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Comparative Effects of Estradiol Benzoate, the Antiestrogen Clomiphene Citrate, and the Progestin Medroxyprogesterone Acetate on Kainic Acid–Induced Seizures in Male and Female Rats

Ferdinando Nicoletti, Carmela Speciale, Maria Angela Sortino, *Gisella Summa, *Giuseppe Caruso, *Francesco Patti, and Pier Luigi Canonico

*Departments of Pharmacology and *Neurology, University of Catania Medical School, Catania, Italy*

Summary: We have investigated the comparative effects of estradiol benzoate (EB), the antiestrogen clomiphene citrate (CC), and the progestin medroxyprogesterone acetate (MPA) on seizures induced by systemic injection of kainic acid (15 mg/kg i.p.) in male and female rats. Subcutaneous administration for 10 days of EB (10 μg/kg) or high doses of CC (50 mg/kg) significantly potentiated kainate-induced seizures, with this effect being more pronounced in male animals. Doses of 2.5 mg/kg of CC potentiated kainate-induced seizures in male rats but were ineffective in female rats. Low doses of CC (0.5 mg/kg) exhibited a mild anticonvulsant effect in both sexes. Repeated administration of MPA (2.5 mg/kg) partially protected female animals against kainate-induced seizures; in male animals, MPA induced a 30% increase in the seizure severity score, although the difference from the score of control male rats was not significant. These data suggest that sex steroids influence kainate-induced seizures in a sex-dependent manner and that the effects of the antiestrogen CC are dose dependent. This should be taken into account in view of a possible use of CC and MPA in hormonal therapy for seizure disorders. **Key Words:** Clomiphene citrate—Estradiol benzoate—Kainic acid—Medroxyprogesterone acetate—Seizures—Sex difference.

Several studies on endocrine–central nervous system interaction concern the influence of sex steroids on seizure disorders (for a review, see Timiras and Hill, 1980). Estrogens increase brain excitability when given systemically or applied topically to the brain, and a relationship between estrogen plasma levels and severity of seizures in epileptic women has been reported (Backstrom, 1976; for a review, see Newmark and Penry, 1980). Based on the proconvulsant action of estrogens, a potential therapeutic use of antiestrogens in seizure disorders has been suggested. Accordingly, anticonvulsant effects of the antiestrogen clomiphene citrate (CC) have been reported by Check et al. (1982) in one epileptic patient.

Progesterone depresses neural excitability and is supposed to exert a protective role against seizures (Timiras, 1969). In epileptic women, the number of seizures is sometimes reduced during the luteal phase of the menstrual cycle (Backstrom, 1976), at the time of the highest progesterone levels, and is often increased just before or during menses ("catamenial epilepsy"), when progesterone levels drop precipitously (for a review, see Newmark and Penry, 1980). Good therapeutic efficacy of progestinic agents (Zimmermann et al., 1973; Hall, 1977) or an estroprogestinic combination (Groff, 1962; Sanchez-Longo and Gonzales-Saldana, 1966; Livingston, 1972) has been reported in some patients affected by catamenial epilepsy.

Despite the contribution of these studies to our knowledge of hormonal effects on seizures, most of the observations are far from conclusive, and the application of hormonal therapy in epilepsy remains elusive. For example, although sex steroids and related compounds have been administered to epileptic patients of both sexes, the differential effects of estrogens, antiestrogens, and progestinic agents in males and females have never been tested. We have investigated this problem in animals injected with kainic acid, a heterocyclic analogue of glutamic acid (for a review, see Coyle, 1983). Systemic injection of kainic acid induces secondarily generalized partial complex motor seizures which progressively evolve into "status epilepticus" (Collins et al., 1980; Ben-Ari

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Address correspondence and reprint requests to Dr. F. Nicoletti at his present address: Laboratory of Preclinical Pharmacology, Saint Elizabeth Hospital, National Institute of Mental Health, Washington, DC 20032, U.S.A.

et al., 1981). Electrophysiological and metabolic data show that the epileptiform activity induced by kainic acid originates in the hippocampal formation (Ben-Ari et al., 1981). Nadler et al. (1978) and Ben-Ari et al. (1980) noted similarities between neuropathological changes induced by kainic acid in animals and limbic lesions of temporal lobe epilepsy in humans. Hence, animals injected with kainic acid may be considered as models of temporal lobe epilepsy.

Patients with menstrual exacerbation of seizures often experience mixed seizure types, including complex partial seizures, and anticonvulsant effects of CC (Check et al., 1982) and the progestin medroxyprogesterone acetate (MPA) (Zimmermann et al., 1973) have been reported in patients affected by temporal lobe epilepsy. This suggests that seizures of limbic origin may be sensitive to hormonal environment or treatment. Binding sites for sex steroids are present in limbic regions (McEwen, 1976), and the cyclicity of the bioelectrical activity in the hippocampus and amygdala parallels the cyclicity of gonadal hormones (McGowan-Sass and Timiras, 1975). For these reasons, the kainic acid model was considered appropriate to investigate the comparative effects of estradiol benzoate (EB), the antiestrogen CC, and the progestin MPA in male and female animals.

MATERIALS AND METHODS

Male and female Wistar rats (body weight 200 ± 20 g) were used. One week before the beginning of the experiment, the animals were housed (six per cage) with a 12 h light–12 h dark cycle and constant temperature (25°C). Twelve groups of animals (six groups of male rats and six groups of female rats) were not treated or were given EB (10 μg/kg), MPA (2.5 mg/kg), or CC (0.5, 2.5, or 50 mg/kg). EB and MPA were dissolved in sesame oil; CC was prepared as a suspension in sesame oil. A commercial mixture (Clomid) of *cis*- and *trans*-CC was used; ~ 40% is zuclomiphene (*trans*-clomiphene), and the rest is enclomiphene (*cis*-clomiphene). All drugs were injected subcutaneously once a day for 10 days. Control rats were injected with the vehicle alone. Female rats were included in the control group irrespective of the phase of the estrous cycle. Twelve hours after the last dose, all the animals were injected with kainic acid (15 mg/kg i.p.) dissolved in phosphate buffer (pH 7.4) and were observed in separate cages for 90 min. The development of kainate-induced seizures proceeded through a succession of behavioral stages, including automatisms (wet shakes, scratching, and myoclonic twitchings of the head and face), rearing with forepaw tremor and clonus (referred to as "limbic motor seizures"), tonic-clonic convulsions with opistotonous, barrel rotations, and generalized clonus alternated with periods of intense agitation. For the quantitative analysis, a rating scale with scores ranging from 0 to 7 was adopted: 0, no response; 1, paroxysmal "wet shake behavior" (more than two episodes per minute); 2, head nodding; 3, rearing with forepaw tremor and clonus (limbic motor seizures); 4, full limbic seizures with tail hypertonus and loss of postural control; 5, full limbic seizures alternated with periods of hypermobility and mild agitation; 6, tonic-clonic convulsions with barrel rotations, opistotonous and generalized clonus alternated with intense agitation, marked hypermobility, continuous circlings, and vigorous jumps ("escape behavior"); and 7, loss of consciousness or death. Autonomic signs, including prooptosis and salivation, were observed throughout stages 3–6. The seizure severity score, the percentage of responsive animals for each behavioral stage, and the latency (in min) to the onset of automatisms (stage 1 or 2) or major seizures (stages 3–6) were calculated. Dunnett's *t* test was used to compare each mean with the mean of the control group.

RESULTS

Repeated administration of EB significantly potentiated kainate-induced seizures in male animals, as indicated by the higher seizure severity score (94%) and the lower latency to onset of automatisms and major seizures in EB-injected male rats as compared with control male rats (Table 1). In EB-pretreated male animals, partial seizures (stage 1 or 2) were partially masked by the high incidence of generalized convulsions (stage 5 or 6; Table 2). The seizure severity score was increased in female rats pretreated with EB (25%), but the difference from control female rats was not significant. However, EB reduced the latency to onset of major seizures in female animals (Table 1).

The lowest dose (0.5 mg/kg) of the antiestrogen CC decreased the seizure severity score in both male and female animals (−43 and −32%, respectively), but the difference from the respective controls was significant only in male animals. The latency to onset of automatisms or major seizures was significantly increased by this dose of CC in both sexes. CC, 2.5 mg/kg, significantly increased the seizure severity score (48%) and reduced the latency to onset of automatisms and major seizures in male animals but was ineffective in female animals. The highest dose (50 mg/kg) of CC dramatically potentiated kainate-induced seizures in both sexes, an effect that was more pronounced in male rats (114% increase in seizure severity score) than in female rats (55% increase in seizure severity score). The latency to onset of automatisms and major seizures was markedly reduced in both sexes (Table 1).

Pretreatment with the progestin MPA protected female rats against kainate-induced seizures (32% decrease in seizure severity score; $p < 0.05$ compared with control

TABLE 1. *Seizure severity score and latency to onset of automatisms (stage 1 or 2) or major seizures (stages 3–6) in male and female rats injected with kainic acid (15 mg/kg i.p.) and pretreated with estradiol benzoate (EB), clomiphene citrate (CC), medroxyprogesterone acetate (MPA), or vehicle*

Rat sex, injectate	Seizure severity score	Latency to	
		Automatisms (min)	Major seizures (min)
Male			
Vehicle	2.92 ± 0.52	39.5 ± 2.4	66.4 ± 2.6
EB (10 μg/kg)	5.66 ± 0.33[a]	25.5 ± 3.6[a]	29.3 ± 3.5[a]
CC (0.5 mg/kg)	1.66 ± 0.39[a]	45.9 ± 2.5	80.0 ± 2.0[a]
CC (2.5 mg/kg)	4.33 ± 0.64[a]	22.7 ± 2.3[a]	34.1 ± 3.7[a]
CC (50 mg/kg)	6.25 ± 0.25[a]	13.7 ± 5.2	20.8 ± 2.8[a]
MPA (2.5 mg/kg)	3.91 ± 0.62[a]	38.7 ± 2.4	68.3 ± 3.5
Female			
Vehicle	3.66 ± 0.41	34.5 ± 2.0	66.4 ± 2.6
EB (10 μg/kg)	4.58 ± 0.37	28.0 ± 2.7	40.2 ± 3.7
CC (0.5 mg/kg)	2.50 ± 0.56	49.6 ± 1.2[a]	78.2 ± 2.0[a]
CC (2.5 mg/kg)	3.58 ± 0.43	34.4 ± 2.3	56.8 ± 3.6
CC (50 mg/kg)	5.66 ± 0.30[a]	12.2 ± 1.9[a]	25.6 ± 5.3[a]
MPA (2.5 mg/kg)	2.16 ± 0.44[a]	45.9 ± 6.3	74.0 ± 3.5

Data are mean ± SEM of 12 determinations.
[a]$p < 0.05$ by Dunnett's t test compared with vehicle-injected animals of the same sex.

female rats). It is surprising that MPA induced a 34% increase in the seizure severity score of male animals, although the difference from the score of control male animals was not significant. MPA failed to influence the latency to onset of automatisms or major seizures in both sexes (Table 1).

A significant difference was not observed between control male and female rats, although the seizure severity score was higher in female rats. However, female animals were included in the control group irrespective of the phase of their estrous cycle, and this makes any comparison between untreated male and female rats equivocal. On the other hand, it is beyond the scope of this article to determine whether control male and female rats have a different susceptibility to the convulsant action of kainic acid.

DISCUSSION

The potentiation of kainate-induced seizures that we have observed in rats pretreated with EB is consistent with previous animal studies. Estrogens have been found to decrease the threshold for electroshock-induced seizures in different species (for a review, see Newmark and Penry, 1980) and to increase the intensity of audiogenic seizures in sensitive rats (Werboff et al., 1963). The reasons for the proconvulsant action of estrogens are unclear as yet. General factors, such as changes in systemic metabolism or hydroelectrolytic balance, may be involved; however, evidence for a direct central action of estrogens is provided by the observations that cortical excitability is increased when estrogens are applied directly to the brain (Hardy, 1970) and that glucose utilization is significantly increased in most of the brain regions at short intervals after intravenous injection of estradiol (Namba and Sokoloff, 1984). The observed effects of EB on kainate-induced seizures might be accounted for by an increased excitability of the hippocampal formation, which is the major "target" for the excitability action of kainic acid. It is consistent with this hypothesis that 17-β-estradiol increases field potentials registered from hippocampal slice preparations (Foy and Teyler, 1983) and that the threshold for electrically induced seizures in the hippocampus is lowest during proestrus and part of estrus (McGowan-Sass and Timiras, 1975), at the time of highest estrogen levels. Repeated administration of EB has also been found to decrease the activity of the γ-aminobutyric acid (GABA)-synthesizing enzyme glutamate decarboxylase in male rat substantia nigra (Nicoletti et al., 1982), an effect that could be related to the high incidence of generalized convulsions observed in male animals pretreated with EB. It has been reported, in fact, that a pharmacologically induced decrease in nigral GABAergic transmission facilitates the generalization of seizure activity emanating from more rostral foci (Iadarola and Gale, 1982).

Whatever the site and mechanism of action of EB, it is relevant that male rats are more sensitive than female rats to its proconvulsant action. A possible explanation for this sex-related difference invokes the involvement of central estrogen receptors in the proconvulsant action of EB. Neural estrogen receptors have been shown to be involved in the excitatory action of 17-β-estradiol on hippocampal slice preparations (Foy and Teyler, 1983), an effect that was greater when hippocampal slices from

TABLE 2. *Percentage of responsive animals injected with kainic acid (15 mg/kg i.p.) and pretreated with estradiol benzoate (EB), clomiphene citrate (CC), medroxyprogesterone acetate (MPA), or vehicle for each behavioral stage*

Rat sex, injectate	Percentage in group at stage							
	0	1	2	3	4	5	6	7
Male								
Vehicle	16.7	83.3	74.9	66.6	41.6	24.9	0	0
EB (10 μg/kg)	0	58.3	74.9	100	91.6	83.3	74.9	16.7
CC (0.5 mg/kg)	24.9	66.6	50	16.7	0	0	0	0
CC (2.5 mg/kg)	8.3	41.6	83.3	74.9	66.6	50	41.6	16.7
CC (50 mg/kg)	0	33.3	66.6	66.6	83.3	58.3	91.6	41.6
MPA (2.5 mg/kg)	16.7	75	83.3	83.3	66.6	41.6	33.3	0
Female								
Vehicle	8.3	66.6	91.6	91.6	58.3	33.3	0	0
EB (10 μg/kg)	0	50	100	100	74.9	50	24.9	8.3
CC (0.5 mg/kg)	16.7	83.3	66.6	41.6	33.3	16.7	8.3	0
CC (2.5 mg/kg)	8.3	58.3	91.6	91.6	50	24.9	8.3	0
CC (50 mg/kg)	0	50	74.9	83.3	83.3	83.3	58.3	24.9
MPA (2.5 mg/kg)	24.9	58.3	66.6	58.3	16.6	0	0	0

The staging criteria were as follows: 0, absence of any behavioral response; 1, paroxysmal "wet shake behavior"; 2, head nodding; 3, limbic motor seizures; 4, limbic seizures with tail hypertonus and loss of postural control; 5, full limbic seizures alternated with mild agitation; 6, tonic-clonic convulsions and/or intense agitation; 7, loss of consciousness or death during the observation period.

male animals were exposed to the hormone (Teyler et al., 1980). If, as has been claimed (Timiras and Hill, 1980), the proconvulsant action of estrogens correlates with the number and affinity of central estrogen receptors, then the high responsiveness of male animals to EB might reflect oversensitivity of male receptors, due to low exposure to endogenous estrogens.

Results with the antiestrogen CC indicate a biphasic dose-response effect. Endocrinological studies show that CC possesses both antiestrogenic and estrogenic properties, depending on the dose used, the injection regimen, and the presence or absence of other hormones (Terenius, 1971; Clark et al., 1974; Katzenellenbogen and Ferguson, 1975; Bulger and Kupfer, 1976). In male animals, the relatively small amount of endogenous estrogens and the possible resulting high sensitivity of estrogen receptors might account for an estrogenic effect of CC, which would explain the strong proconvulsant action exhibited by intermediate and high doses. The lack of effects of intermediate doses of CC in female animals might reflect a balance between the intrinsic estrogenic activity of CC and the antagonism of endogenous estrogens.

Pretreatment with the progestin MPA reduced the severity of kainate-induced seizures in female rats. This is consistent with the evidence that progesterone depresses neural excitability in the hippocampus and amygdala (Kawakami et al., 1970) and that prolonged administration of MPA improved intractable seizures associated with menstruation (Zimmermann et al., 1973). Thus, these results suggest that a sexually dimorphic response to progestinic agents may occur, at least as far as the modulation of seizure activity is concerned.

In conclusion, we have demonstrated that repeated administration of EB, the antiestrogen CC, and the progestin MPA influences kainic acid–induced seizures in a sex-dependent manner. Sex steroids might act peripherally, by inducing changes in the pharmacokinetics of kainic acid (including changes in hepatic metabolism or in the permeability of the blood–brain barrier to kainate). However, at least in the case of CC and MPA, this seems unlikely, because both drugs either potentiate or inhibit kainate-induced seizures, depending on the dose used or the sex of the animals. The different response to EB, CC, and MPA exhibited by male and female animals might reflect sex-related differences in the number or affinity of central receptors for sex steroids. However, the final effect on seizure activity might result from a complex interaction between the administered steroids and the "hormonal status" of male and female animals. In male animals, for example, estrogens, antiestrogens, and progestinic agents influence testicular function, and this raises the question of whether male sex hormones are involved in the modulation of seizure threshold.

CC and MPA have been reported to improve seizures in one male and one female epileptic patient (Zimmermann et al., 1973; Check et al., 1982), respectively. The results presented in this article suggest that the possibility of dose- and sex-related responses must be taken into account, in view of a possible use of CC and MPA in hormonal therapy for seizure disorders.

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RÉSUMÉ

On a étudié les effets du Benzoate d'oestradiol (EB), de l'antioestrogène citrate de clomifène (CC) et du progestatif acétate de médroxyprogesterone (MPA) sur les crises produites par l'injection d'acide kainique (15 mg/kg par voie intrapéritonéale) à des rats mâles et femelles. L'administration sous-cutanée pendant 10 jours d'EB (10 ug/kg), ou des doses élevées de CC (50 mg/kg) potentialisent significativement les crises induites par l'acide kainique, cet effet étant plus prononcé chez les mâles. Des doses de 2,5 mg/kg de CC potentialisent les crises induites par l'acide kainique chez les mâles, mais pas chez les femelles. De faibles doses de CC (0,5 mg/kg) ont un effet anticonvulsivant faible dans les 2 sexes. L'administration répétée de MPA (2,5 mg/kg) protège partiellement les femelles contre les crises induites par l'acide kainique. Chez les mâles, le MPA entraîne une augmentation de 30% du score de sévérité des crises, quoique cependant la différence avec le score des mâles de contrôle ne soit pas significative ($p < 0.05$). Les données suggèrent que les stéroïdes sexuels influencent les crises induites par l'acide kainique d'une manière dépendant du sexe, et que les effets de l'antioestrogène CC sont dose-dépendants. Cela doit être pris en considération dans l'utilisation possible du CC et du MPA dans le traitement hormonal des épilepsies.

(J. Roger, *Marseille*)

RESUMEN

En ratas hembras y machos hemos investigado los efectos comparativos del benzoato de estradiol (EB), del antiestrógeno citrato clomifeno (CC) y del progestin acetato medroxiprogesterona (MPA) sobre los ataques inducidos mediante la inyección sistémica de ácido kaínico (15 mg/kg, intraperitonealmente). La administración subcutánea durante 10 días de EB (10 μg/kg) o dosis altas de CC (50 mg/kg) potenciaron significativamente los ataque inducidos por el kainato, siendo este efecto más pronunciado en los animales macho. Dosis de 2.5 mg/kg de CC potenciaron los ataques inducidos por el kainato en los machos pero no produjeron efectos en las hembras. Dosis bajas de CC (0.5 mg/kg) mostraron un efecto anticonvulsivo ligero en ambos sexos. La administración repetida de MPA (2.5 mg/kg) protegieron parcialmente a las hembras de los ataques inducidos por el kainato; en los machos, el MPA produjo un 30% de incremento en la escala de severidad de los ataques aunque la diferencia con la escala de los machos control no fué significativa ($p > 0.05$). Toda esta información sugiere que los esteriodes, según el sexo, influencian los ataques inducidos por el kainato de un modo sexo-dependiente y que los efectos del antiestrógeno CC son dosis-dependientes. Estos datos podrían ser tenidos en cuenta en vista de una posible utilización del CC y del MPA en la terapeútica hormonal de los trastornos convulsivos.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

Wir untersuchten die Wirkungen von Oestradiolbenzoat (EB), dem Antioestrogen Clomiphencitrat (CC) und dem Progestinmedroxyprogesteronacetat (MPA) auf Anfälle, die durch die systemische Injektion von Kainsäure (15 mg/kg intraperitoneal) bei männlichen und weiblichen Ratten hervorgerufen wurden, 10-tägige subkutane Anwendung von EB (10 ug/kg) oder hohe Dosen von CC (50 mg/kg) potenzierten in signifikanter Weise Kain-induzierte Anfälle. Diese Wirkung trat besonders bei männlichen Tieren auf. Dosen von 2,5 mg/kg CC potenzierte Kainat-induzierte Anfälle bei männlichen aber nicht bei weiblichen Ratten. Niedrige Dosen von CC (0,5 mg/kg) zeigten eine milde antikonvulsive Wirkung bei beiden Geschlechtern. Die wieder-

holte Anwendung von MPS (2,5 mg/kg) schützte weibliche Tiere partiell gegen Kainatinduzierte Anfälle. Bei männlichen Ratten bewirkte MPA eine 30-prozentige Zunahme der Schwere der Anfälle, obwohl der Unterschied zu dem Score der Kontrolltiere nicht signifikant war ($p > 0,05$). Diese Ergebnisse legen nahe, daß Geschlechtssteroide Kainat-induzierte Anfälle in einer geschlechtsabhängigen Art und Weise beeinflussen und daß die Wirkungen des Antioestrogens CC dosisabhängig sind. Das muß bei einer möglichen Anwendung von CC und MPA in der Hormontherapie von Anfallsleiden [berücksichtigt werden].

(D. Scheffner, *Heidelberg*)