

## EFFECT OF ANTIHORMONES IN AMYGDALA-KINDLED SEIZURES IN RATS

*Kinga K. Borowicz*<sup>#</sup>

Department of Pathophysiology, Medical University, Jaczewskiego 8, PL 20-090 Lublin, Poland

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Tamoxifen (TXF; an antiestrogen), cyproterone acetate (CYP; an antiandrogen) and mifepristone (MIF; an antigestagen) did not affect kindling parameters (afterdischarge threshold, seizure severity, seizure duration and afterdischarge duration) in fully-kindled rats. TXF (50 mg/kg) and CYP (50 mg/kg), when combined with carbamazepine, or phenobarbital, both antiepileptics administered at their highest subprotective doses of 15 mg/kg, resulted in significant reduction of the seizure and afterdischarge durations, both in male and female rats. Additionally, the combination of carbamazepine and cyproterone markedly increased the afterdischarge threshold in fully-kindled rats of both genders. The interaction between antihormones and carbamazepine, or phenobarbital, was not reversed by the respective gonadal hormones (estradiol, progesterone, and testosterone), kainic acid, or strychnine. However, the TXF-, and CYP-induced effect on the action of carbamazepine was abolished by bicuculline, N-methyl-D-aspartic acid and aminophylline. The effect of TXF on the protective activity of phenobarbital was reversed by bicuculline and N-methyl-D-aspartic acid. Finally, the CYP-mediated effect on phenobarbital action was abolished by bicuculline and aminophylline. Neither TXF nor CYP altered free plasma levels and brain levels of carbamazepine or phenobarbital, so a pharmacokinetic interaction between antihormones and antiepileptic drugs is not probable. In view of the present data, it may be suggested that the protective activity of the antiestrogen and antiandrogen are mostly associated with the enhancement of GABA-ergic and purinergic transmission in the central nervous system. Also the augmentation of glutamatergic transmission, realized through NMDA receptors, may be involved in the mechanism of antiseizure action of TXF and CYP.

**Key words:** *antihormones, tamoxifen, cyproterone, antiepileptics, amygdala-kindled seizures*

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<sup>#</sup> *correspondence*; e-mail: kornel@asklepios.am.lublin.pl

As it was previously reported, gonadal hormones may influence both seizure initiation and propagation. For instance, estradiol showed proconvulsive properties either in experimental animals [8, 9, 12] or in epileptic patients [1, 2, 11]. However, progesterone treatment evoked anticonvulsive action in generalized motor seizures [4, 7, 10, 13], but exacerbated absence seizures in woman [6]. Testosterone was reported to exert both protective [3, 5] and proconvulsive [14] action in experimental models of epilepsy.

Hitherto reported data have not elucidated the role of gonadal hormone antagonists in seizure processes. In our previous study (unpublished data), we found that tamoxifen (TXF, an antiestrogen) significantly elevated the threshold for electroconvulsions in female mice, and cyproterone (CYP, an antiandrogen) raised the threshold in male ones. Moreover, TXF potentiated the protective activity of valproate, diphenylhydantoin and clonazepam, but not that of carbamazepine or phenobarbital against maximal electroshock-induced convulsions in female mice. On the other hand, CYP enhanced the anticonvulsive action of valproate, carbamazepine, diphenylhydantoin and clonazepam, but not that of phenobarbital against maximal electroshock in male animals (Tab. 1). Mifepristone (MIF, a progesterone antagonist) failed to affect either the electroconvulsive threshold, or the efficacy of antiepileptic drugs against maximal electroshock in mice of both genders.

In the present study, we wanted to investigate the effect of TXF, CYP, and MIF on the anticonvulsive activity of conventional antiepileptic drugs against amygdala-kindled seizures in rats, which represent an animal model of partial seizures with secondary generalization. None of three antihormones used in this study affected any kindling parameter in fully-kindled rats. TXF (50 mg/kg) and CYP (50 mg/kg), when combined with carbamazepine, or phenobarbital, applied at their subprotective doses of 15 mg/kg, resulted in significant reduction of the seizure and afterdischarge durations, both in male and female rats. Additionally, the combination of carbamazepine and CYP markedly increased the afterdischarge threshold in fully-kindled rats of both genders. The present results appear quite different from those obtained with maximal electroshock test in mice (Tab. 1).

The interaction between antihormones and carbamazepine, or phenobarbital, was not reversed by

respective sex steroid hormones (estradiol, progesterone, and testosterone), kainic acid, or strychnine. However, the TXF-, and CYP-induced effect on the action of carbamazepine was abolished by bicuculline, N-methyl-D-aspartic acid and aminophylline.

Table 1. Effect of tamoxifen (TXF) and cyproterone (CYP) on seizure activity in maximal electroshock (MES) in mice and amygdala-kindled seizures in rats (AKS)

Treatment +	saline	VPA	CBZ	DPH	PB	CLO	ETX
MES:							
TXF <sup>f</sup>	(+)	(+)	0	(+)	0	(+)	ND
CYP <sup>m</sup>	(+)	(+)	(+)	(+)	0	(+)	ND
AKS:							
TXF	0	0	(+)	0	(+)	0	0
CYP	0	0	(+)	0	(+)	0	0

VPA – valproate, CBZ – carbamazepine, DPH – diphenylhydantoin, PB – phenobarbital, CLO – clonazepam, ETX – ethosuximide, AKS – amygdala-kindled seizures in rats, (+) – potentiating effect, 0 – no effect, ND – not determined, <sup>f</sup> – females, <sup>m</sup> – males

Table 2. Effect of some convulsants upon the protective effects of antihormones and their combinations with antiepileptics in maximal electroshock (MES) in mice and amygdala-kindled seizures (AKS) in rats

Treatment +	BIC	AMI	NMDA	KA
MES:				
TXF <sup>f</sup>	(+)	(+)	(++)	(++)
CYP <sup>m</sup>	(++)	(+)	0	0
VPA+TXF <sup>f</sup>	(+)	(+)	0	(+)
VPA+CYP <sup>m</sup>	(+)	(+)	(+)	0
DPH+TXF <sup>f</sup>	(++)	(++)	(+)	(+)
DPH+CYP <sup>m</sup>	(++)	0	(+)	0
CLO+TXF <sup>f</sup>	(++)	(++)	(++)	(++)
CLO+CYP <sup>m</sup>	(+)	(+)	(+)	0
CBZ+CYP <sup>m</sup>	(++)	(++)	(+)	(++)
AKS:				
CBZ+TXF	(++)	(++)	(++)	0
CBZ+CYP	(++)	(++)	(++)	0
PB+TXF	(++)	0	(++)	0
PB+CYP	(++)	(++)	0	0

BIC – bicuculline, AMI – aminophylline, NMDA – N-methyl-D-aspartic acid, KA – kainic acid, (++) – abolishing effect, (+) partial reversing effect, 0 – no effect, <sup>f</sup> – females, <sup>m</sup> – males. See also the legend to Table 1

The effect of TXF on the protective activity of phenobarbital was reversed by bicuculline and N-methyl-D-aspartic acid. The CYP-mediated effect on phenobarbital action was abolished by bicuculline and aminophylline (Tab. 2).

Neither TXF nor CYP altered free plasma levels and brain levels of carbamazepine or phenobarbital, so a pharmacokinetic interaction is not probable.

The combined treatment of the two antihormones with antiepileptic drugs did not affect motor performance, and did not result in significant long-term memory deficits.

Our data confirm the hypothesis that gonadal hormone antagonists-mediated events may play some role in seizure processes in the central nervous system and can modulate the protective activity of some conventional antiepileptic drugs against kindled seizures. The nature of the activity of antihormones does not seem to be related to their influence on steroid hormonal receptors, or glycinergic transmission in the central nervous system. The mechanism of action of gonadal hormone antagonists might be most probably associated with GABA- and adenosine-mediated events in the brain.

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