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BRIEF COMMUNICATION

Inhibitory Influence of Morphinans on Ictal and Interictal EEG Changes Induced by Cortical Application of Penicillin in Rabbits: A Comparative Study With NMDA Antagonists and Pentobarbitone

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ZENG, Y. C., A. PEZZOLA, A. S. DE CAROLIS AND S. SAGRATELLA. *Inhibitory influence of morphinans on ictal and interictal EEG changes induced by cortical application of penicillin in rabbits: A comparative study with NMDA antagonists and pentobarbitone.* PHARMACOL BIOCHEM BEHAV 43(2) 651–656, 1992.—The effects of dextrorphan (DX) and dextromethorphan (DM) were tested using the electroencephalogram (EEG) and behavioral effects induced by topical cortical application of penicillin in rabbits. For comparison, the influence of the NMDA antagonists, dizocilpine (MK 801) and 3-((±-2-carboxypiperazine-4-*yl*)propyl-1-phosphonic acid (CPP), and of pentobarbitone was investigated. Intracortical injection of 500 IU of penicillin produced an EEG spiking followed by a repeated generalization of the electrical and behavioral symptoms. Within a few minutes, DX (5–15 mg/kg, IV) or pentobarbitone (5–10 mg/kg, IV) reduced dose dependently and significantly ($p < 0.01$) the interictal and ictal EEG and behavioral effects elicited by cortical injection of 500 IU of penicillin. Higher doses of pentobarbitone (20 mg/kg, IV) but not of DX (20 mg/kg, IV) completely blocked the ictal behavioral and EEG effects elicited by cortical injection of 500 IU of penicillin. Within a few minutes, MK 801 (0.1–0.2 mg/kg, IV) or CPP (10–20 mg/kg, IV) reduced dose dependently and significantly ($p < 0.01$) the ictal EEG and behavioral effects elicited by cortical injection of 500 IU of penicillin, while they did not affect the penicillin-induced interictal EEG changes. Higher doses of MK 801 (0.3 mg/kg, IV) completely blocked the ictal behavioral and EEG effects elicited by cortical injection of 500 IU of penicillin. Within a few minutes, DM (10–20 mg/kg, IV) blocked the behavioral effects, but failed to affect either the interictal or the ictal EEG effects induced by cortical injection of 500 IU of penicillin. The data promote an involvement of NMDA receptors in the electrical and behavioral generalization of the epileptiform activity elicited by penicillin in rabbits. The results also indicate that morphinans might be successfully used for the acute treatment of epileptic and convulsive phenomena.

Morphinans NMDA Penicillin Epilepsy Rabbit

MORPHINAN derivatives are a chemical opiate-related class, which includes dextrorphan (DX) and dextromethorphan (DM). This kind of drug was introduced in the 1960s for their antitussive properties. Renewed interest in them has arisen from recent studies that show that DM and DX act in several experimental models as anticonvulsant and neuroprotective-antiischemic drugs (20,22).

The anticonvulsant properties of DM and DX—which are dependent upon their noncompetitive NMDA antagonistic effects (2,4,5)—have been demonstrated on the behavioral convulsions induced by a maximal electroshock (MES) (22), penthylenetetrazole (PTZ) (8), or NMDA (11). From the electrophysiological point of view, DX has been reported to counteract the "magnesium-free" and NMDA-induced epileptiform

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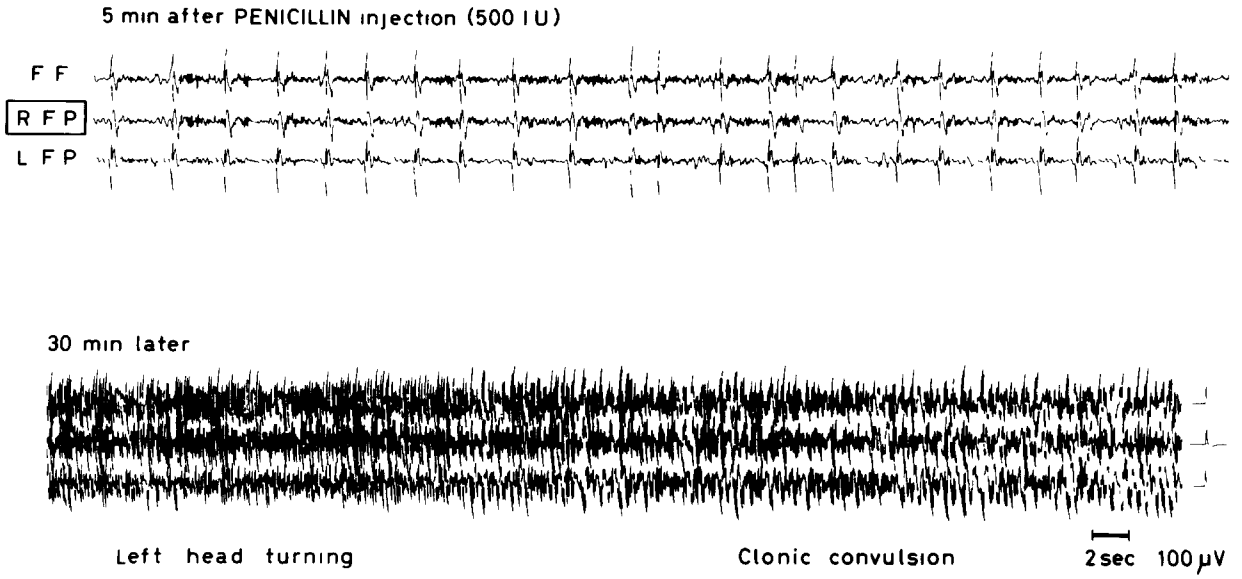

FIG. 1. EEG and motor pattern induced by injection of 500 U penicillin into the sensorimotor cortex in the rabbit. (Top) An interictal period, made of intermittent spike-wave complexes, is shown. (Bottom) An ictal EEG seizure is shown. High-frequency (10–15 Hz), high-voltage (500–600 μV) spikes occurred and were paralleled by an adversive attack of the head followed by clonic convulsions. The square surrounds the locus of injection of penicillin. L, left; R, right; F, anterior sensorimotor cortex; P, posterior sensorimotor cortex.

bursting in the cortex (2) and hippocampus of rats (5,18). In in vivo studies, DM failed to affect hippocampal excitability after acute treatment, while it reduced amygdaloid kindling after chronic treatment in rats (7). The electrical changes in the brain that accompany behavioral convulsions induced by several convulsant drugs can be defined as electrical seizures (15). Even if competitive and noncompetitive NMDA antagonists have been reported to affect electrical changes induced by penicillin in rats and rabbits (11,16), there are no reports in the literature about an influence of morphinans on electrical seizures. The capability of an anticonvulsant drug to affect electrical seizures is an important finding because behavioral and electrical dissociative phenomena have been described after administration of several anticonvulsants (10,17).

In the present article, we compared the influence of DX and DM on the ictal and interictal behavioral and electroen-

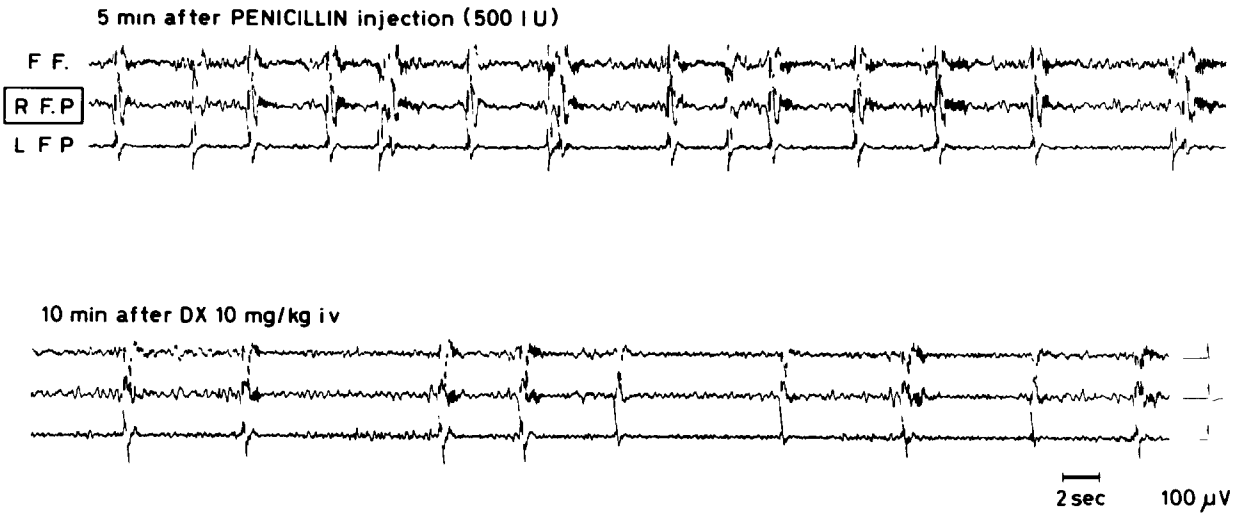

FIG. 2. Effects of dextrorphan (DX) on interictal EEG changes induced by penicillin in the rabbit. (Top) The record shows the interictal EEG changes occurring in the cortical leads 5 min after the intracortical injection of 500 IU of penicillin in the rabbit. (Bottom) DX 10 mg/kg (IV), administered 1 min after, within 10 min induced a decrease of the frequency of the cortical spike-wave complexes. The square surrounds the locus of injection of penicillin. R, right; L, left; F, anterior sensorimotor cortex; P, posterior sensorimotor cortex.

TABLE 1

EFFECTS OF MORPHINANS ON PENICILLIN-INDUCED CHANGES

			EEG Interictal Changes			
			Spike-Wave Complexes/min (± SEM)			
Drug	Dose	n	t = 20′	t = 40′	t = 60′	
PEN	500 IU	6	32 ± 3	48 ± 3	51 ± 4	
+DX	5 mg/kg	6	22 ± 4	37 ± 4	33 ± 4	
+DX	10 mg/kg	6	12 ± 2*	21 ± 2*	20 ± 3*	
+DX	15 mg/kg	6	8 ± 3*†	19 ± 4*†	18 ± 4*†	
+DM	20 mg/kg	6	34 ± 5	47 ± 4	49 ± 5	
			EEG Ictal Changes			
			No. EEG Seizures/20 min (± SEM)			TSD
Drug	Dose	n	Up to 20′	Up to 40′	Up to 60′	(s ± SEM)
PEN	500 IU	6	8 ± 2	9 ± 1	8 ± 2	1,120 ± 67
+DX	5 mg/kg	6	4 ± 1	6 ± 2	7 ± 3	705 ± 84*
+DX	10 mg/kg	6	2 ± 1*	4 ± 2*	5 ± 2*	520 ± 63*
+DX	15 mg/kg	6	2 ± 1*†	3 ± 2*†	3 ± 1*†	320 ± 56*†
+DM	20 mg/kg	6	5 ± 1	7 ± 2	8 ± 2	1,190 ± 110
			Behavioral Changes			
			No. Tonic Seizures/20 min			
Drug	Dose	n	Up to 20′	Up to 40′	Up to 60′	TSD (s ± SEM)
PEN	500 IU	6	7 ± 2	8 ± 1	7 ± 2	340 ± 24
+DX	5 mg/kg	6	0*	0*	2 ± 1*	21 ± 05*
+DX	10 mg/kg	6	0*	0*	0*	0*
+DM	10 mg/kg	6	2 ± 1*	4 ± 2	6 ± 3	185 ± 42*
+DM	20 mg/kg	6	0*	3 ± 2	5 ± 2	45 ± 12*

PEN, penicillin; TSD, total seizure time during 1 h of recording.
*Different from PEN alone ($p < 0.01$).
†Different from DX 5 mg/kg ($p < 0.01$).

cephalogram (EEG) changes after intracortical injection of penicillin in rabbits. For further comparison, we also studied the inhibitory influence of the NMDA antagonists, dizocilpine (MK 801) and 3-((±)-2-carboxypiperazine-4-*yl*propyl-1-phosphonic acid (CPP), and of the well-known anticonvulsant, pentobarbitone, on the penicillin-induced electrical and behavioral changes.

METHOD

The experiments were performed on 78 male rabbits, weighing 2.0–2.5 kg. Animals were prepared for EEG recording under local anesthesia (2% xilocaine). Six electrodes were fixed into the skull over the sensorimotor and optic cortices on both sides. The epileptic focus was produced by intracortical injection of sodium penicillin G (500 U) dissolved in water. A volume of 10 μl was injected with a Hamilton syringe through a 1-mm hole made in the skull, at a depth of 1 mm from the cortical surface, into the sensorimotor cortex of one side.

In each experiment, the frequency of interictal spikes or spike-wave complexes, and the incidence of behavioral and EEG ictal seizures were measured each 20 min for 1 h of recording. The total duration of EEG and behavioral seizures [total seizure duration (TSD)] was obtained by adding the various lengths of time each seizure lasted during a 1-h recording session. The effects of drugs were studied by administering DX (5–20 mg/kg), DM (10–20 mg/kg), MK 801 (0.1–0.3 mg/kg), CPP (10–20 mg/kg), or pentobarbitone (10–20 mg/kg) intravenously 5–10 min after injection of penicillin. The measuring of the seizure duration was limited to the first hour because in preliminary experiments it was noted that the inhibitory effect of the tested drugs never exceeded 40–50 min.

The statistical analysis [analysis of variance (ANOVA) followed by the Student-Newmen-Kuels' test for multiple comparison] was performed on the mean of the values (± SEM) in drug-treated and untreated animals. All drugs were dissolved in water. All doses refer to the weight of the base.

RESULTS

Intracortical injection of 500 IU penicillin elicited, within 0.5–2 min, epileptiform activity, which lasted for 1.5–2.5 h. This epileptiform activity was characterized by the intermittent generalization of the behavioral and electrical seizures. In particular, ictal, high-frequency (10–15 Hz), high-voltage (600–800 μV) biphasic spikes occurred and were concomitant with tonic adversive attacks (Fig. 1). These behavioral alterations consisted of spastic turning of the head to the contralat-

TABLE 2

EFFECTS OF NMDA ANTAGONISTS ON PENICILLIN-INDUCED CHANGES

			EEG Interictal Changes			
			Spike-Wave Complexes/min (± SEM)			
Drug	Dose	n	t = 20′	t = 40′	t = 60′	
PEN	500 IU	6	32 ± 3	48 ± 3	51 ± 4	
+MK 801	0.2 mg/kg	5	26 ± 4	38 ± 6	44 ± 7	
+CPP	20 mg/kg	5	35 ± 5	44 ± 5	48 ± 6	
			EEG Ictal Changes			
			No. EEG Seizures/20 min (± SEM)			
Drug	Dose	n	Up to 20′	Up to 40′	Up to 60′	TSD (s ± SEM)
PEN	500 IU	6	8 ± 2	9 ± 1	8 ± 2	1,120 ± 67
+MK 801	0.1 mg/kg	5	3 ± 1*	4 ± 1*	6 ± 3	421 ± 65*
+MK 801	0.2 mg/kg	5	2 ± 1*	2 ± 1*	3 ± 2*†	210 ± 45*†
+MK 801	0.3 mg/kg	4	0*†	0*†	0*†	0*†
+CPP	10 mg/kg	5	5 ± 2	7 ± 3	7 ± 3	1,010 ± 130
+CPP	20 mg/kg	5	3 ± 2*	4 ± 2*†	5 ± 3	765 ± 112*
			Behavioral Changes			
			No Tonic Seizures/20 min			
Drug	Dose	n	Up to 20′	Up to 40′	Up to 60′	TSD (s ± SEM)
PEN	500 IU	6	7 ± 2	8 ± 1	7 ± 2	340 ± 24
+MK 801	0.1 mg/kg	5	0*	0*	1 ± 1*	12 ± 04*
+MK 801	0.2 mg/kg	5	0*	0*	0*	0*
+CPP	10 mg/kg	5	2 ± 1*	3 ± 1*	6 ± 3	256 ± 89*
+CPP	20 mg/kg	5	0*	0*‡	0*‡	0*

PEN, penicillin; TSD, total seizure time during 1 h of recording.
*Different from PEN alone ($p < 0.01$).
†Different from MK 801 0.1 mg/kg ($p < 0.01$).
‡Different from CPP 10 mg/kg ($p < 0.01$).

eral side with respect to the penicillin-treated cortex, followed by generalized clonic convulsions. Each seizure lasted 0.5–1.5 min and, after a brief flattening of the EEG, was followed by an interictal period. Each interictal period lasted 1–2 min, and was characterized by intermittent spike-wave complexes accompanied by jerks of the head and forelimbs (Fig. 1) [see (16) for further details].

DX (5, 10, and 15 mg/kg, IV) and DM (10–20 mg/kg, IV) were administered to 18 and 10 animals, respectively, 5 min after application of penicillin, during the phase of intermittent generalization of the epileptiform activity. Within a few minutes, DX affected the interictal EEG and behavioral changes and the ictal generalization of the epileptiform activity. As compared with control animals, the drug dose dependently and significantly ($p < 0.01$) reduced the frequency of interictal spike-wave complexes (Fig. 2, Table 1) and the incidence of the behavioral and electrical ictal seizures (Table 1) and the behavioral and electrical TSD (Table 1). Higher doses of DX (20 mg/kg, IV) failed to completely block the ictal or interictal EEG changes.

Within 1 h, DM failed to affect either the ictal or interictal EEG changes elicited by topical application of penicillin. EEG seizures and interictal spike-wave complexes, as far as incidence and frequency are concerned, were similar to those in control animals (Table 1). The EEG TSD was not significantly affected with respect to control animals (Table 1). Behaviorally, DM reduced dose dependently and significantly ($p < 0.01$) the behavioral TSD (Table 1), and the incidence of the behavioral seizures for a period of 15–20 min (Table 1).

MK 801 (0.1–0.2 mg/kg, IV) and CPP (10–20 mg/kg, IV) were administered to 10 and 10 animals, respectively, 5 min after application of penicillin, during the phase of intermittent generalization of epileptiform activity.

Within a few minutes, NMDA antagonists affected the ictal generalization of the epileptiform activity but failed to affect the interictal EEG and behavioral changes. As compared with control animals, the drugs dose dependently and significantly ($p < 0.01$) reduced the incidence of the behavioral and electrical ictal seizures and the behavioral and electrical TSD but did not change the frequency of interictal spike-wave complexes (Table 2). Higher doses of MK 801 (0.3 mg/kg, IV) completely blocked the ictal EEG changes during the 1-h recording session but did not affect the interictal EEG changes (Table 2).

Pentobarbitone (10–15 mg/kg, IV) was administered to 10 animals 5 min after application of penicillin, during the phase of intermittent generalization of the epileptiform activity. Within a few minutes, pentobarbitone affected the interictal

EEG and behavioral changes and the generalization of the epileptiform activity. As compared with control animals, the drug dose dependently and significantly ($p < 0.01$) reduced the frequency of interictal spike-wave complexes (Table 3), incidence of behavioral and electrical ictal seizures (Table 3), and behavioral and electrical TSD (Table 3). Higher doses of the drug (20 mg/kg, IV) completely blocked the ictal, but not the interictal EEG changes during the 1-h recording session (Table 3).

DISCUSSION

Morphinan drugs, such as DX and DM, have been reported to present anticonvulsant activity in in vivo and in vitro experiments in rats. These drugs were particularly efficacious in blocking behavioral epileptic activity induced by chemical agents such as PTZ (8) or NMDA (11) or by direct brain electrical stimulation such as MES (22). In the present article the antiepileptic effects of DX have been confirmed on the EEG and behavioral epileptiform activities induced by cortical application of penicillin in rabbits. Penicillin-induced cortical epileptogenic foci, where seizures begin focally and then generalize, may be regarded as a model of "grand mal" epilepsy. In fact, well-known anticonvulsants such as diphenylhydantoin, benzodiazepines and barbiturates block the spreading of the epileptiform activity, counteracting especially the ictal EEG and behavioral seizures induced by penicillin topically applied on the cortex of cats and rabbits (16,19). In the present article, the anticonvulsant effects of DX and DM have been compared with those of NMDA antagonists and of pentobarbitone, a well-known anticonvulsant. The rank of inhibitory potency against the penicillin-induced ictal EEG and behavioral effects was: MK 801 > pentobarbitone > DX > CPP > DM. The rank of inhibitory potency against penicillin-induced interictal EEG and behavioral effects was: pentobarbitone > DX > MK 801 = CPP = DM. Thus, pentobarbitone was the most active drug against interictal EEG changes, while MK 801 was the most active drug against ictal EEG changes. This indicates a specific involvement of NMDA receptors in the generalization of the epileptiform activity elicited by penicillin. The lack of effect of NMDA antagonists against interictal changes is confirmed by the slight inhibitory influence that these drugs present toward the interictal epileptiform activity induced by penicillin or other GABA antagonist drugs in cortical or hippocampal slices (9,14). IV injection of DX (4–6 mg/kg, IV) specifically reduced the excitatory effects of NMDA in the spinal cord of rats (4). At the same doses, DX reduced the behavioral and EEG seizures elicited by penicillin in rabbits. This indicates that the antiepileptic effects of DX probably depend upon the NMDA antagonistic properties of this drug. In agreement with this hypothesis, other drugs endowed with NMDA antagonistic properties, such as MK 801, CPP, and the "dissociative anesthetics" phencyclidine and ketamine, reduced penicillin-induced EEG and behavioral ictal seizures in rabbits (16). However, as opposed to NMDA antagonists, which specifically reduced only the ictal phase of the seizures, DX also presented an influence on interictal EEG pictures, reducing significantly the interictal

TABLE 3

EFFECTS OF PENTOBARBITONE ON PENICILLIN-INDUCED CHANGES

			EEG Interictal Changes			
			Spike-Wave Complexes/min (±SEM)			
Drug	Dose	*n*	*t* = 20′	*t* = 40′	*t* = 60′	
PEN	500 IU	6	32 ± 3	48 ± 3	51 ± 4	
+PB	10 mg/kg	5	18 ± 3*	28 ± 4*	34 ± 5*	
+PB	15 mg/kg	5	6 ± 1*†	7 ± 2*†	8 ± 3*†	
+PB	20 mg/kg	4	3 ± 1*†	4 ± 2*†	5 ± 3*†	
			EEG Ictal Changes			
			No EEG Seizures/20 min (±SEM)			TSD
Drug	Dose	*n*	Up to 20′	Up to 40′	Up to 60′	(s ± SEM)
PEN	500 IU	6	8 ± 2	9 ± 1	8 ± 2	1,120 ± 67
+PB	10 mg/kg	5	3 ± 1*	4 ± 1*	5 ± 1	625 ± 85*
+PB	15 mg/kg	5	1 ± 1*	2 ± 2*	2 ± 1*†	256 ± 12*†
+PB	20 mg/kg	4	0*†	0*†	0*†	0*†
			Behavioral Changes			
			No. Tonic Seizures/20 min			TSD
Drug	Dose	*n*	Up to 20′	Up to 40′	Up to 60′	(s ± SEM)
PEN	500 IU	6	7 ± 2	8 ± 1	7 ± 2	340 ± 24
+PB	10 mg/kg	5	0*	0*	1 ± 1*	18 ± 09*
+PB	15 mg/kg	5	0*	0*	0*	0*

PEN, penicillin; TSD, total seizure time during 1 h of recording.
*Different from PEN alone ($p < 0.01$).
†Significantly different from PB 10 mg/kg ($p < 0.01$).

spike-wave frequency. This may indicate that the antiepileptic effects of DX do not only depend upon an NMDA antagonism. Similarly, Leander et al. (11) reported that DX was a more potent anticonvulsant than ketamine, but a much weaker NMDA antagonist after IV or microelectrophoretic administration (3,4). At least some of the anticonvulsant effects of DX may be mediated, not only by an interaction with the NMDA receptor-ionophore complex, but also by an activity at a distinct DM binding site (13,21). In our study, DM also presented an anticonvulsant effect toward the behavioral ictal seizures due to penicillin. Caramiphen and carbetapentane, which bind to the DM binding sites, also present anticonvulsant activity (13) without affecting NMDA excitability (2). In fact, the ligands of DM binding sites affect synaptic transmission, reducing the release of neurotransmitters (23) and the electrical synaptic responses (1,6,18).

DM, as opposed to DX, presented a less anticonvulsant activity and did not affect electrical ictal or interictal EEG seizures due to penicillin. In agreement with this finding, DX, but not DM, was able to block "magnesium-free" epileptiform bursting in rat hippocampal slices (6,18). This incapability of DM to block electrical seizures may reflect a lesser NMDA antagonism of DM with respect to DX. Moreover, DM, in contraposition to DX, failed to induce full electrocortical changes in rats, which indicates a complete interaction with PCP/σ-receptors linked to the NMDA receptor-ionophore complex (18). However, when chronically administered DM might present full antiepileptic effects. In fact, although it was not able to modify hippocampal excitability in acute administration DM blocked amigdaloid kindling after chronic treatment in rats (7).

In conclusion, our results point toward a possible use of DX in the acute treatment of ictal seizures or acute cerebral ischemia because, in addition to its clear postsynaptic NMDA antagonism, this drug presents an ability to affect the synaptic transmission by acting on DM binding sites.

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