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Non involvement of γ-aminobutyric acid in catechol-induced seizures

D.G. Dewhurst

Department of Biological Sciences, Sheffield City Polytechnic, Pond Street, Sheffield S1 1WB

1 The effects of certain anticonvulsant agents, namely, vaproate, diazepam and phenobarbitone were investigated on catechol-induced spontaneous and evoked convulsions, in anaesthetized rats and mice.

2 Valproate and diazepam significantly reduced the intensity of spontaneous convulsions and the frequency of occurrence of the longer-latency components (M2 and M3) of the evoked muscle response.

3 Phenobarbitone significantly reduced spontaneous convulsions and the M3 component of the evoked muscle response.

4 None of the drugs affected the short latency M1 component indicating a supra-spinal site of action of these drugs.

5 Agents which modify γ-aminobutyric acid (GABA)-mediated transmission were without effect on the frequency of occurrence of M1, M2 or M3.

6 The results suggest that the convulsant action of catechol is not dependent on antagonism of GABA-mediated inhibition.

Introduction

Catechol (1,2 dihydroxybenzene) which occurs naturally in grapefruit and the scales of the onion, is the most potent convulsant of the polyhydroxylic-phenols (Angel & Rogers, 1968). Administration of catechol to anaesthetized rodents induces a dose-dependent increase in motor activity which is central in origin. Low doses produce a stimulus-sensitive excitatory state during which a variety of sensory stimuli, e.g. tactile, electrical and auditory, will evoke brief myoclonic jerks (Angel & Lemon, 1973; Dewhurst, 1984). The evoked electromyographic activity associated with these convulsions can be recorded from both flexor and extensor muscles of fore and hindlimbs and typically consists of three temporally distinct components (M1, M2 and M3), each resulting from activation of a different reflex pathway. These resonses which are absent in the non-catechol treated, anaesthetized animal are probably the result of an increased transmission in the dorsal column sensory pathway at the level of the ventrobasal thalamus (Angel, 1969). M1 is probably a propriospinal reflex; M2 is dependent on a long-loop reflex involving the sensorimotor cortex and M3 is possibly a cerebellar reflex (Angel & Lemon, 1973; Dewhurst, 1984).

Higher doses of catechol produce spontaneous convulsions, which occur in the absence of any intentional stimulus (Angel & Rogers, 1968; Angel *et al.*, 1977) and are thought to result from an action of catechol on the brainstem reticulo-spinal system (Angel & Lemon, 1973).

The mechanism of action of catechol is still largely unknown, although both spontaneous catechol convulsions and those components of the sensory-evoked jerks dependent on supra-spinal structures (M2 and M3) are partially blocked by cholinoceptor blocking drugs (Angel *et al.*, 1977; Angel & Dewhurst, 1978; Dewhurst, 1984) indicating a possible central cholinergic involvement. Several convulsants e.g. picrotoxin bicucullin and penicillin, exert their effects by blocking γ-aminobutyric acid (GABA)-mediated inhibition (Woodbury, 1980) and it is possible that catechol has a similar action. This work examines the sensitivity of catechol-induced convulsions to a number of anticonvulsants and further investigates a possible involvement of GABA in the mechanism of action of catechol. A preliminary account of some of this work has been published (Dawson & Dewhurst, 1984).

Methods

Spontaneous convulsions

Catechol-induced convulsions, occurring in the absence of intentional stimuli, were assessed by

measuring total locomotor activity of anaesthetized mice. Female albino mice (Sheffield strain), in the weight range 16–25 g, anaesthetized with urethane (2 g kg^{-1} i.p.) were used in these experiments. Catechol was administered as two successive doses (80 mg kg^{-1} i.p.) and the C2/C1 ratio was measured by the method described by Angel *et al.* (1977). Briefly this involved suspending groups of three mice in a plastic container from a strain gauge which formed part of a bridge circuit. The bridge output which was proportional to the total locomotor activity of the animals was then amplified, half-wave rectified and integrated over 30 s time intervals. A typical experimental protocol (shown diagramatically in Figure 1) would be to record a 10 min control period, to inject catechol and to record the following 20 min activity (C1) and then to administer a second dose of catechol exactly 60 min after the first and record a further 20 min activity (C2). The total integrated locomotor activity in the 20 min period following each injection of catechol was measured, corrected for basal activity and used to calculate the C2/C1 activity ratio. It has been shown previously that the convulsion following a single dose of catechol (80 mg kg^{-1}) is always contained within a 20 min period (Dewhurst, 1976). Anticonvulsants were administered intraperitoneally in a volume of 0.2 ml at a suitable time before the second injection of catechol, such that any effects would occur during the C2 response and hence change the C2/C1 activity ratio. Thus a test-drug which reduced the convulsion would be expected to reduce the total locomotor activity recorded in the 20 min C2 period and to reduce the C2/C1 ratio. Body temperature was maintained at 37 ± 1°C by means of an overhead heating lamp.

Sensory-evoked convulsions

Sensory-evoked convulsions were measured by recording electromyographic activity from forelimb flexor muscles of anaesthetized rats, evoked by electrical stimulation of cutaneous afferents at the wrist. Female albino rats (Sheffield strain) in the weight range 190–210 g were used in all experiments. Animals were anaesthetized with urethane (1.2–1.4 g kg^{-1} i.p.) such that reflex withdrawal of the hindlimb to a strong pinch was just abolished. Polythene cannulae were inserted into a jugular and femoral vein, and catechol (25 mg ml^{-1}) was infused continuously into the jugular vein at a rate of 0.02 ml min^{-1} giving a dose of 2.5 mg kg^{-1} min^{-1}. At this dose convulsions (brief myoclonic jerks) could be evoked by a variety of sensory stimuli, e.g. auditory, mechanical or electrical but animals showed negligible spontaneous convulsive activity.

Electromyographic activity was measured from Flexor carpii using conventional recording techniques as described previously (Angel & Dewhurst, 1978). Cutaneous afferents were stimulated by applying electrical stimuli (Digitimer DS2 isolated stimulator) by means of a strip of gauze soaked in 3 M NaCl tied loosely around the wrist, and a metal pin inserted through a digit. Stimuli were of 60 μs duration and applied at a frequency of 1 per 6 s (Digitimer D100). The voltage (10–20 V) was adjusted at the start of each experiment to be just suprathreshold for the short-latency (M1) component of the evoked muscle response.

Muscle action potentials were amplified, displayed on a cathode ray oscilloscope and stored on magnetic tape (Trio KX-440). Responses were also simultaneously averaged (Neurolog NL 750). Averages were taken of a 50 ms post-stimulus sweep, each average consisting of a total of 128 sweeps. The sampling frequency was approximately 5 per ms. Averaged responses were used to assess possible changes in latency caused by the drugs used.

After a suitable control period, usually 10–15 min, drugs were administered intravenously in a volume of 0.2 ml into the femoral vein and washed in with the same volume of 0.9% w/v NaCl solution (saline). Evoked muscle responses were then continuously recorded for a further 35–45 min. The number of times each component of the evoked muscle response (M1, M2 and M3) occurred per applied stimulus was measured in the pre-drug (control) and post-drug (test) periods. For convenience, the percentage probability of occurrence was calculated in two-minute periods, stimuli being applied at a rate of 1 per 6 s.

Drug effects were evaluated by plotting the probability of occurrence of each component of the evoked muscle response against time, after administration of the test drug (test) and subtracting from the area under this curve the area under the control curve, obtained by extrapolating the mean probability of occurrence during the control period (control). Results are expressed as the percentage difference in areas: (test − control)/test × 100 in arbitrary units. Significance of difference was calculated by means of a Student's paired *t* test.

In control animals the mean % probability of occurrence of all three components was unchanged up to 60 min after administration of 0.4 ml saline. The amplitude of each component was measured directly from the oscilloscope, within selected two-minute periods during the control and test periods. In all experiments body temperature was maintained at 37 ± 1°C by means of an overhead heating lamp and continuously monitored using a rectal thermometer. All drugs were dissolved in saline with the exception of diazepam, which was first dissolved in a few drops of 0.1 M HCl, and sodium valproate, which was first dissolved in 0.1 M NaOH. The pH was then adjusted to pH 6–7. Ro-151788 was administered in saline to which one drop of Tween 80 per ml had been added.

Table 1 Effects of certain anticonvulsants on the C2/C1 activity ratio

Drug	*Dose* (mg kg^{-1})	*ratio*	P *paired* t *test*
Control (Saline)		1.44 ± 0.08	
Valproic acid	200	1.21 ± 0.03	<0.01
	400	0.65 ± 0.09	<0.001
Diazepam	5	0.80 ± 0.18	<0.001
	10	0.78 ± 0.10	<0.001
Phenobarbitone	5	0.46 ± 0.08	<0.001
	10	0.37 ± 0.07	<0.001

The results are the means ± s.e. of 10 experiments.

The following drugs were used: catechol (BDH), sodium valproate (Sanofi UK Ltd), muscimol, aminooxyacetic acid, γ-aminobutyric acid, picrotoxin, ethylene diamine, and bicuculline (Sigma), diazepam, clonazepam and Ro-151788 ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo [1,5-a] [1,4] benzodiazepine-3-carboxylate) were kind gifts from Roche.

Results

Spontaneous convulsions

As can be seen from Table 1, the anticonvulsants valproic acid, diazepam and phenobarbitone all significantly reduced the C2/C1 activity ratio, compared to saline controls. At the highest doses used valproate produced a 54.9% reduction, diazepam 45.8% and phenobarbitone 74.3%. All three anticonvulsants reduced the intensity of the convulsions. Valproate and phenobarbitone had no effect on the time course of the convulsion, i.e. time to onset of convulsion, time to peak and total duration, while diazepam prolonged the duration of the convulsive response (Figure 1).

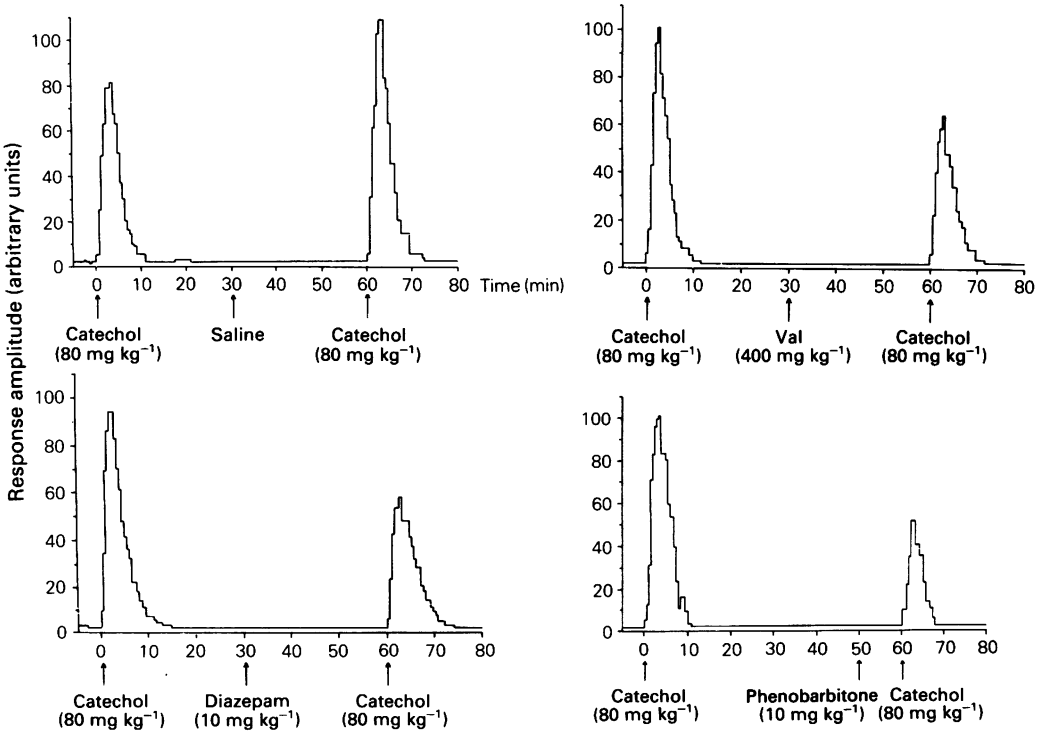

Figure 1 The effects of valproate (Val), diazepam and phenobarbitone on spontaneous catechol convulsions. Each record shows the results of a single experiment. Catechol (80 mg kg^{-1} i.p.) was administered after a suitable control period and again 1 h later. Following administration of catechol increased activity begins within 1 min, reaches peak intensity in the third minute and returns to a baseline level after about 15 min. Test drugs were administered (i.p.) at a suitable time before the second injection of catechol and their effects evaluated by measuring the total integrated activity in the 20 min period following each injection of catechol. From these measurements the C2/C1 ratio was calculated. As can be seen, all three drugs significantly reduced the C2 convulsion, whereas in control experiments (saline) C2 is always greater than C1. Only diazepam appeared to prolong the convulsive response. Similar results were obtained in all other experiments.

Table 2 The effects of certain anticonvulsants and drugs which modify GABA-ergic transmission on the probability of occurrence of the three components (M1, M2 and M3) of the catechol-induced sensory evoked muscle response

Drug	*Dose* (mg kg^{-1}) i.v.	*% probability of occurrence*			n
		M1	*M2*	*M3*	
Sodium valproate	100		− 15.7 ± 15.3*	− 61.3 ± 21.7**	8
	250	− 20.7 ± 19.7	− 48.8 ± 38.4*	− 84.4 ± 6.6**	6
Diazepam	1		− 41.3 ± 30.6*	− 60 ± 12.9**	5
Clonazepam	1		− 45.8 ± 30.1**	− 67.2 ± 27.7**	5
Phenobarbitone	5		− 0.2 ± 24.5	− 11.8 ± 7.1*	6
GABA	50		− 15.1 ± 20	− 9.4 ± 26.6	8
Amino-oxyacetic acid	5		+ 1.2 ± 4.6	− 2.1 ± 5.6	5
Ethylenediamine	100		+ 9.8 ± 17	− 4.7 ± 8.3	5
Muscimol	0.1		− 6.1 ± 28	+ 7.9 ± 11.1	7
Picrotoxin	2		+ 23.8 ± 20.1*	+ 17 ± 15.9*	5
Ro-151788	2		− 13.3 ± 26.5	− 6.9 ± 7.9	5

Results shown are mean % difference (arbituary units) ± s.d. (see Methods section). n = number of experiments
*$P<0.05$, **$P<0.01$ (paired t test).

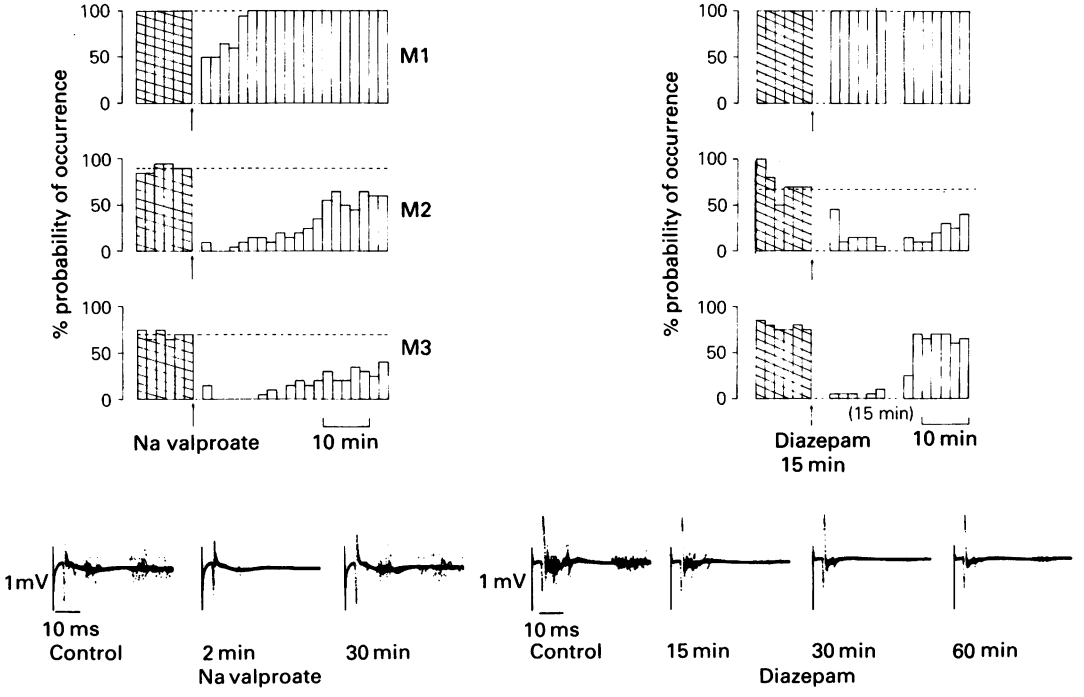

Figure 2 The effects of valproate (250 mg kg^{-1} i.v.) and diazepam (1mg kg^{-1} i.v.) on the % probability of occurrence of the three components (M1, M2 and M3) of the evoked electromyographic response recorded from Flexor carpii to electrical stimulation at the wrist. Catechol was infused throughout the experiment and test drugs were administered after a suitable control period as indicated. Each record shows the results from a single experiment and illustrates how the results presented in Table 2 were calculated. The histograms show the time course of the responses before and after injection of the test drugs and the lower records show photographic records taken during the control period and at suitable times after drug administration. Each shows 20 superimposed responses and represents 2 min activity. As can be seen both drugs decrease the frequency of occurrence of M2 and M3 and recovery is seen between 30 and 60 min later. Valproate also decreased the amplitude of M1 shortly after administration. Similar results were obtained in all other experiments.

Sensory-evoked convulsions

The effects of drugs on the % probability of occurrence of each of the three components of the sensory evoked muscle response induced by administration of the catechol are shown in Table 2. The characteristics of these three components (M1, M2 and M3) have been described previously (Angel & Dewhurst, 1978; Dewhurst, 1984) and in this study each component was identified by its latency: M1 (4–7 ms), M2 (12–18 ms), and M3 (30–50 ms).

(i) *Anticonvulsants*

The most effective of the anticonvulsant drugs used was sodium valproate which significantly reduced the probability of occurrence of M2 and M3, within two minutes of administration (Figure 2). Its effects lasted for 15–20 min, and a return to a near control probability of occurrence for both M2 and M3 was observed 20–30 min later. Valproate at the highest dose used also reduced the probability of occurrenc of M1 by 20–30% in four of the six experiments, and also reduced its amplitude from a mean of 1.78 ± 0.24 mV in the control period to 1.32 ± 0.10 mV 5 min after administration (Figure 2).

Diazepam and clonazepam also significantly reduced the probability of occurrence of M2 and M3, but did not affect that of M1, or M1 amplitude. These agents had little effect until 12–15 min after administration, these effects lasting 15–20 min (Figure 2).

Phenobarbital produced a small but significant decrease in the probability of occurrence of M3, but had no effect on M2 or M1.

None of the drugs had any significant effect on the amplitude of M2 or M3, or on the latencies of the three components.

(ii) *Drugs affecting GABA*

GABA, amino-oxyacetic acid, ethylene diamine, muscimol and Ro-151788 had no significant effect on the probability of occurrence (Table 2), amplitude or latency, of M1, M2 or M3.

Picrotoxin significantly increased the probability of occurrence of M2 and M3 (Table 2) and increased the amplitude of M1. These effects were evident 5 min after administration and lasted for approximately 30 min. This dose of picrotoxin (1.5 mg kg^{-1} i.v.) produced no convulsions or sensory evoked electromyographic activity in the anaesthetized non-catechol treated animal.

Discussion

The results show clearly that anticonvulsants such as the benzodiazepines, valproic acid and phenobarbitone antagonize both spontaneous catechol convulsions and the longer latency components (M2 and M3) of the catechol-induced sensory evoked myoclonic response. Interestingly phenobarbitone was the most effective in blocking spontaneous catechol convulsions, but the least effective in reducing the probability of occurrence of the M2 and M3 components of the sensory evoked muscle response, suggesting that catechol might have more than one action.

The benzodiazepines and sodium valproate probably produce their anticonvulsant effects by facilitating the inhibitory actions of GABA (Costa *et al.*, 1975; MacDonald & Bergey, 1979; Study & Barker, 1982) while phenobarbitone has little effect on GABA-ergic transmission (Willow & Johnston, 1981). Since spontaneous catechol convulsions are sensitive to all three anticonvulsants, it is probable that their actions are relatively non-specific and due to a general decrease in central nervous system excitability.

However, the longer-latency components of the catechol-induced evoked muscle response are antagonized to a much greater degree by those anticonvulsants working via GABA facilitation. Sodium valproate was found to be particularly effective, its action being apparent within two minutes of administration. The rapidity of this effect makes it unlikely that the action of valproate is dependent on elevation of brain GABA levels which occurs 1–2 h after administration (Anlezark *et al.*, 1975) and supports the view that its primary action might be in augmenting the effect of GABA at the receptor level. The lack of effect of all three anticonvulsants on M1, which probably results from activation of a propriospinal reflex (Angel & Lemon, 1973), shows that these agents must have a supraspinal site of action. This is consistent with the view that anticonvulsants whose activity is mediated by GABA act at midbrain level (Iadarola & Gale, 1982).

The marked reduction in the probability of occurrence of M2 and M3 after valproate and diazepam, suggests that GABA might be involved in the mechanism of action of catechol particularly as phenobarbitone was relatively ineffective. Catechol could reduce the availability of GABA by decreasing synaptic release or increasing uptake, or it could decrease the postsynaptic effects of GABA as do many other convulsants e.g. picrotoxin, bicuculline, penicillin and pentylenetetrazol (Woodbury, 1980). Previously Minchin & Pearson (1981) have shown catechol to decrease only slightly the K^+-stimulated release of GABA from rat cortical slices and to have no effect on uptake. Also, as can be seen from Table 2, administration of GABA or amino-oxyacetic acid (AOAA) a GABA-transaminase inhibitor which has been shown to produce rapid accumulation of GABA in both whole brain and cerebellum (Biswas & Carls-

son, 1978; Pagliusi *et al.*, 1983), failed to affect either M2 or M3. Similarly, muscimol, a GABA-receptor agonist which protects against some chemically-induced seizures (DeFeudis, 1980; Meldrum, 1981), and ethylene diamine, a GABA-mimetic which antagonizes a number of other convulsants (Perkins *et al.*, 1981; Morgan & Stone, 1982), were also without effect. The possibility that catechol might produce convulsions by interacting with benzodiazepine receptors, in a similar way to Ro-5-4864 (File *et al.*, 1984) was eliminated by the lack of effect of Ro-151788, a selective benzodiazepine-receptor antagonist (Nutt *et al.*, 1982). Sub-convulsive doses of picrotoxin, a GABA-receptor antagonist, increased the probability of occurrence of M2 and M3, and the amplitude of M1, though it is likely that this effect too is non-specific and due to catechol acting against a decreased level of central inhibition.

It thus seems that both catechol-induced spontaneous convulsions (Angel *et al.*, 1977) and sensory evoked jerks are not dependent on an action of catechol on central GABA-ergic transmission. Catechol has been shown to presynaptically increase the release of acetylcholine at the neuromuscular junction (Gallagher & Blaber, 1973), and although catechol may have a similar action in the central nervous system it is unlikely that this can explain all of its excitatory effects (Angel *et al.*, 1977; Angel & Dewhurst, 1978; Dewhurst, 1984). More recently catechol has also been shown to increase the K^+-stimulated release of [^{3}H]-aspartate from rat thalamic slices (Minchin & Pearson, 1981) and to increase the release of endogenous aspartate (but not glutamate or GABA) from slices of rat olfactory cortex (Dewhurst & Collins, 1985). A more detailed investigation of this latter action might yield additional informatin about the mechanism of action of catechol on the central nervous system.

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