Pharmacology Biochemistry & Behavior, Vol. 31, pp. 153–162. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Episodic Barrel Rotations Induced by Intrastriatal Injection of Quinolinic Acid in Rats. Inhibition by Anticonvulsants

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Received 2 April 1987

MARRANNES, R. AND A. WAUQUIER. *Episodic barrel rotations induced by intrastriatal injection of quinolinic acid in rats. Inhibition by anticonvulsants.* PHARMACOL BIOCHEM BEHAV 31(1) 153–162, 1988.—Unilateral intrastriatal injection of quinolinic acid (2,3 pyridine dicarboxylate; QUIN) in the rat produces episodic barrel rotations and tonic-clonic forepaw movements, lasting for several hours. We investigated whether intraperitoneal posttreatment with anticonvulsants could abolish this phenomenon when it is already fully developed, and whether their potency ratio was similar in models of epilepsy. All 8 tested antiepileptics, namely carbamazepine, clonazepam, diazepam, diphenylhydantoin, ethosuximide, flunarizine, phenobarbital and sodium valproate decreased this behaviour in a dose-dependent way. Six other drugs with anticonvulsant properties were also effective: DL-2-amino-7-phosphonoheptanoic acid, desipramine, etomidate, ketamine, meprobamate and sabeluzole. The ED_{50}-values for halving the frequency of the episodes of barrel rotation correlated well with published ED_{50}-values for inhibition of tonic hindpaw extension in the maximal metrazol seizure test ($r_s = .95, p < 0.001$) and with the ED_{50}-values for halving the duration of the forepaw clonus in the rat-kindling model ($r_s = .93, p < 0.001$). This quinolinic acid test allows visualization of the onset of action of anticonvulsants, with each animal as its own control. In order to assess whether this test is also sensitive to drugs influencing the symptoms of Huntington's disease, the effect of the dopamine antagonists haloperidol and pimozide, the acetylcholinesterase inhibitor physostigmine and the anticholinergics atropine and dexetimide were investigated as well. The experiments suggested that the barrel rotations and clonic forepaw movements, only 3–6 hours after intrastriatal injection of QUIN respond to anticonvulsants, but are not specifically sensitive to drugs used in the symptomatic treatment of Huntington's disease.

Anticonvulsants Antiepileptics Barrel rotation Epilepsy Huntington's disease
Excitotoxic amino acids Quinolinic acid Striatum 2-APH Carbamazepine Clonazepam
Desipramine Diazepam Diphenylhydantoin Ethosuximide Etomidate Flunarizine
Ketamine Meprobamate Phenobarbital Sabeluzole Sodium valproate Pentylenetetrazole
Apomorphine Haloperidol Pimozide Dexetimide Atropine Physostigmine

QUINOLINIC acid (2,3 pyridine dicarboxylate; QUIN) is a natural constituent of the brain and a tryptophan metabolite [9, 23, 24, 51]. QUIN is also an excitotoxic amino acid which is reported to act on the N-methyl-D-aspartate (NMDA) receptor [21, 38, 45]. Intracerebral injection of QUIN produces neuronal excitation and axon sparing lesions in the brain [28, 29, 40, 42]. Intrahippocampal injection of excitotoxic amino acids such as QUIN or kainic acid in the rat has been proposed as an animal model of temporal lobe epilepsy in man [39], intraamygdaloid injection as a model for status epilepticus [7] and intrastriatal injection as a model for Huntington's disease [18, 34, 42]. The rationale is that these injections provoke seizures or produce lesions which resemble those found in the corresponding human diseases.

In several studies, the possibility of protection against the aforementioned effects of excitotoxic amino acids by means of anticonvulsants has been investigated. Intraperitoneal pretreatment with several anticonvulsants prevented convulsions and decreased neurochemical alterations produced by intrahippocampal [47,53], intraamygdaloid [8], intracerebroventricular [30,44] or intraperitoneal [43] injection of excitotoxic amino acids.

After intrastriatal injection of QUIN, there are clonic-tonic movements of the contralateral limbs and episodic barrel rotations [42]. We found that this behaviour could be quantified reliably for several hours. Because of its seizure-like appearance, we investigated whether posttreatment with anticonvulsants could abolish it.

Since intrastriatal injection of QUIN may also serve as a model for Huntington's disease, the effect of drugs which influence the balance of the dopaminergic system versus the cholinergic system was tested as well.

METHOD

Subjects

Adult male Wistar rats (approximately 250 g) were deprived of food from 1 p.m. of the day before the experiment, but were allowed to drink ad lib.

Injection of QUIN

The animals were anesthetized with ether and placed in a David Kopf stereotaxic apparatus. A Hamilton cannula (0.5 mm o.d.) was inserted into the right nucleus caudatus-putamen through a burr hole in the calvarium at the coordinates: 7.8 A; 2.5 L; 2.0 V [19]. Six hundred nmol quinolinate in a volume of 1 μl (at pH 7.4, buffered with 3 mM phosphate) were injected at a rate of 0.5 μl/min. One minute after injection the cannula was slowly withdrawn and the skin was sutured.

Behavioural Measures

Six to nine animals were observed simultaneously, starting 2.5–3 hours after intrastriatal injection of QUIN. By this time, the behaviour was stabilized and on the average, once a minute there was an episode of several barrel-like rotations and tonic-clonic forepaw movements, alternating with quiescence. Every 15 min the animals were scored during 5 min. The number of episodes with barrel-like rotations per 5 min (NEBR) was counted. Since barrel rotations appeared in well-defined bouts, each episode of barrel rotation thus yielded only one score point, irrespective of the number of times the animal turned about its long axis. If the animal did not turn completely (360°) about its long axis, but still showed clonic movements of the forepaw contralateral to the injection site, then the number of episodes of contralateral myoclonies per 5 min (NEC) was scored. NEC was not scored when clonic movements were accompanied by complete barrel rotations.

Drugs

After three control counting periods of 5 min (i.e., 3–3.5 hours after intrastriatal QUIN injection) the tested drugs were injected IP in a volume of 10 ml/kg body weight, with the exception of pentylenetetrazole, which was injected subcutaneously. Thereafter scoring was continued every 15 min. The drugs used were: DL-2-amino-7-phosphonoheptanoic acid (2-APH) (5, 10, 20, 40 mg/kg) apomorphine·HCl·$5H_2O$ (1.25 mg/kg), atropine (2.5 mg/kg), carbamazepine (5, 10, 20 mg/kg), clonazepam (0.31, 0.63, 1.25, 2.5 mg/kg), desipramine·HCl (10, 20, 40 mg/kg), dexetimide·HCl (0.63 mg/kg), diazepam (2.5, 5, 10, 20, 40 mg/kg), diphenylhydantoin (10, 20, 40 mg/kg), ethosuximide (160, 320 mg/kg), etomidate·H_2SO_4 (5, 10, 20 mg/kg), flunarizine·2HCl (10, 20, 40, 80 mg/kg), haloperidol (0.63, 1.25 mg/kg), ketamine (20, 40 mg/kg), meprobamate (40, 80, 160 mg/kg), pentylenetetrazole (20 mg/kg), phenobarbital (10, 20, 40 mg/kg), physostigmine·0·$5H_2SO_4$ (0.63 mg/kg), pimozide (0.63, 1.25 mg/kg), sabeluzole (R 58 735) (1.25, 2.5, 5, 10, 20 mg/kg), sodium valproate (80, 160, 320 mg/kg). Apomorphine, atropine, desipramine, dexetimide·HCl, etomidate, meprobamate, pentylenetetrazole, phenobarbital and pimozide were dissolved in distilled water. Carbamazepine, clonazepam, diazepam, diphenylhydantoin, ethosuximide, flunarizine, ketamine and sodium valproate were given as suspensions, to which one drop of Tween 80 was added per 10 mg drug.

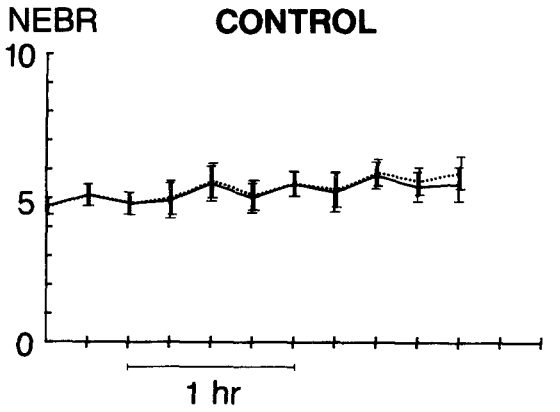

FIG. 1. Control group. Six hundred nmol QUIN was injected intrastriatally about 2.5 hours prior to the origin of the abscissa, which represents time. The ordinate represents the number of episodes of barrel rotations per 5 min (NEBR, full line). The difference between the full and the dotted line corresponds to the number of weaker excitation episodes per 5 min (NEC), in which the animals showed clonic contralateral forepaw movements without a complete (360°) barrel rotation. The dotted line thus represents the total number of excitation episodes per 5 min (NEBR + NEC). Results are given as mean±SEM, n=10.

Sabeluzole, haloperidol and pimozide were dissolved using 0.1, 0.05 or 0.15 nmol tartaric acid, respectively, per 10 mg drug. 2-APH was dissolved in 1 equivalent sodium hydroxide. In addition, the highest concentrations of Tween 80 and tartrate necessary to dissolve the drugs were tested. After injection of the drugs, NEBR and NEC were scored for 90–150 more minutes. In Figs. 1–4, only those time points are shown for which data were available for all animals of the corresponding series.

Statistics

The approximate ED_{50}-values were calculated according to the method of Litchfield and Wilcoxon [32]. The mean NEBR of the last 3 observation periods before injection of the anticonvulsant was calculated for each animal separately and considered as 100%. This was the reference value used to calculate the ED_{50} for a 50% reduction of NEBR. The Spearman rank correlation test was used to correlate the ED_{50}-values obtained with different epilepsy models and parameters.

RESULTS

Behavioural Effects

During the first 60–90 minutes after injection of QUIN, the behaviour was difficult to quantify and to use for testing anticonvulsants because it was rather irregular. The animals mostly sat quiet although some showed running fits and jumping. From about 30 min postinjection, several animals showed slight clonic head movements away from the injection site. In addition, from then, the rats generally sat flexed to the left. Contralateral turning in the horizontal plane was also observed in some animals.

After about 90 min the behaviour became more regular with episodes of several barrel-like rotations. The frequency of these episodes gradually increased and stabilized. During such an episode, the animal showed a group of behavioural

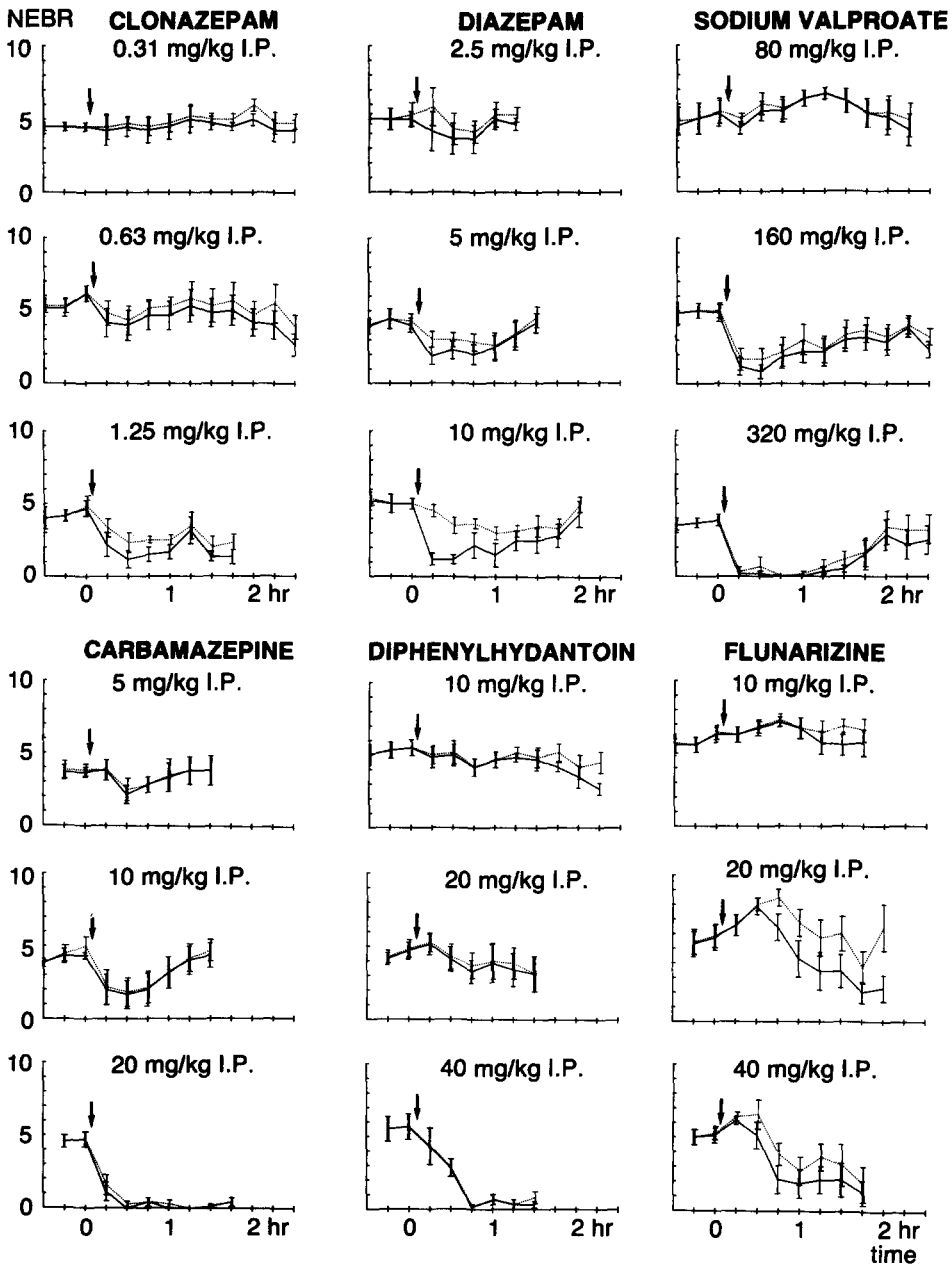

FIG. 2. Influence of anticonvulsants (same axis representation as in Fig. 1) on NEBR (full line) or on the total frequency of episodes of excitation (NEBR + NEC, dotted line) after intrastriatal injection of QUIN (mean±SEM, n=6 or 7). The arrow indicates the moment of IP injection of the anticonvulsant. Graphs with different doses of the same drug are grouped vertically.

phenomena. It often started by chewing. The head was drawn posteriorly to the left side by clonic-tonic movements. Then, the whole body twisted about its long axis in such a manner that the dorsal aspect rotated towards the injection side. Soon the rostral end twisted over completely and the caudal end followed, producing a complete barrel rotation. During such an episode, the animal rotated from 1 up to 17 times about its long axis. Then also regularly the left forepaw was extended caudally whilst the right forepaw was extended rostrally. During and at the end of an episode of barrel rotations, the animal chewed and made clonic movements of the left forepaw, neck, and less frequently the left hindpaw. The direction of the barral rotations was always the same and depended on the injection side. Between the episodes of barrel rotations, the animal sat quietly. The frequency of episodes of barrel rotations during the last observation period before injection of the test drug was 0.99±0.30 episodes per minute (mean±standard deviation, n=273). This episode frequency was nearly constant in time for every rat and remained so for about 3–4 hours (Fig. 1). Subsequently, the number of barrel rotations per episode decreased until there were weaker episodes of similar excita-

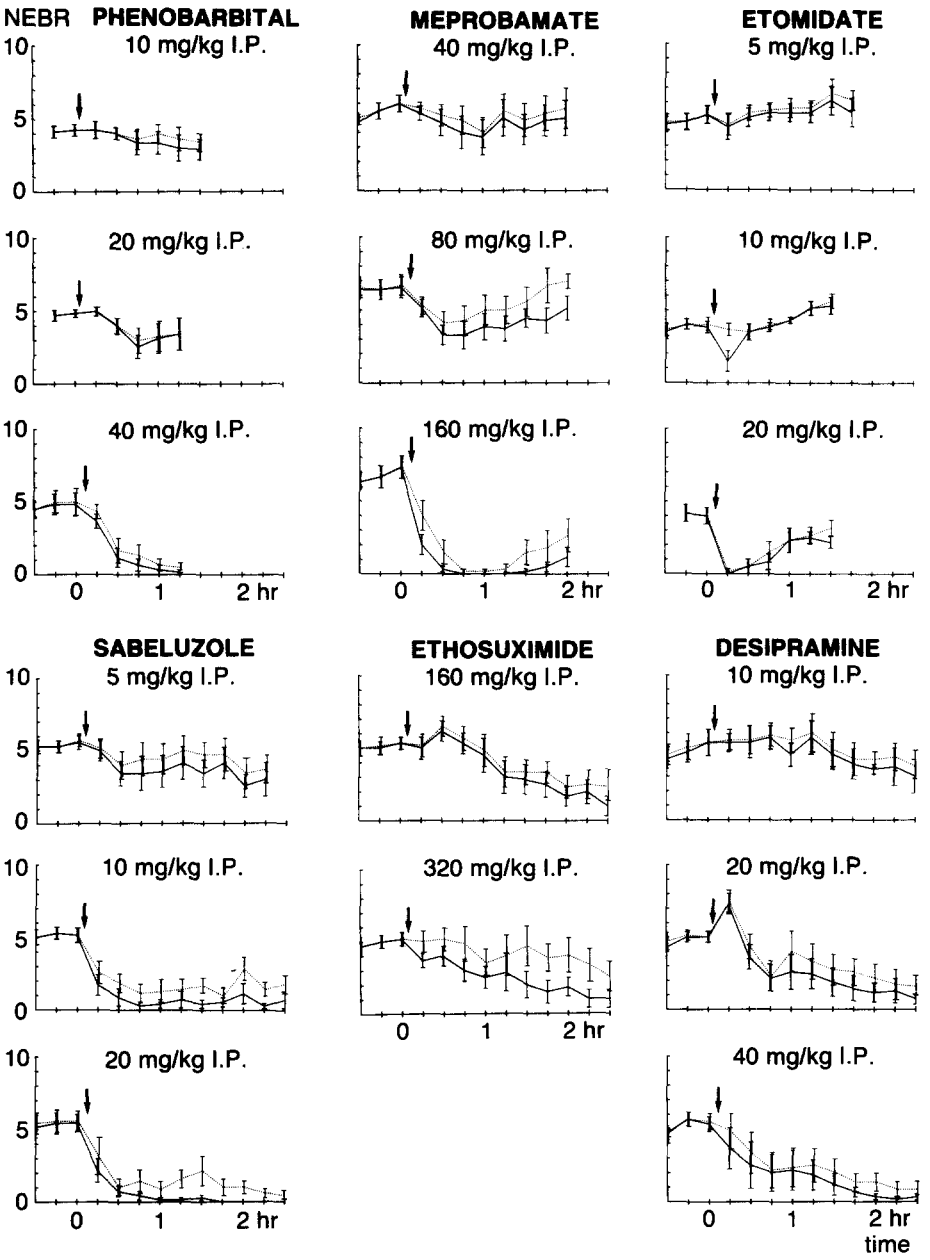

FIG. 3. Influence of anticonvulsants (same axis representation as in Fig. 1) on NEBR (full line) or on the total frequency of episodes of excitation (NEBR + NEC, dotted line) after intrastriatal injection of QUIN (mean±SEM, n=6 or 7). the arrow indicates the moment of IP injection of the anticonvulsant. Graphs with different doses of the same drug are grouped vertically.

tion with clonic contralateral forepaw movements but without a complete (360°) barrel rotation. Finally, this weaker excitation extinguished as well.

Influence of Anticonvulsants

All 14 anticonvulsants decreased the frequency of barrel rotations (NEBR) in a dose-dependent way (Figs. 2–4). The curves also show the speed and duration of action of the drugs. The short-acting hypnotic and anticonvulsant etomidate [48] very rapidly depressed NEBR. Its effect on NEBR lasted less than 30 min at 10 mg/kg and was more prolonged at 20 mg/kg (Fig. 3). Ketamine (Fig. 4), diazepam, carbamazepine, meprobamate and sodium valproate (Figs. 2 and 3) also rapidly diminished NEBR, after which this behaviour recovered again. A slower and more prolonged effect on NEBR was obtained with diphenylhydantoin, phenobarbital, sabeluzole and especially with flunarizine, ethosuximide, 2-APH and desipramine.

After drug injection, clonic contralateral forepaw movements could persist. This can be seen as a smaller effect on the total number of excitation episodes (NEBR + NEC, dot-

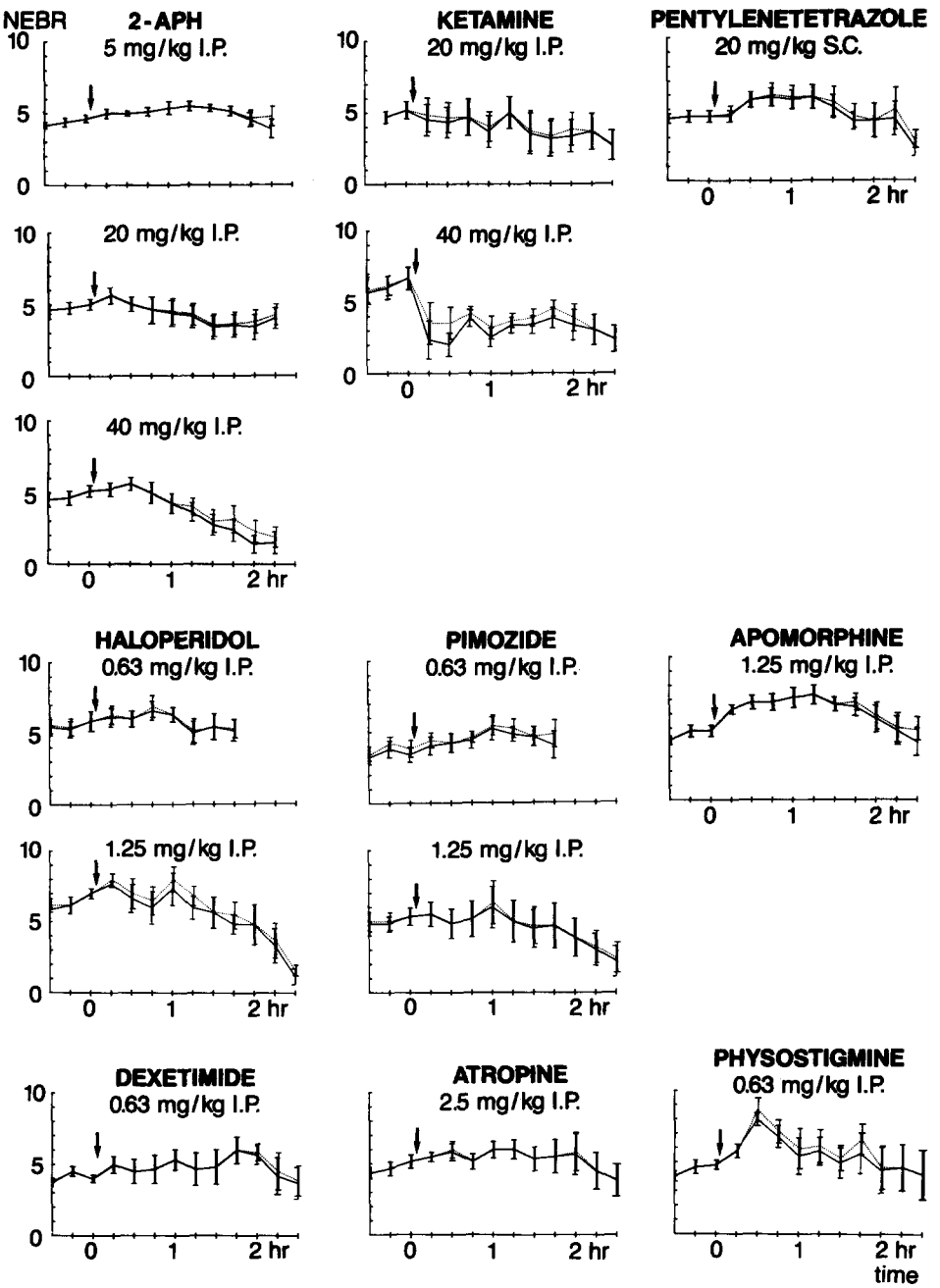

FIG. 4. Influence of various drugs (same axis representation as in Fig. 1) on NEBR (full line) or on the total frequency of excitation episodes (NEBR + NEC, dotted line) after intrastriatal injection of QUIN (mean±SEM, n=6 or 7). The arrow indicates the moment of injection of the drug. 2-APH stands for DL-2-amino-7-phosphonoheptanoic acid.

ted line in Figs. 2–4) than on NEBR (full line). A clear dissociation in effect on NEBR and (NEBR + NEC) was observed with 10 mg/kg etomidate (Fig. 3) and diazepam (Fig. 2). At the higher dose of 20 mg/kg, etomidate and diazepam also suppressed the clonic contralateral forepaw movements. A larger effect on NEBR than on (NEBR + NEC) was also observed with clonazepam, flunarizine, meprobamate, sabeluzole, ethosuximide and ketamine. Remarkably, in 5/7 of the animals injected with 20 mg/kg desipramine an initial increase in NEBR preceded the final decrease (Fig. 4). This was not observed at 10 and 40 mg/kg.

In Table 1, the calculated ED_{50}-values for decreasing NEBR or (NEBR + NEC) by 50% or by 100% are given as are the ED_{50}-values from different animal models of epilepsy. For purposes of comparison with the latter models, the ED_{50}-values for a 100% decrease in NEBR or (NEBR + NEC) were not used since the ED_{50} is sometimes larger than the highest tested dose, yielding missing points in the comparison. Generally

TABLE 1

ED_{50}-VALUES OF THE QUIN TEST AND ANIMAL MODELS OF EPILEPSY

	QUIN Test				MMS				BIC	Kindling
	50% Decrease NEBR	100% Decrease NEBR	50% Decrease (NEBR + NEC)	100% Decrease (NEBR + NEC)	Ataxia	CLO	TFP	THP	THP	FC
Carbamazepine	11	11	11	12	18	160	18	2.6	10	5
Clonazepam	1.3	>2.5	1.3	>2.5	0.4	0.8	0.5	0.15	14.5	0.28
Diazepam	7	10	10	>20	1.8	6	2.8	1.5	9.5	0.28
Diphenylhydantoin	21	40	21	40	64	>160	39	6.7	25.9	31.5
Ethosuximide	320	>320	320	>320	227	166	166	88	>640	158
Etomidate	20	>20	20	>20	11	33	18	7	20	2.8
Flunarizine	26	65	34	>40	106	>320	82	3.2	10.8	43
Meprobamate	59	82	73	142	66	95	68	20	10.8	11
Phenobarbital	19	24	22	30	23	45	22	2	5	
Sabeluzole	5	8	7	10	19	>40	20	0.6	4	
Sodium valproate	169	169	169	203	287	450	450	112	285	65
Correlation with ED_{50} for 50% Decrease in NEBR					$r_s=.89$ $p<0.001$	$r_s=.8$ $p<0.01$ +	$r_s=.89$ $p<0.001$	$r_s=.95$ $p<0.001$	$r_s=.72$ $p<0.01$ +	$r_s=.93$ $p<0.001$

ED_{50}-values of anticonvulsants relative to a 50% or 100% decrease of QUIN-induced NEBR (columns 2, 3) or of the total frequency of episodes of excitation (NEBR + NEC) (columns 4, 5) one hour after IP injection. Also the published ED_{50}-values for ataxia (column 6) or for inhibition of the clonic convulsions (CLO), tonic forepaw extension (TFP) and tonic hindpaw extension (THP) in the maximal metrazol seizure test (MMS), 1 hr after oral drug administration (columns 6–9) [20]. Column 10 gives the ED_{50} (1 hr orally) for inhibition of tonic hindpaw extension in the bicuculline test [49,50]. Column 11 shows the ED_{50} necessary to obtain a 50% decrease in the duration of forepaw clonus in amygdaloid kindled rats [5] 30 min after IP drug injection. Below, the Spearman rank correlation coefficient (r_s) and the probability (p) are given for correlation of the corresponding parameter with the ED_{50} for a 50% decrease in NEBR in the QUIN test. In the columns indicated with a + sign, the r_s-value is overestimated and the corresponding p-value is underestimated because of omission on the points for which the ED_{50} exceeded the highest tested dose.

the difference was not great between the ED_{50}-values for a 50% decrease in NEBR and that for a 50% decrease in (NEBR + NEC). To calculate the correlation of the QUIN model with other models of epilepsy only the ED_{50} for a 50% decrease in NEBR was used. Differences in pretreatment time and route of administration of the antiepileptic drugs (see legend of Table 1) may have influenced the comparison between the different tests.

The ED_{50} for inhibition of NEBR correlated very well with the published ED_{50} for inhibition of tonic hindpaw extension in the maximal metrazol test ($r_s=.95$, $p<0.001$, Fig. 5A) [20, 49, 50]. All ED_{50}-values for QUIN were higher than the corresponding ED_{50}-values for tonic hindpaw extension. The ED_{50} for QUIN correlated somewhat less with the ED_{50} for inhibition of clonic convulsions in the maximal metrazol seizure test (MMS) ($r_s \approx .8$, $p<0.01$, Fig. 5B). The latter r_s-value is overestimated due to omission of the least correlating points, for which the ED_{50} for clonic convulsions was unknown since it was larger than the highest tested dose of the corresponding drug. Carbamazepine, diphenylhydantoin, flunarizine and sabeluzole do not protect, or do so only at higher doses, against the clonic convulsions in the MMS. Thus these drugs have a higher ratio of this ED_{50} to the ED_{50} for QUIN than the other tested drugs.

There was also a good correlation between the ED_{50} for QUIN and the published ED_{50} for reduction in duration of the forepaw clonus in the kindling model, for which the ED_{50}-values were generally lower ($r_s=.93$, $p<0.001$, Fig. 5D) [5]. Again diphenylhydantoin and flunarizine had a higher ratio of their ED_{50} in kindling to the ED_{50} for QUIN than the other tested anticonvulsants, but the difference in ratio was smaller than in the comparison with the forepaw clonus in the MMS.

The ED_{50} for QUIN correlated moderately with the ED_{50} for tonic hindpaw extension in the bicuculline test ($r_s=.72$, $p<0.01$) [49,50].

The ED_{50} for QUIN correlated with the ED_{50} for ataxia [20] (C. Niemegeers, unpublished observations) ($r_s=.89$, $p<0.001$, Fig. 5C). Ataxia correlated very well with the ED_{50} for tonic forepaw extension in MMS ($r_s=1.0$, $p<0.001$), for which the ED_{50}-values were very similar.

In 4 out of 6 animals injected with the convulsant pentylenetetrazole (20 mg/kg SC), NEBR increased (Fig. 4).

Influence of Drugs Acting on the Dopaminergic and Cholinergic System

In 1/7 of the animals treated with 0.63 mg/kg, haloperidol NEBR was clearly decreased. With the very high dose of 1.25 mg/kg, a clear effect was only seen in 2 out of 6 animals. Similarly the specific dopamine antagonist pimozide had no clear effect at 0.63 mg/kg (Fig. 4). At the very high dose of 1.25 mg/kg barrel rotation stopped in 2 out of 6 animals. In the other animals the effect was small or invisible. With the dopamine agonist apomorphine there was a slight increase in mean NEBR (Fig. 4).

With the acetylcholinesterase inhibitor physostigmine (0.63 mg/kg), NEBR initially showed a rise and in 3 out of 6

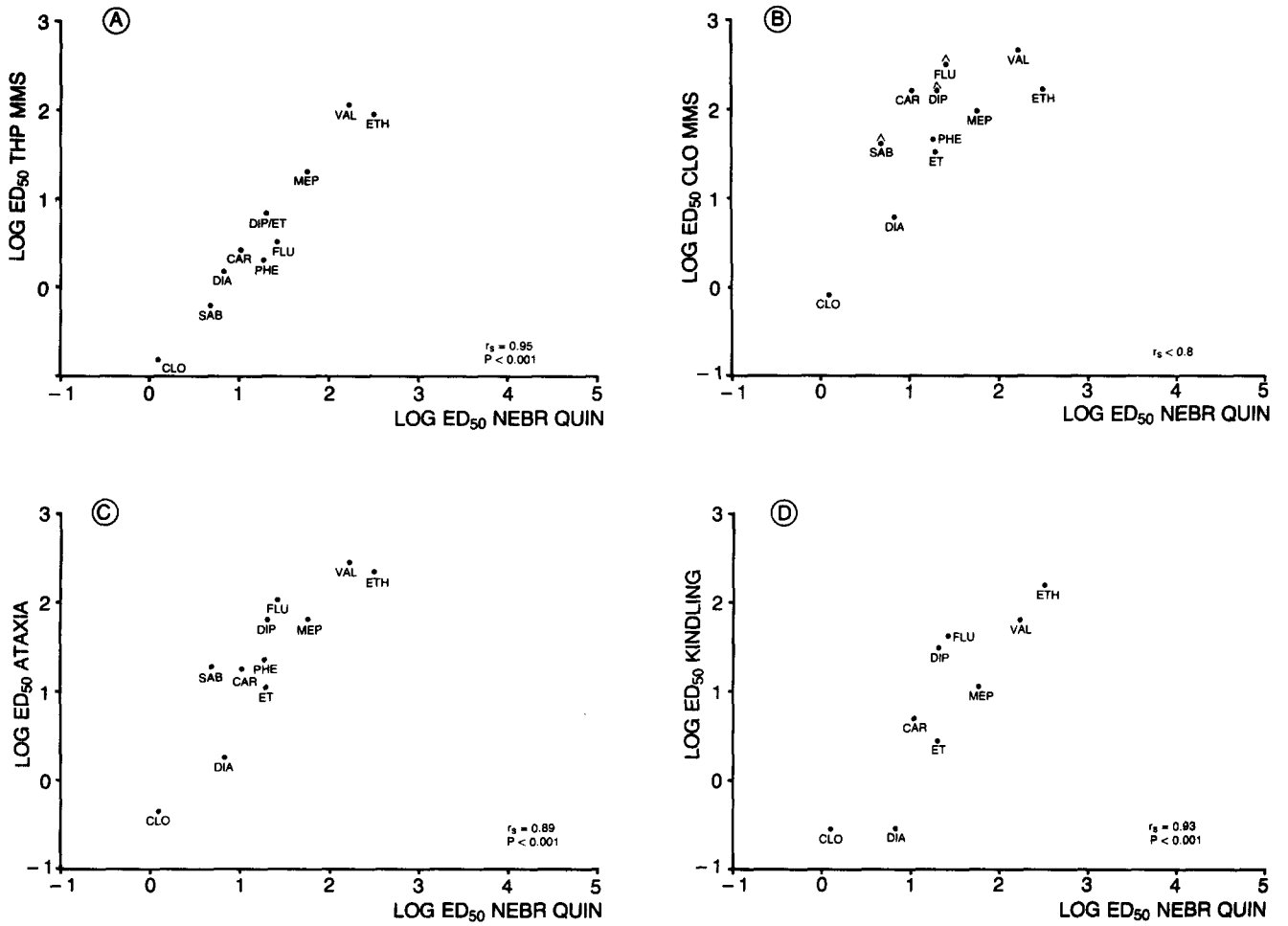

FIG. 5. Comparison of the ED_{50}-values necessary to obtain a 50% decrease in NEBR in the QUIN test (abscissa) with the published ED_{50}'s for inhibition of tonic hindpaw extension (THP) in the maximal metrazol seizure test (A), for inhibition of clonic convulsion (B), for ataxia (C) [20,50] and for a 50% reduction in duration of forepaw clonus in amygdaloid kindled rats (D) [5]. When the ED_{50} is higher than the highest tested dose, the symbol ◊ is used at the coordinates of the highest tested dose to indicate that the point lies higher than the shown value. Abbreviations: carbamazepine (CAR), clonazepam (CLO), diazepam (DIA), diphenylhydantoin (DIP), ethosuximide (ETH), etomidate (ET), flunarizine (FLU), meprobamate (MEP), phenobarbital (PHE), sabeluzole (SAB) and sodium valproate (VAL).

animals it thereafter decreased again, to values lower than before physostigmine (Fig. 4). No clear effect was seen with the anticholinergics dexetimide (0.63 mg/kg) and atropine (2.5 mg/kg).

Influence of Solvents

The highest used doses of drug solvents did not influence NEBR. This was tested by IP injection of a solution of 32 drops of Tween 80 per kg (n=6) or 0.2 mmol/kg sodium tartrate (n=6), dissolved in 10 ml of distilled water/kg.

DISCUSSION

All 8 tested antiepileptic agents, namely carbamazepine, clonazepam, diazepam, diphenylhydantoin, ethosuximide, flunarizine, phenobarbital and sodium valproate, decreased NEBR in a dose- and time-dependent way. Six other drugs, which were effective in reducing NEBR, also possess anticonvulsant properties. These drugs were as follows: the antihypoxic drug sabeluzole (R 58 735) [16,50], the tricyclic antidepressant desipramine [15], the hypnotic etomidate [48], the tranquilizer meprobamate [20], the analgesic ketamine, which is a potent NMDA antagonist [1,37] and the specific NMDA antagonist 2-APH [36], which thus directly antagonizes quinolinic acid [21,39]. However, 2-APH crosses the blood-brain barrier only very slowly [14], which may explain the slow onset of its effect. This suggests that QUIN-induced barrel rotations are inhibited by anticonvulsants. Conversely, a subconvulsant dose (20 mg/kg SC) of the convulsant pentylenetetrazole increased the mean NEBR. The dopamine agonist apomorphine, which facilitates convulsions in several models [4,6] also increased NEBR.

In order to determine whether the inhibition of barrel rotation by anticonvulsants is related to their anticonvulsant effect, the obtained approximate ED_{50}-values were compared to published ED_{50}-values from epilepsy models [5, 20, 50]. The ED_{50} for inhibition of NEBR by the anticonvulsants correlated very well with the ED_{50} for tonic hindpaw extension in the maximal metrazol seizure test [20] and with the ED_{50} for forepaw clonus in the amygdaloid kindled rat [5].

This suggests that inhibition of these barrel rotations by the anticonvulsants may be related to some component of their anticonvulsant action.

Substances such as diphenylhydantoin, flunarizine, sabeluzole and carbamazepine are not active against clonic convulsions in the maximal metrazol seizure test. The latter substances, however, effectively inhibit tonic hindpaw extension in MMS, the allylglycine test and the bicuculline test [49,50], and also inhibit QUIN-induced barrel rotation. Hence, the QUIN-induced barrel rotations are sensitive to a broad spectrum of anticonvulsants.

However, are QUIN-induced barrel rotations and clonic contralateral forepaw movements real convulsions? It has been suggested that the behavioural effects of kainic acid or QUIN after intrastriatal injection are related to increased activity of dopamine-containing elements in the striatum [3, 35, 42]. Barrel rotation can be induced by injection of a variety of substances in different sites of the brain [10, 13, 17, 25, 41]. Some authors describe barrel rotation as seizures [26,52], whereas others have not observed epileptic EEG changes in cortex, hippocampus and amygdala during chlorpromazine methiodide and somatostatin-induced barrel rotations [12,13]. The proximity of barrel rotations to epileptic phenomena may also depend on the method by which the barrel rotations are induced. The behavioural appearance of barrel rotation also differs with the induction method. For example, during chlorpromazine methiodide-induced barrel rotations, there are no clonic movements and the barrel rotations are continuous instead of episodic [12,13]. In contrast, during and after barrel rotations induced by the convulsant picrotoxin [13] or QUIN, tonic-clonic movements are observed.

Possibly a common basic feature of all known types of barrel rotation is that there is a general, important dominance of skeletal muscle tone of one side of the body over the other. By contraction of the neck muscles, this may lead to a deviation of the head towards the body side with the higher muscle tone and to twisting of the rostral body segment in that direction. Thereafter, the caudal body segment will follow, which results in a complete rotation about the long axis.

Intrahippocampal injection of QUIN (or ibotenic acid) produces repetitive seizure episodes. These are associated with simultaneous paroxysmal cortical and hippocampal EEG changes and appear after a latency period of 20–30 min [2, 40, 42]. Likewise after intrastriatal or intranigral injection of QUIN, one might expect overactivation of the injected site and/or other basal ganglia to which QUIN could diffuse. This could lead to activation of the muscles of the contralateral body side, dominating the ipsilateral muscles, and in this way produce the barrel rotations. We found that also after intranigral injection of QUIN, barrel rotations develop with the same latency as the seizures after intrahippocampal injection, namely 20–30 min. Then the barrel rotations extinguished earlier than after intrastriatal injection. The latency for barrel rotations after intrastriatal injection of QUIN was around 75–90 minutes. However, clonic movements of neck muscles away from the injection side could already be seen after about 30 min. To explain the latency after intrahippocampal injection, indirect effects of QUIN or other excitotoxic amino acids, such as release and accumulation of an endogenous convulsant or gradual exhaustion of neuro-inhibition have been suggested [27, 31, 40, 46]. An alternative explanation is that QUIN would first have to diffuse to another region than the injected site before it could exert its excitatory influence.

After intrastriatal injection of QUIN, the concentration of QUIN in the striatum decreases with a half-life of 22 min [22]. Yet we observed that there is a gradual increase in intensity and frequency of barrel rotation and clonic forepaw movements until a plateau is reached lasting several hours. Thereafter these excitation phenomena weakened again, to episodes with incomplete or no barrel rotations, but still with clonic forepaw movements. A possibly analogous transition to a weaker excitation form without complete barrel rotations could be seen after injection of several antiepileptic drugs, such as diazepam (10 mg/kg), etomidate (10 mg/kg) or ethosuximide (320 mg/kg) (Figs. 2 and 3). In the latter three cases the summed frequency of excitation episodes (NEBR + NEC) changed only little, although NEBR decreased markedly. This suggests that the basic frequency for NEBR and NEC is the same and that barrel rotations and the latter weaker excitation form are due to the same phenomenon, mainly differing in degree. Such a transition to the weaker form may reflect a decrease in intensity or spread of the overexcitation, and may thus be related to the antiepileptic effect of a drug. The weaker form appears to be more resistant to anticonvulsants, possibly because of a greater difficulty to suppress this overexcitation completely or to stabilize also the most labile brain areas, or the areas most affected by QUIN. The decrease in total episode frequency (NEBR + NEC) by anticonvulsants, especially at higher doses, may reflect a decrease in intensity of excitatory and depolarizing mechanisms in proportion to the inhibitory and hyperpolarizing mechanisms. This could lead to a later and thus less frequent overexcitation. The reverse, namely an increase in frequency, can be seen under influence of the convulsant pentylenetetrazole (Fig. 4).

Although it is not yet proven unequivocally that the QUIN-induced barrel rotations are due to real seizure activity in some part of the brain, one may expect episodic neuronal overexcitation. Inhibition of this overexcitation and of the barrel rotations may thus be closely related to an anticonvulsant effect of drugs. This is supported by the high correlation between the ED_{50} for QUIN and the ED_{50} in some models of epilepsy. A possible application of the QUIN-induced barrel rotation is that it allows to follow the time course of action of anticonvulsants, with each animal as its own control.

Intrastriatal injection of excitotoxic amino acids such as kainic acid or QUIN has been suggested to produce an experimental model for Huntington's disease, because of the similarity of the provoked striatal lesions 4 days post injections [18, 33, 42]. At this point the striatal GABAergic and cholinergic neurons are destroyed by overexcitation, whereas the dopaminergic axon terminals passing through the region are spared. Consequently, there can be an imbalance between cholinergic neurons versus dopaminergic neurons. An important element in the symptomatic treatment of Huntington's disease appears to be the restoration of this balance.

Stereotyped movements of rats 2 weeks after intrastriatal injection of kainic acid have been reported to function as a model to find drugs for the symptomatic treatment of Huntington's disease [11]. In parallel with effects on Huntington's patients, these investigators found that an anticholinergic drug (trihexyphenidyl) potentiated and that the cholinesterase inhibitor physostigmine and the dopamine antagonist haloperidol decreased stereotypy in QUIN-treated rats.

By contrast, in rats, only 3–5 hours after intrastriatal in-

jection of QUIN, we did not observe such a parallelism at the tested doses with the anticholinergics atropine and dexetimide and with the acetylcholinesterase inhibitor physostigmine. With a high dose of 1.25 mg/kg of the dopamine antagonists haloperidol and pimozide, a decrease in NEBR was only seen in 2 out of 6 rats. Early (3–5 hours) after QUIN injection, the QUIN-induced barrel rotations were thus not specifically sensitive to drugs used in the symptomatic treatment of Huntington's disease. Instead, during this period in which the animals still showed episodic strong excitation phenomena, anticonvulsants were able to inhibit the barrel rotations.

ACKNOWLEDGEMENTS

The authors would like to thank W. Melis and J. Van Loon for their valuable technical assistance and Dr. D. Ashton for reading the manuscript. Part of this work was supported by a grant from the I.W.O.N.L. (Instituut voor Aanmoediging van Wetenschappelijk Onderzoek in Nijverheid en Landbouw), Brussels, Belgium.

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