the pharmacokinetic interaction between ethosuximide and valproic acid. Concurrent administration of valproic acid with ethosuximide was reported either to increase (Mattson and Cramer 1980; Pisani et al. 1984; Posner et al. 2005) or decrease (Battino et al. 1982) plasma levels of ethosuximide. A drug interaction study of ethosuximide with contraceptive hormones revealed that ethosuximide does not interact significantly with oral contraceptives. In healthy volunteers, rifampicin was shown to increase ethosuximide clearance (Bachmann and Jauregui 1993). Isoniazid, an antituberculosis agent, may precipitate ethosuximide toxicity through inhibition of ethosuximide metabolism (Van Wieringen and Vrijlandt 1983). By acute administration, cimetidine was reported to potentiate the anticonvulsant activity of ethosuximide; its median effective dose (ED_{50})was reduced from 134 to 103 mg/kg in pentylenetetrazol-induced seizures in mice (Swiader et al. 2006). This effect was associated with a 74% elevation of ethosuximide plasma levels. However, coadministration of cimetidine with valproic acid, clonazepam, or phenobarbital had no significant impact on pentylenetetrazol-induced seizures in mice. Neither their anticonvulsant properties nor their plasma levels were affected.

SAFETY

Animal Studies

Valproic acid and ethosuximide are two important agents known to decrease the incidence of absence-like spike-and-wave discharges in the electroencephalogram (EEG) of Wistar Albino Glaxo/Rijsloijk (WAG/Rij) rats. The median effective doses (ED_{50} values) of the two drugs in this model were 121 and 21.5 mg/kg for valproic acid and ethosuximide, respectively (Van Rijn et al. 2004). When both agents were administered together, the interaction between the two agents was shown to be infraadditive in diminishing the incidence of spike-and-wave discharges in WAG/Rij rats. Ethosuximide has been found ineffective in the maximal electroshock seizure test, since the ED_{50} value was reported to be >500 mg/kg in mice and rats; however, in "audiogenic seizure susceptible mouse," the ED_{50} was found to be 328 mg/kg. The results of this study denoted that the correlation between ED_{50} values for ethosuximide and its plasma levels was poor in these models (Bialer et al. 2004). In a guinea pig kindling model, ethosuximide failed to exhibit anticonvulsant properties, but produced moderate sedation and muscle relaxation without having any effect on body weight (Gilbert and Corley 2002; Gilbert and Teskey 2007). Teratogenicity of ethosuximide was compared with that of phenytoin in Swiss CD-1 mice. The teratogenic potency was estimated using the minimum teratogenic dose (tD_{05}) (Fabro et al. 1982). In this study, tD_{05} for phenytoin was 0.17 mmol/kg/day and for ethosuximide, 5.2 mmol/kg/day. The "Relative Teratogenic Index" (LD_{01}/tD_{05}), which reflects the teratogenic hazard of a test agent was also computed in this study. The indices were 1.0, 1.2, 1.6, and 4.1 for phensuximide, ethosuximide, phenytoin, and valproic acid, respectively (Brodie and Dichter 1997). The effects of chronic administration of gradually increasing doses of the antipetit mal agents, ethosuximide and valproic acid, on the performance of "incremental repeated acquisition" and "incremental fixed-ratio tasks" were studied in the epileptic baboon (*Papio papio*). At approximately equipotent anticonvulsant doses, ethosuximide was reported to be more behaviorally toxic than valproic acid. The behavioral deficits induced by ethosuximide were still present at 8 weeks after cessation of drug treatment in two of the four animals, suggesting that cognitive processes can be disrupted by chronic administration of ethosuximide (Paule and Killam 1986).

Human Studies

Commonly observed dose-dependent side effects of ethosuximide in patients are related to the gastrointestinal tract or central nervous system (Mattson 1995; Rogvi-Hansen and Gram 1995; Brodie and Dichter 1997). Nausea, abdominal discomfort, vomiting, diarrhea, and anorexia are common at the onset of ethosuximide therapy. Central nervous system effects include drowsiness, dizziness, hiccups, fatigue, insomnia, tiredness, headache, and psychotic behaviors (Wallace 1996; Posner et al. 2005). Ethosuximide has been also associated with a wide variety of idiosyncratic reactions, including allergic dermatitis, rash, Stevens-Johnson syndrome, systemic lupus erythematosus, lupus-like syndrome, serum sickness reaction, agranulocytosis, and aplastic anemia (Teoh and Chan 1975; Glauser 2000). Hematopoietic adverse effects include leukopenia, agranulocytosis, eosinophilia, and pancytopenia (Posner et al. 2005). Ethosuximide-induced agranulocytosis was observed

in a 16-month-old male infant with Down syndrome (Imai et al. 2003). Masruha et al. (2005) reported the development of pseudolymphoma in a 12-year-old boy taking ethosuximide at 30 mg/kg/day. In another study, four patients with chronic renal disease who were given ethosuximide, 500 mg, 4 hours before dialysis, the drug was rapidly cleared by hemodialysis, suggesting the usefulness of dialysis in the treatment of ethosuximide overdosage (Marbury et al. 1981). Two major malformations, bilateral clefting and harelip, were observed in two neonates whose mothers received either ethosuximide and phenobarbital or ethosuximide and primidone (Kuhnz et al. 1984).

PHARMACOLOGY

Genetic Model of Absence Seizures

The International League Against Epilepsy (ILAE) defines absence epilepsy as a generalized form of epilepsy that affects children worldwide (Commission on Classification and Terminology of the International League Against Epilepsy 1989). The prevalence has been estimated to range from 0.4 per 1000 persons to 0.7 per 1000 persons (Pazzaglia and Frank-Pazzaglia 1976). Absence epilepsy is characterized by a sudden interruption of both physical and mental activity without major loss of postural tone. Bilateral synchronous spike-and-wave discharges in the EEG are coupled to the behavioral manifestations (Panayiotopoulos 1997).

The results of many neurophysiological, behavioral, pharmacological, and genetic studies have validated "Genetic absence epilepsy rats from Strasbourg" (GAERS) as an experimental model of human absence epilepsy (Marescaux et al. 1992). This is a selective inbred strain of Wistar rats generating spike-and-wave discharges spontaneously throughout their lifetimes. The seizures in GAERS are bilateral and synchronous over the surface of the somatosensory cerebral cortex where they start and end abruptly (Vergnes et al. 1987). In this model, absences are associated with behavioral immobility and a lack of responses to sensory stimuli; they thus reproduce the seizures observed in humans during absence epilepsy and represent a good experimental model. The spike-and-wave discharges generated in the GAERS occupy one-third of the rat's time; that is, on an average, the rats experience a seizure of 20 sec every 1 min (Marescaux et al. 1992). Ethosuximide is a first-order anti-absence agent in controlling the spike-and-wave discharges of GAERS, and so is valproate (Manning et al. 2003).

Typical absence seizures are generated as a result of complex interactions between the thalamus and cortical structures (McLean and Macdonald 1986; Gloor and Fariello 1988; Avanzini et al. 1992; Blumenfeld and McCormick 2000; Crunelli and Leresche 2002a; Sirvanci et al. 2005). This thalamocortical circuitry is under the control of several specific inhibitory and excitatory systems arising from the forebrain and brainstem. The involvement of the thalamocortical circuits, particularly the contribution of the ventrobasal thalamus and the reticular thalamic nucleus, in the propagation of absence seizures has been established in several species (Avoli and Gloor 1982; Vergnes et al. 1984). Corticothalamic rhythms are believed to be involved in the generation of spike-and-wave discharges. Thalamic neurons have the ability to shift between a tonic and burst firing mode (Blumenfeld and McCormick 2000), and this shift is important in the regulation of the transmission of external stimuli. Oscillatory neuronal behavior of the circuit is driven by the reticular thalamic nucleus, which

is situated between the thalamus and the cortex and influences the flow of information to the cerebral cortex (Avanzini et al. 1992). The reticular thalamic nucleus is made up mainly of γ-aminobutyric acid (GABA)–containing neurons that project to the thalamic relay nuclei. Systemic administration of either $GABA_A$ or $GABA_B$ receptor agonists enhances the duration of spike-and-wave discharges in GAERS in a dose-dependent fashion (Vergnes et al. 1984). Moreover, local microinjection of γ-vinyl GABA, an irreversible inhibitor of GABA transaminase, into the thalamic relay nuclei has been shown to increase the duration of spike-and-wave discharges in GAERS (Liu et al. 1992). Furthermore, blockade of the $GABA_B$ receptor at the level of the ventrobasal thalamus or reticular thalamic nucleus is known to result in a reduction in seizure activity (Liu et al. 1991; Richards 1995). Collectively, the expression of typical absence seizures is known to involve a tight interaction between thalamic and cortical structures (Steriade 2001; Crunelli and Leresche 2002a). However, the role of the component parts of this circuitry is still a matter of debate.

Excess GABA-mediated activity has also been suggested as contributing to the pathogenesis of absence seizures (Gören et al. 1997), since long-standing hyperpolarization is required to activate low-threshold Ca^{2+} currents (I_T), which play a crucial role in the production of rhythmic burst discharges in the thalamus (Mirsky et al. 1986). It has been shown that basal GABA levels in the primary motor cortex area and to a lesser degree in the ventrolateral thalamus are increased in nontreated GAERS compared to the nonepileptic Wistar control rats (Richards et al. 1995; Gören et al. 1997). This information and the pharmacological effects of ethosuximide on the GABA levels together point to the importance of corticothalamic circuitry in this genetic model of absence epilepsy.

The Mechanism of Action of Ethosuximide in GAERS and Other Strains of Rats

Ca^{2+} channels have been classified (Nowycky et al. 1985) as L- (long lasting), T- (transient) and N-types (neither). Their magnitude, voltage dependence, activation properties, and pharmacologic profiles differ. The low-threshold Ca^{2+} channels and the T-type Ca^{2+} channels are transient and have low conductance. It has been shown by microelectrode recording in brain slices that ethosuximide decreases low-threshold T-type Ca^{2+} currents in thalamic neurons, and has no effect on the high voltage-activated Ca^{2+} currents (Coulter et al. 1989; Macdonald and Kelly 1993; White 1999). Ethosuximide reduces the peak amplitude of the low-threshold T-type Ca^{2+} current in the neurons of the thalamic ventrobasal complex, as well as in the reticular nucleus of the thalamus (Avoli and Gloor 1982; Avanzini et al. 1992; Huguneard and Prince 1994; Williams et al. 2004). The blockade of voltage-dependent low-threshold T-type Ca^{2+} current was demonstrated at clinically relevant ethosuximide concentrations in a dose-dependent manner in thalamic neurons isolated from cats, guinea pigs, Wistar, or Sprague Dawley rats (Coulter et al. 1989; MacDonald and Kelly 1993; White 1999). In a study by Gomora et al. (2001), the cloned DNAs of three T-type Ca^{2+} channels were transfected into mammalian cells, leading to the appearance of typical T-type currents. In this preparation, both ethosuximide and the active metabolite of methsuximide blocked T-type channels in a state-dependent manner. The effects of anticonvulsants and other drugs on the Na^+-adenosine triphosphatase (ouabain-sensitive) and Mg^{2+}-ATPase activities of synaptosomes and their components have also been determined. The Mg^{2+}-ATPase activity of synaptosomes was not affected by the drugs. However, the

Na^+– K^+-ATPase activity was inhibited by ethosuximide, phenytoin, or diazepam (Gilbert et al. 1974; Albright and Burnham 1980).

The spontaneous pacemaker oscillatory activity of thalamocortical circuitry involves low-threshold T-type Ca^{2+} currents (Davies 1995). These oscillatory currents are associated with the characteristic 3-Hz spike-and-wave discharges of absence epilepsy. Tsakiridou et al. (1995) have demonstrated a partial reduction of T-type Ca^{2+} conductance produced by clinically relevant concentrations of ethosuximide in coronal slices that include the ventrobasal complex and reticular nucleus of the thalamus of GAERS, indicating that the blockade of low-threshold Ca^{2+} currents is not entirely responsible for the suppressive effect on spike-and-wave discharges in absence epilepsy. Nonetheless, it is generally accepted that ethosuximide affects T-type Ca^{2+} currents in thalamocortical neurons and thus prevents the synchronized firing that produces spike-and-wave discharges (White 2003).

In contrast to the classical view described previously, some groups have failed to detect any action of therapeutically relevant concentrations of ethosuximide on low-threshold T-type Ca^{2+} currents of thalamic and nonthalamic neurons. Leresche et al. (1988), using patch microelectrode recordings, have shown that ethosuximide has no effect on low-threshold Ca^{2+} currents in neurons of the ventrobasal and reticular nuclei of rat and cat. A partial reduction of T-type Ca^{2+} currents (16%) was observed with 500 μM ethosuximide in cultured rat dorsal root ganglion neurons (Groos et al. 1997). Ethosuximide had no effect on Ca^{2+} currents in tissue from temporal neocortex obtained from patients undergoing temporal lobe surgery for medically intractable epilepsy (Sayer et al. 1993). The insensitivity of T-type Ca^{2+} currents to ethosuximide may be explained by differences of species and techniques used in this study.

In addition to the effect of ethosuximide on voltage-dependent Ca^{2+} currents of the thalamus, the drug also has complex actions on the persistent Na^+ and sustained K^+ currents in cortical and thalamic neurons. Ethosuximide decreases the persistent Na^+ and Ca^{2+} activated K^+ currents (Crunelli and Leresche 2002b) but has no effect on the transient Na^+ current. It has been observed to decrease the persistent Na^+ and sustained K^+ currents in layer V cortical pyramidal and thalamic relay neurons of rats and cats *in vitro*. Likewise, ethosuximide was shown to produce Na^+ and K^+ channel block and altered K^+ channel gating in squid giant axons (Fohlmeister et al. 1984). Although the effect on membrane properties occurred only at high concentrations, this suggests a possibility of a direct action of ethosuximide on action potential generation. However, ethosuximide was reported to have no effect on high-frequency sustained repetitive firing of Na^+ action potentials and at high concentration (700 μM) to slightly reduce GABA responses in mouse central neurons (McLean and Macdonald 1986). In addition to the effects on Na^+ and K^+ currents, ethosuximide attenuated seizures and enhanced seizure-associated increases in thalamic activator protein 1 DNA-binding activities in lethargic (lh/lh) mice, a genetic model of absence seizures. In this model, ethosuximide attenuated seizure behavior and the increased DNA-binding activity (Ishige et al. 2001).

The blockade of either thalamic low-threshold T-type Ca^{2+} channels or slow inactivated Na^+ currents and Ca^{2+}-activated K^+ currents is commonly believed to be responsible for the action of the drug on spike-and-wave discharges. Other mechanisms put forward to explain the action of ethosuximide in suppressing spike-and-wave discharges are actions related to GABA. However, a study performed in mice showed that ethosuximide administered at a single dose did not produce a change in GABA level in mouse brains (Lin-Mitchell and Chweh 1986).

In a microdialysis study (Richards et al. 2003), GABA levels were reported to be higher in the ventrolateral thalamus of GAERS relative to nonepileptic controls. It was also demonstrated that systemic injection of ethosuximide reduced the GABA levels in the primary motor cortex area of GAERS (Terzioglu et al. 2006). Although there is a discrepancy between the two studies, the effects observed in a model exhibiting pathological EEG signs are more valuable and the findings gathered in GAERS seem to account for the real mechanism of action exerted by ethosuximide. The reduction of GABA in GAERS in response to the administration of ethosuximide is also in agreement with the previous studies showing that the site of action of ethosuximide involves the primary somatosensory cortex (Manning et al. 2004). An earlier study of WAG/Rij rats, which is one of the best characterized genetic rat models of absence epilepsy (Meeren et al. 2002), showed a seizure initiation site within the perioral region of the primary somatosensory cortex rather than in other cortical and thalamic areas. This study used nonlinear association analysis of cortical and thalamic EEG signals during the first 500 msec of spike-and-wave discharges. A dose-dependent decrease in the number of spike-and-wave discharges in the WAG/Rij model was found after intracerebroventricular administration of ethosuximide (Van Luijtelaar et al. 2000). Moreover, in another study, it was also demonstrated that microinfusion of ethosuximide into the perioral region of the primary somatosensory cortex immediately abolished the spike-and-wave discharge activity in the GAERS model (Manning et al. 2004), whereas the infusion of ethosuximide into the ventrobasal thalamus and reticular thalamic nuclei produced a modest and delayed reduction in the duration of spike-and-wave discharges (Richards et al. 2003).

However, it was also demonstrated that the time-course of action of ethosuximide on spike-and-wave discharge activity does not match the action on GABA release in GAERS, and this suggests that the anti-absence properties of ethosuximide cannot be fully explained by the action on GABA levels in the primary motor cortex area (Terzioglu et al. 2006). In addition to the changes in the GABAergic system in both the specific areas of the thalamus and the cortex, this same study reported a decrease in basal glutamate levels in the primary motor cortex of GAERS. In an earlier study, basal extracellular glutamate levels in the hippocampus of GAERS were found to be increased when compared to a nonepileptic control group (Rogvi-Hansen and Gram 1995). Moreover, an increase in the density of glutamate immunolabeling within the mossy terminals of the hippocampal Cornis Ammonis field 3 (CA_3) region and a decrease in the dentate gyrus were seen electron microscopically in GAERS (Sirvanci et al. 2005). These findings suggest that a change in the glutamatergic system may also contribute to the development and/or maintenance of absence seizures in the GAERS model. If glutamatergic transmission is involved in a pathological situation, nitric oxide involvement is likely. 7-Nitroindazole, a nitric oxide synthase inhibitor, has also been shown to enhance the anticonvulsive action of ethosuximide and clonazepam against pentylenetetrazol-induced convulsions (Borowicz et al. 2000). It has been suggested that nitric oxide is involved in sleep mechanisms and in the pathophysiology of epilepsy (Faraddji et al. 2000). Data are, however, controversial because it is not clear whether nitric oxide facilitates sleep or waking, or whether it exerts pro- or antiepileptic effects. It was shown that the circadian regulation of spike-and-wave discharges as well as of paradoxical sleep is reciprocally related and that nitric oxide levels were higher during seizures than during wakefulness. Antiepileptic effects of either valproic acid or ethosuximide are associated with an increase in paradoxical sleep and a significant release of nitric oxide, suggesting that nitric oxide may prevent absence epilepsy and act as an antiepileptic substance

by facilitating paradoxical sleep, providing evidence for another mechanism of action of ethosuximide.

The Effects of Ethosuximide in Diverse Models of Epilepsy

The most prominent characteristic of ethosuximide at nontoxic doses is its highly selective action on clonic motor seizures induced by pentylenetetrazol in experimental animals (Löscher et al. 1991a; White 2003). The model of pentylenetetrazol-induced clonic seizures has been traditionally used as a routine test for screening of anticonvulsants in mice, rats, and monkeys. In addition to the described Ca^{2+} channel-blocking and neurochemical effects of ethosuximide, another in the brainstem localized action of ethosuximide was proposed (Mares et al. 1994; Mares 1998). The effect of ethosuximide in the pentylenetetrazol model was lost after intercollicular transsection of the brainstem in rats (Mares et al. 1994).

The kindling phenomenon, which is induced by periodic administration of brief, low-intensity electrical stimulation of the amygdala or other limbic structures, has been used since the 1970s in the evaluation of drugs thought to have anticonvulsant properties. In this model, repeated electrical stimulations results in a progressive intensification of symptoms that finally culminate in secondary generalized tonic–clonic seizures. Once established, the animal is accepted as fully kindled and the enhanced sensitivity to electrical stimulation persists for the life of the animal. In the systematic evaluation of ethosuximide in fully developed kindled seizures, the drug was found ineffective against kindled behavioral seizures and did not affect the after-discharge duration in the EEG (Albright and Burnham 1980). At very high doses, the drug reduced, however, the duration of kindled seizures and after-discharge in rats (Albertson et al. 1980). The effect of ethosuximide on the evolution of kindling was evaluated in rats (Silver et al. 1991). Similar to the results on fully kindled animals, ethosuximide at the high dose of 300 mg/kg significantly delayed the development of kindling (Schmutz et al. 1988). It appears that ethosuximide has no effect on either kindled seizures or the evolution of kindling process, except at neurotoxic concentrations. The profile of ethosuximide in experimental studies correlates with its efficacy against generalized seizures of the absence type in humans.

The anticonvulsant activity profile of ethosuximide has been also established with the maximal electroshock seizure test that is one of the most frequently used anticonvulsant screening methods (Löscher et al. 1991b). However, the agent is ineffective against tonic hindlimb extension of maximal electroshock seizures in either mouse or rat (Battino et al. 1982).

By i.v. administration in a rat model of nonconvulsive seizures induced by brain ischemia, ethosuximide significantly attenuated seizures in a dose-related manner. This finding suggested that ethosuximide could improve outcome in patients with brain ischemia–induced seizures (Williams 2006).

The Use of Ethosuximide in Various Models of Pain: State-of-the-Art Reports

Recently, a novel therapeutic use of ethosuximide has come to light with the findings of powerful analgesic effects in experimental models as well as in humans (McGivern 2006).

The analgesic effects of ethosuximide were explored in various nociceptive models. Following intraperitoneal administration, ethosuximide dose-dependently reversed chemotherapy-induced peripheral neuropathic pain and capsaicin-induced mechanical hyperalgesia, and produced antinociceptive effects in the rat-tail flick reflex test in male rats (Barton et al. 2005; Flatters and Bennett 2004). Furthermore, ethosuximide was reported to have analgesic effects in the formalin-induced model of persistent pain and in the model of acute peripheral thermal nociception in rats (Todorovic et al. 2003; Shannon et al. 2005). Ethosuximide appears to have a function as a new potential treatment for pain disorders through blockade of T-type voltage-gated Ca^{2+} currents in sensory neurons, comparable to its action in absence seizure. Likewise, ethosuximide was also demonstrated to reduce noise-induced hearing loss in mice due to a direct action on the α1G and/or α1I subunits of one or more Ca_V3 Ca^{2+} channels in hair cells and supporting cells of the cochlea (Shen et al. 2007).

CLINICAL STUDIES

Ethosuximide, a succinimide-based molecule, has a narrow therapeutic profile in the treatment of epilepsy. The agent is the drug of choice in the monotherapy or polytherapy of children with generalized absence (petit mal) epilepsy (Weinstein and Allen 1966; Berkovic 2005; Posner et al. 2005). Ethosuximide and valproate were demonstrated to be equally effective in reducing generalized spike-and-wave discharges in previously untreated patients with absence seizures in a crossover study, and to have equal efficacy in achieving complete remission of absence seizures (Sato et al. 1982). Moreover, the combination therapy with ethosuximide and valproate was found to be superior to the monotherapy with either valproate or ethosuximide in terms of efficacy in patients with refractory absence seizures in a five-patient open-label study (Rowan et al. 1983). Patients with atypical absence epilepsy who exhibit other types of seizures including tonic–clonic seizures and drop attacks may respond to ethosuximide combined with other antiepileptic agents. Even though (due to poor design of studies) there is no conclusive evidence for a high degree of efficacy of any epileptic drug in the initial monotherapy of childhood and juvenile absence epilepsy, ethosuximide is considered to have similar efficacy/effectiveness as valproate in this condition (Glauser et al. 2006).

Ethosuximide is not used as the monotherapy in myoclonic seizures. When given in combination therapy with valproate, it is of some help in myoclonia associated with other conditions, including childhood and juvenile absence epilepsies, benign infantile and juvenile myoclonic epilepsies, and eyelid myoclonia with absences (Wolf and Inoue 1984; Wallace 1998; Perucca 2001). The addition of ethosuximide to valproate was reported to be helpful in the treatment of epilepsy with myoclonic absences, where this combination appears more beneficial than either valproate or ethosuximide alone. A recent recommendation suggests that valproate and ethosuximide combination therapy should be the first choice in the treatment of myoclonic absences. In this condition, it is probably necessary to administer both drugs at high doses and to reach ethosuximide plasma leves of 500–770 μmol/L (71–109 mg/L). At these levels, ethosuxumide can be well tolerated if administered by slow titration (Wallace 1996). Ethosuximide was also found effective in the treatment of epileptic negative myoclonus. Capovilla et al. (1999) have shown that this motor disorder disappeared in nine patients after ethosuximide was added to the other antiepileptic drugs, suggesting that ethosuximide can be considered as one of the options in the treatment of

epileptic negative myoclonus in childhood partial epilepsy. Similarly, ethosuximide has been shown to completely control epileptic negative myoclonus in six of 10 patients and has been recommended as adjunctive therapy when epileptic negative myoclonus develops during the clinical course of localization-related epilepsy (Oguni et al. 1998). Furthermore, Schmidt and Bourgeois (2000) suggested ethosuximide as a fourth-line and adjunctive therapy in Lennox-Gastaut syndrome.

CONCLUSIONS

In conclusion, the use of ethosuximide is very well accepted in idiopathic generalized epilepsy. It has also been studied in various conditions, such as neuropathic or inflammatory pain in which anticonvulsant agents are commonly used in the management of pain because of their effects on voltage- or ligand-gated channels involved in nociceptive transmission. It appears that ethosuximide exerts its effects through multiple mechanisms. The blockade of low-threshold Ca^{2+} currents is likely to be responsible for its efficacy in primary generalized absence type epilepsy. The antiseizure effect of ethosuximide may also be related to neurotransmitter/neuromodulator mediated effects, which play a critical role in the cortical structures of genetic absence epilepsy rats. Collectively the actions of ethosuximide in terms of site, neurotransmitter, and channel types suggest a combination of direct and indirect effects at various levels of the brain.

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