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THE ROLE OF ESTROGENS IN SEIZURES AND EPILEPSY: THE BAD GUYS OR THE GOOD GUYS?

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Abstract—Estrogens influence neuronal activity and are important for normal brain functions. Effects of estrogens on seizures are contradictory. It is commonly accepted that estrogens may increase neuronal excitability and thus mediate proconvulsant effects. However, clinical and animal data show that estrogen may also have no effect or anticonvulsant effects. The action of estrogens on seizures depends on various factors, such as treatment duration and latency prior to the seizure testing, estrogen dose, hormonal status (naïve vs gonadectomized animals), estrogenic substance, the region/neurotransmitter system involved, the seizure type/model used, and sex.

Besides the effects on seizure susceptibility, estrogens may also play an important role in seizure-induced damage. Pretreatment with β-estradiol in ovariectomized female rats has neuroprotective effects on status epilepticus-induced hippocampal damage and prevents the loss of inhibition in the dentate gyrus during the early post-status epilepticus period determined by the *in vitro* paired pulse paradigm. Several signaling pathways may be involved in the neuroprotective effects of β-estradiol on status epilepticus-induced hippocampal damage but at least one of these pathways involves interactions with neuropeptide Y. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: estrogen, seizure, epilepsy, status epilepticus, hippocampal damage.

Sex hormones influence the brain from early development (organizational and nutritional effects) and modulate its ongoing activity during adulthood (activational effects). Due to the small molecular weight and lipophilic properties, sex hormones cross the blood–brain barrier and easily reach the neuronal tissue. Their effects are mediated either via specific receptors or as direct effects on the neurotransmitter receptors (McEwen, 1991). Sex hormone receptors are widely distributed in the CNS. Specifically, the estrogen receptors (ER) exist as intracellular form (identified within the cytoplasm as an inactive form and in the nucleus as both an inactive and active form) (Monje and Boland, 2001) and as putative cell membrane receptors (Watson and Gametchu, 2001). Intracellular ER mediate delayed (minutes to hours) effects, which involve regulation of gene transcription (Gruber et al., 2002). Although, some authors use term "nuclear" ER (Clark and Mani, 1994), there is clear evidence that nucleo-cytoplasmic ER trafficking exists (DeFranco et al., 1998). In the brain, intracellular ERα and ERβ have been identified (McEwen, 2002). Both ER types have similar structure but distinct brain distribution and mediate discrete effects (Patrone et al., 2000; Hewitt and Korach, 2002). The membrane ER seem to act through a second messenger system and mediate rapid (seconds to minutes) effects (McEwen, 2002).

This review will focus on the activational effects of estrogens in adulthood with particular interest to their ability to influence neuronal excitability, to modulate seizures and their role in seizure-induced neuronal damage.

Estrogens and seizures: human studies

The possible relationship between estrogens and neuronal excitability has been observed and described almost 150 years ago (Locock, 1857; Gowers, 1881). Since that time, several investigators have reported that seizure frequency varies during menstrual cycle in some women (Laidlaw, 1956; Logothetis et al., 1959; Mattson and Cramer, 1985; Herzog et al., 1997). This condition is referred to as catamenial epilepsy. Among women with epilepsy, the incidence of catamenial epilepsy is around 40% as shown by a recent carefully designed study (Herzog et al., 2004). Herzog et al. (1997) described three distinct patterns of catamenial epilepsy based on charting seizures and menstrual cycles. This study recognized two catamenial epilepsy patterns in women with normal ovulatory cycles, who reported increased daily seizure frequency during either perimenstrual or preovulatory phase. The third catamenial pattern was observed in women with inadequate luteal phase cycles, who observed a decrease in seizure frequency during the midfollicular phase compared with the other phases (Herzog et al., 1997).

Changes in hormonal levels during perimenarche and perimenopause may also influence the course of seizures. Increased risk for seizure onset or epilepsy worsening during perimenarche has been reported (Rosciszewska, 1975; Klein et al., 2003). Increase in seizures during perimenopause reported by some women may be related to elevation in the estrogen:progesterone ratio (Rosciszewska, 1978; Abbasi et al., 1999; Harden et al., 1999), while a decline in estrogen levels after the menopause seems to be associated with a decrease in seizure frequency, especially in women with catamenial epilepsy in the medical history (Harden et al., 1999). On the other hand, in the same study some women had no change in seizures and some reported an increase in seizure frequency at menopause (Harden et al., 1999).

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Abbreviations: CA, cornu ammonis; ER, estrogen receptor; NMDA, *N*-methyl-D-aspartate; NPY, neuropeptide Y; SE, status epilepticus.

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Finally, addition of oral contraceptives may increase paroxysmal activity in some patients (Logothetis et al., 1959; Bickerstaff, 1975). Thus, the clinical observations led to the conclusion that estrogens may act as proconvulsant agents.

However, generalization of such a "rule" would be incorrect. Several authors reported that the use of oral contraceptives has not been associated with exacerbation of seizures (Marcus et al., 1963; Toivakka, 1967; Mattson et al., 1986; Harden et al., 1999). Others have shown that seizures were controlled following the administration of contraceptives (Sanchez Longo and Gonzalez Saldana, 1966). Additionally, hormonal replacement therapy initiated as estrogen monotherapy in a postmenopausal woman, was associated with a decrease in seizure incidence (Peebles et al., 2000). Improvement in seizures has been observed following estrogen treatment in patients with absence and tonic–clonic seizures (Whitehead and McNeil, 1952). A decrease in seizure rate has been also reported in women with primary generalized seizures around the ovulation, suggesting an anticonvulsant effect of estrogens (Jacono and Robertson, 1987). Inconclusive data are available for the influence of hormonal changes during pregnancy on seizure frequency in epileptic women. The majority of women did not observe any change in seizure pattern during their pregnancy. While some remaining women reported an increase, others reported a decrease in seizure frequency (Schmidt, 1982).

Estrogens and seizures: animal studies

Animal studies have also contributed controversial data. Several studies have reported that acute administration of estrogens is proconvulsant (Woolley et al., 1960; Woolley and Timiras, 1962b; Hom and Buterbaugh, 1986; Edwards et al., 1999). A lower threshold for electroshock-induced seizures and amygdala kindling afterdischarges during the female rat proestrus has been attributed to high circulating estradiol levels (Woolley and Timiras, 1962a; Edwards et al., 1999). Interestingly, focal application of conjugated equine estrogens on the cerebral cortex had epileptogenic effects (Logothetis and Harner, 1960; Marcus et al., 1966; Hardy, 1970), while the application of β-estradiol on the cerebral cortex did not lead to the development of epileptogenic focus (Marcus et al., 1966). These findings suggest that the conjugated equine estrogens may have higher pro-epileptogenic potency than β-estradiol. Electrophysiological field potential recordings from naïve (gonadally intact) female hippocampal slices did not show any changes in excitability following the bath application of β-estradiol (Teyler et al., 1980). In addition, no increase in seizure susceptibility was recorded from the CA1 hippocampal region and the entorhinal cortex in low-Mg^{2+} medium in slices from ovariectomized females pretreated with a low dose of β-estradiol (2 μg) (Velíšek et al., 1999).

Several studies have demonstrated that the dose of estrogen could play a role in seizure susceptibility. In ovariectomized rats, several day pretreatment with doses lower than 10 μg of β-estradiol delayed the onset of the first kainic acid-induced clonic seizure (Velíšková et al., 2000), while 20 μg of β-estradiol did not alter the seizure threshold and 40 μg of β-estradiol was proconvulsant (Reibel et al., 2000). The chronic pretreatment with the low-dose of β-estradiol (2–5 μg) also significantly suppressed mortality following kainic acid-induced status epilepticus (SE) (Velíšková et al., 2000; Hoffman et al., 2003). On the other hand in naïve female rats, chronic administration of β-estradiol (2 μg) decreased the kainic acid seizure threshold, although it did not significantly affect seizure severity (Nicoletti et al., 1985). Similarly in naïve females, chronic administration of β-estradiol (6 μg) lowered the threshold for corneal electroshock seizures, although acute injection prior to seizure testing had no effect on seizure threshold (Stitt and Kinnard, 1968). The proconvulsant effect of acute estrogen administration on corazole (pentylenetetrazole)-induced seizures in naïve females has been also reported (Gevorkyan et al., 1989). The data in naïve females clearly demonstrate that elevation of physiological estrogen levels by administration of exogenous doses of β-estradiol and thus leading to supraphysiological estrogen levels, has proconvulsant properties.

The controversial data may also arise from the fact that estrogens have region-specific effects. Administration of β-estradiol facilitates kindling from the dorsal but not from the ventral hippocampus (Buterbaugh and Hudson, 1991). Electrical seizure threshold is increased for seizures evoked from the lateral but not from the medial amygdala (Terasawa and Timiras, 1968). Thus, estrogen effects may depend on the structure of seizure origin and accordingly, on the seizure model used. Further, estrogen effects may include interactions with the neurotransmitter systems involved in the seizure generation. Pretreatment with low doses of β-estradiol (10 μg) increases high-affinity muscimol binding in the hippocampus of ovariectomized rats suggesting increased sensitivity of hippocampal neurons to GABA (Schumacher et al., 1989). The same β-estradiol pretreatment also increases GABA production and GABA-mediated inhibitory input to the CA1 pyramidal cells (Rudick and Woolley, 2001; Nakamura et al., 2005). The enhancement of GABA system following β-estradiol pretreatment seems to be a compensatory effect reflecting the β-estradiol-induced increases in *N*-methyl-D-aspartate (NMDA) binding and increased sensitivity of CA1 pyramidal neurons to NMDA receptor-mediated synaptic input (Woolley et al., 1997; Nakamura et al., 2005). Application of β-estradiol potentiates kainate currents in the hippocampal CA1 region (Gu and Moss, 1996, 1998; Gu et al., 1999). By increasing acetylcholine release and choline uptake, β-estradiol also interacts with the cholinergic system (Marriott and Korol, 2003; Pongrac et al., 2004). Accordingly in ovariectomized female rats, β-estradiol administration has an anticonvulsant effect on seizures induced by agents affecting the GABA system such as picrotoxin (Schwartz-Giblin et al., 1989) or cyclosporin A (Tominaga et al., 2001) and seizures induced by NMDA (Kalkbrenner and Standley, 2003) or kainic acid (Velíšková et al., 2000) compared with ovariectomized rats with no estrogen replacement. Also similarly to the ovariectomized females, natural decline of sex hormone levels in aged female rats