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Interactions of Pentobarbital and Phenobarbital With GABAergic Drugs Against Chemoconvulsants in Rats

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MEHTA, A. K. AND M. K. TICKU. *Interactions of pentobarbital and phenobarbital with GABAergic drugs against chemoconvulsants in rats.* PHARMACOL BIOCHEM BEHAV 30(4) 995–1000, 1988.—Pentobarbital and phenobarbital exhibited anticonvulsant effects against picrotoxin (10 mg/kg, IP) as well as against strychnine (4 mg/kg, IP). Pentobarbital was also effective against bicuculline whereas only hypnotic doses of phenobarbital provided some protection against bicuculline- (8 mg/kg, IP) induced convulsions. Diazepam as well as THIP, but not baclofen, were also effective against all the three chemoconvulsants. Baclofen or subeffective doses of diazepam or THIP, when combined with subeffective dose of pentobarbital exhibited anticonvulsant activity against all the chemoconvulsants studied. On the other hand, a combination of subeffective doses of these agents with subeffective doses of phenobarbital provided protection only against picrotoxin and strychnine. These observations indicate that pentobarbital is quite effective against convulsions caused by agents acting at picrotoxin site, $GABA_A$ receptor or glycine receptor whereas phenobarbital is effective only against agents acting at picrotoxin site and glycine receptor, and is very weak anticonvulsant against agents causing blockade of $GABA_A$ receptors. Furthermore, activation of $GABA_A$ receptors or benzodiazepine receptors also provide protection against agents acting at GABAergic system or glycine receptors. On the contrary, activation of only $GABA_B$ receptors is inadequate to provide the protective effect. However, the activation of $GABA_A$ as well as $GABA_B$ receptors facilitate the anticonvulsant effect of both the barbiturates. Furthermore, pentobarbital, but not phenobarbital, facilitates the anticonvulsant effect of benzodiazepines against chemoconvulsants acting at GABAergic site or glycine receptors.

Pentobarbital Phenobarbital Convulsions Bicuculline Picrotoxin Strychnine $GABA_A$ receptors $GABA_B$ receptors Benzodiazepine receptors

BARBITURATES have been demonstrated to bind to a distinct allosteric site coupled to GABA, benzodiazepine and picrotoxin sites of the benzodiazepine GABA receptor-ionophore complex [14,33]. Neurophysiological studies also lend support to the concept that barbiturates mediate their effects via GABAergic mechanisms [13, 22, 23, 26, 27]. GABA is considered to be a major inhibitory neurotransmitter which plays an important role in the etio-pathology of epilepsy [7, 11, 19]. Agents which facilitate GABAergic transmission are potent anticonvulsants against a variety of experimental seizures [19, 20, 29]. Thus, while both pentobarbital and phenobarbital facilitate GABAergic transmission, there are also reports that these two barbiturates differ in their interaction with GABA and benzodiazepine receptors and in their pharmacological responses [1, 12, 13, 16, 18, 22, 23, 30, 31, 34]. However, it is not known whether the anticonvulsant profile of these two barbiturates differ in any way or not against chemoconvulsants acting at GABAergic site or glycine receptor site. Furthermore, GABA receptors have been classified into subtypes, namely $GABA_A$ and $GABA_B$ receptors [8]. $GABA_A$ receptors, unlike $GABA_B$ receptors, are susceptible to blockade by bicuculline. $GABA_B$ receptors are antagonized by phaclofen [10], and activated by baclofen [5,8]. Although homotaurine [6] and δ-aminovaleric acid [9,15] are reported to block $GABA_B$ receptors, there are also reports that homotaurine [3–5] as well as δ-aminovaleric acid [9,21] activate $GABA_A$ receptors. Recently, the role of these subtypes of receptors has been demonstrated in maximal electroshock seizures [16] and catatonia [17], the exact role of GABA receptor subtypes in the action of chemoconvulsants and in the anticonvulsant effect of barbiturates against chemoconvulsants is not well documented. Hence, the present study was undertaken (a) to investigate the role of GABA receptor subtypes in chemoconvulsion, (b) to compare the anticonvulsant profile of pentobarbital and phenobarbital against chemoconvulsants, and (c) to study whether the coadministration of agents activating GABA receptor subtypes or benzodiazepine receptors modifies the anticonvulsant effect of these two barbiturates against various chemoconvulsants.

METHOD

Adult male Sprague-Dawley rats, weighing 180–200 g, were used. The animals were kept at a constant room tem-

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TABLE 1

EFFECT OF VARIOUS DRUGS ON BICUCULLINE- (8 mg/kg, IP) INDUCED COVULSIONS IN RATS

Drug	Dose (mg/kg, IP)	n	Onset of Convulsion (min) Mean ± S.D.	Duration of Seizures (min) Mean ± S.D. Clonic	Duration of Seizures (min) Mean ± S.D. Tonic	Mortality Following Administration of Convulsant (min) Mean ± S.D.	Mortality (N)
Control	—	11	1.2 ± 0.48	0.6 ± 0.33	7.6 ± 2.05	11.7 ± 3.84	11/11
Pentobarbital	7.5	6	1.7 ± 0.41	1.2 ± 0.27	11.1 ± 1.85	16.5 ± 5.28	6/6
	10	8	2.1 ± 0.79*	1.0 ± 0.09	7.8 ± 1.58	30.6 ± 2.61†	5/8
	20	7	5.0 ± 1.00†	1.9 ± 2.04	1.8 ± 1.95†	65.0 ± 7.07†	2/7†
Phenobarbital	45	9	1.0 ± 0.20	1.2 ± 0.23	11.1 ± 1.85	16.2 ± 2.54	9/9
THIP	15	6	1.2 ± 0.42	0.7 ± 0.11	8.1 ± 1.42	15.0 ± 3.22	6/6
	30	6	2.6 ± 1.02†	0.6 ± 0.18	2.1 ± 0.45†	24.3 ± 14.01*	3/6*
Baclofen	20	6	0.8 ± 0.25	0.5 ± 0.19	8.0 ± 1.69	13.3 ± 3.08	6/6
Diazepam	0.5	6	1.0 ± 0.44	0.5 ± 0.24	8.9 ± 1.02	15.0 ± 4.20	6/6
	2	6	3.3 ± 0.44†	0.7 ± 0.26	4.4 ± 1.36*	25.7 ± 12.50†	3/6*
THIP + pentobarbital	15 + 10	6	2.9 ± 0.66†	0.5 ± 0.08	3.5 ± 0.89†	24.5 ± 7.78*	2/6*
Baclofen + pentobarbital	10 + 10	6	1.6 ± 0.49	0.6 ± 0.23	3.0 ± 0.73†	26.0 ± 5.66†	2/6*
Pentobarbital + diazepam	10 + 0.5	6	3.0 ± 0.64†	0.6 ± 0.41	2.5 ± 1.24†	40.0 ± 0.00†	1/6†
THIP + phenobarbital	15 + 30	6	1.0 ± 0.26	0.5 ± 0.09	8.7 ± 0.88	17.8 ± 2.79	6/6
Baclofen + phenobarbital	10 + 30	6	0.8 ± 0.26	0.6 ± 0.18	8.2 ± 1.38	17.7 ± 3.01	6/6
Phenobarbital + diazepam	30 + 0.5	6	1.0 ± 0.18	0.6 ± 0.27	10.5 ± 3.86	16.7 ± 2.16	6/6

*$p<0.05$, †$p<0.005$ as compared to control.

perature (25°C), on a 12 hr light/dark cycle (light on 7:00 a.m.), and had free access to food and water.

Pilot studies were conducted examining the dose-response relationship of bicuculline, picrotoxin and strychnine in rats. The dose producing clonic and tonic seizures, followed by 100% mortality, was selected for study. The appearance of tremors, facial twitching, increased motor activity, piloerection and clonic forelimb seizures was considered as clonic phase whereas the appearance of tonic extension of hindlimbs, followed by generalized clonic and tonic convulsions of both limbs was recorded as tonic phase [25]. Each animal was observed individually for the onset, duration of convulsion and mortality rate. During the course of study, a control group, which received only the convulsant agent, was always tested at the beginning and at the end of each experimental session.

The efficacy of barbiturates and GABAergic drugs was determined against 100% convulsive doses of bicuculline (8 mg/kg, IP), picrotoxin (10 mg/kg, IP) and strychnine (4 mg/kg, IP). The drugs were administered intraperitoneally (IP) 30 min prior to exposure to the convulsants. In order to study the interaction between barbiturates and GABAergic drugs, subeffective doses of these agents were administered prior to challenge with a 100% effective dose of the convulsant.

Statistics

The data are expressed as mean±S.D. The results for onset, duration of seizures and mortality time were analyzed by one-way analysis of variance, and the level of significance was determined by the Bonferroni α-splitting technique. To determine differences in death rate between control and test groups Fisher's Exact Test was used. A value of $p<0.05$ was considered statistically significant.

Drugs

(+)Bicuculline, muscimol, pentobarbital sodium, phenobarbital, picrotoxin and strychnine hydrochloride were purchased from Sigma Chemicals (St. Louis, MO). (±)Baclofen was a gift from Ciba-Geigy (Basel, Switzerland) and diazepam from Hoffmann-LaRoche, Inc. (Nutley, NJ). THIP was purchased from Sandoz Pharmaceuticals (E. Hanover, NJ).

(+)Bicuculline, diazepam, phenobarbital and picrotoxin were dissolved in dimethylsulphoxide (DMSO) whereas (±)baclofen, muscimol, pentobarbital sodium, strychnine hydrochloride and THIP were dissolved in double distilled water. All the drugs were injected intraperitoneally (IP) in a volume of 1 ml/kg body weight. Doses refer to the salt or base as specified above.

TABLE 2

EFFECT OF VARIOUS DRUGS ON PICROTOXIN- (10 mg/kg, IP) INDUCED CONVULSIONS IN RATS

Drug	Dose (mg/kg, IP)	n	Onset of Convulsion (min) Mean ± S.D.	Duration of Seizures (min) Mean ± S.D. Clonic	Duration of Seizures (min) Mean ± S.D. Tonic	Mortality Following Administration of Convulsant (min) Mean ± S.D.	Mortality (N)
Control	—	16	6.0 ± 1.05	0.7 ± 0.28	12.7 ± 3.63	23.9 ± 6.02	16/16
Pentobarbital	5	6	6.4 ± 1.02	0.8 ± 0.45	13.4 ± 2.95	28.2 ± 5.71	6/6
	7.5	10	6.9 ± 0.58	1.3 ± 0.67	10.6 ± 5.49	35.3 ± 9.09*	6/10*
	10	6	6.3 ± 1.62	0.8 ± 0.28	3.6 ± 1.11†	80.0 ± 0.00†	1/6†
	20	6	12.3 ± 2.16†	0.8 ± 0.16	0.3 ± 0.51†	—†	0/6†
Phenobarbital	10	8	6.2 ± 0.71	1.1 ± 0.14	14.3 ± 3.35	32.0 ± 5.10	6/8
	20	12	8.2 ± 1.42	0.9 ± 0.21	2.4 ± 1.77†	37.0 ± 20.66	3/12†
	30	8	9.0 ± 0.76	1.3 ± 0.77	2.2 ± 0.82†	30.0 ± 0.00	2/8†
THIP	15	6	6.1 ± 0.80	0.7 ± 0.09	14.7 ± 1.90	25.3 ± 3.78	6/6
	30	6	14.7 ± 3.50†	0.5 ± 0.11	6.2 ± 0.89†	40.5 ± 13.70†	4/6
Baclofen	20	6	6.6 ± 1.36	0.6 ± 0.19	12.8 ± 4.52	31.0 ± 12.84	6/6
Diazepam	0.5	6	7.5 ± 1.52	0.7 ± 0.28	12.1 ± 1.70	23.2 ± 3.97	6/6
	2	6	15.8 ± 1.47†	0.9 ± 0.37	0.7 ± 0.60†	—†	0/6†
THIP + pentobarbital	15 5	6	13.8 ± 2.79†	0.8 ± 0.45	5.3 ± 1.69†	52.5 ± 10.61†	2/6†
Baclofen + pentobarbital	10 5	6	14.0 ± 3.16†	0.6 ± 0.16	4.3 ± 1.28†	45.0 ± 0.00†	1/6†
Pentobarbital + diazepam	5 0.5	6	11.7 ± 1.91†	0.8 ± 0.15	1.6 ± 1.44†	—†	0/6†
THIP + phenobarbital	15 10	6	16.5 ± 1.87†	0.5 ± 0.17	2.9 ± 0.83†	60.0 ± 15.00†	3/6*
Baclofen + phenobarbital	10 10	6	8.0 ± 2.28	0.8 ± 0.24	3.6 ± 1.67†	30.0 ± 7.07	2/6†
Phenobarbital + diazepam	10 0.5	6	6.4 ± 0.53	1.0 ± 0.06	13.8 ± 2.64	36.8 ± 3.95†	4/6

*$p<0.05$, †$p<0.005$ as compared to control, (—) indicates no mortality.

RESULTS

Effect of Barbiturates, GABAergic Drugs and Diazepam Against Various Chemoconvulsants

(+)Bicuculline (8 mg/kg, IP), picrotoxin (10 mg/kg, IP) and strychnine (4 mg/kg, IP) produced severe clonic and tonic seizures followed by 100% mortality in rats (Tables 1–3). Pentobarbital and phenobarbital were effective against picrotoxin- (Table 2) as well as against strychnine- (Table 3) induced convulsions. Pentobarbital (20 mg/kg, IP) was also effective against bicuculline- (8 mg/kg, IP) induced convulsions (Table 1) whereas phenobarbital (up to 45 mg/kg, IP) was ineffective (Table 1). However, higher doses of phenobarbital produced severe sedation and sleep, and provided some protection against bicuculline-induced convulsions (data not shown).

THIP (30 mg/kg, IP) as well as diazepam (2 mg/kg, IP) exhibited anticonvulsant effect against all the chemoconvulsants studied (Tables 1–3). However, baclofen (up to 20 mg/kg, IP) was ineffective in providing protective effect against any of the chemoconvulsants (Tables 1–3).

Interaction of Barbiturates With GABAergic Drugs and Diazepam

Baclofen (10 mg/kg, IP) or subeffective dose of THIP (15 mg/kg, IP) when combined with subeffective dose of pentobarbital provided protection against various chemoconvulsants (Tables 1–3). However, the combination of these drugs with subeffective dose of phenobarbital was effective only against picrotoxin and strychnine (Tables 2,3) but not against bicuculline (Table 1). Diazepam, in subeffective dose, when combined with subeffective dose of pentobarbital provided protection (Tables 1–3). However, the combination of subeffective doses of diazepam and phenobarbital did not exhibit anticonvulsant effect against any of the chemoconvulsants (Tables 1–3).

DISCUSSION

The GABA receptor complex with which various drugs interact is an oligomeric complex with multiple sites comprising of GABA, benzodiazepine, barbiturate and picrotoxin binding sites coupled to chloride channel [14,24]. It is

TABLE 3

EFFECT OF VARIOUS DRUGS ON STRYCHNINE- (4 mg/kg, IP) INDUCED CONVULSIONS IN RATS

Drug	Dose (mg/kg, IP)	n	Onset of Convulsion (min) Mean ± S.D.	Duration of Seizures (min) Mean ± S.D. Clonic	Duration of Seizures (min) Mean ± S.D. Tonic	Mortality Following Administration of Convulsant (min) Mean ± S.D.	Mortality (N)
Control	—	11	3.2 ± 0.93	0.3 ± 0.16	6.0 ± 1.78	10.1 ± 2.55	11/11
Pentobarbital	7.5	6	3.5 ± 0.55	1.2 ± 0.83	8.3 ± 3.37	13.5 ± 3.87*	4/6
	10	7	4.1 ± 1.77	0.2 ± 0.13	6.6 ± 4.19	11.8 ± 2.84	3/7*
	20	7	5.9 ± 1.57†	0.2 ± 0.03	0.3 ± 0.13†	70.0 ± 14.14†	2/7†
Phenobarbital	10	7	2.9 ± 0.90	0.2 ± 0.03	5.5 ± 2.33	10.0 ± 3.11	6/7
	20	7	4.1 ± 0.73	0.3 ± 0.16	5.3 ± 1.90	18.3 ± 6.05†	7/7
	30	6	7.0 ± 2.76†	0.8 ± 0.14	0.7 ± 0.21†	—†	0/6†
THIP	15	6	4.4 ± 1.04	0.2 ± 0.04	5.6 ± 0.81	12.3 ± 2.07	6/6
	30	6	6.3 ± 1.03†	0.3 ± 0.17	1.6 ± 0.90†	26.0 ± 5.29†	3/6*
Baclofen	20	6	2.9 ± 0.66	0.3 ± 0.10	6.5 ± 2.17	18.0 ± 6.66†	6/6
Diazepam	1	6	3.1 ± 1.20	0.2 ± 0.06	6.7 ± 1.15	11.5 ± 3.33	6/6
	5	6	6.0 ± 1.47†	0.3 ± 0.13	3.1 ± 1.95†	25.5 ± 10.21†	4/6
THIP + pentobarbital	15 + 10	6	7.1 ± 0.92†	0.5 ± 0.25	2.8 ± 1.74†	60.0 ± 0.00†	1/6†
Baclofen + pentobarbital	10 + 10	6	3.4 ± 0.49†	0.2 ± 0.09	1.5 ± 0.59†	12.5 ± 3.54	2/6*
Pentobarbital + diazepam	10 + 1	6	4.5 ± 1.38	0.4 ± 0.41	2.0 ± 1.15†	23.0 ± 7.00†	3/6*
THIP + phenobarbital	15 + 10	6	7.1 ± 0.97†	0.2 ± 0.04	2.0 ± 0.87†	50.0 ± 14.14†	2/6*
Baclofen + phenobarbital	10 + 10	6	5.1 ± 0.71†	0.2 ± 0.08	2.4 ± 0.72†	12.3 ± 2.52	3/6*
Phenobarbital + diazepam	20 + 1	6	4.1 ± 0.93	0.3 ± 0.10	6.0 ± 1.42	18.8 ± 6.88*	6/6

*$p<0.05$, †$p<0.005$ as compared to control, (—) indicates no mortality.

widely accepted that GABA agonists and bicuculline bind to GABA receptors, benzodiazepine agonists/antagonists bind to the benzodiazepine receptors, whereas picrotoxin and related cage convulsants bind to the picrotoxin site of this complex [24,32]. While it is assumed that strychnine acts at glycine receptors, it is well known that high concentrations of strychnine will also block GABA receptor chloride channels. Furthermore, depressant barbiturates bind to a distinct allosteric (depressant) site, which is coupled to GABA and picrotoxin sites of the benzodiazepine GABA receptor-ionophore complex [32,33]. Both pentobarbital and phenobarbital facilitate GABAergic transmission, and activate $GABA_A$ receptor-coupled channels directly [13, 22, 23]. There are also reports that pentobarbital is much more potent than phenobarbital in enhancing GABA responses [13, 22, 23], muscimol responses [27], in reducing the potency of picrotoxin as a GABA antagonist [23] and directly activating GABA receptor-gated Cl^- channels [26]. There also exist differences in the ability of pentobarbital and phenobarbital to interact with various binding sites on the oligomeric GABA receptor complex. Thus, while both the barbiturates inhibit [^{3}H]α-dihydropicrotoxinin (DHP) and [S^{35}]t-butylbicyclophosphorothionate (TBPS) binding [33], and accelerate the dissociation of [^{35}S]TBPS binding as compared to the convulsant dissociation pattern [14], only pentobarbital enhances both [^{3}H]GABA and [^{3}H]benzodiazepine binding [1, 12, 18, 30, 31, 34]. Interestingly, phenobarbital inhibits the enhancing effect of pentobarbital [12], suggesting that the two barbiturates may bind to the same site.

The present study demonstrated that pentobarbital and phenobarbital were effective anticonvulsants against picrotoxin as well as strychnine. However, pentobarbital, but not phenobarbital, in nonsedative doses also exhibited protective effect against bicuculline-induced convulsions. This is in agreement with our previous report that bicuculline reverses the anticonvulsant effect of pentobarbital, but not that of phenobarbital, against maximal electroshock seizures [16]. However, the hypnotic doses of phenobarbital provided some protection against bicuculline-induced convulsions. These observations indicated that pentobarbital is an effective anticonvulsant against drugs acting at picrotoxin site, $GABA_A$ receptors and glycine receptors whereas phenobarbital is only effective against drugs acting at picrotoxin site and glycine receptors, and exhibits very weak protective ef-

fect against drugs blocking $GABA_A$ receptors. It is likely that the anticonvulsant effect observed with various agents against strychnine could be due to its $GABA_A$ receptor antagonistic effect [28]. THIP, $GABA_A$ receptor agonist, exhibited anticonvulsant effect whereas baclofen, $GABA_B$ receptor agonist, even at a dose reported to produce severe catatonia [17] did not provide any protection against any of the chemoconvulsants studied. These observations are consistent with the notion that $GABA_A$ receptors, but not $GABA_B$ receptors, play an important role in providing protection against various chemoconvulsants. This is also in agreement with earlier reports that activation of $GABA_A$ receptors, but not $GABA_B$ receptors, provides protection against maximal electroshock seizures [2,16]. However, subeffective doses of THIP as well as baclofen when combined with subeffective doses of pentobarbital or phenobarbital provided protection thereby demonstrating the beneficial interaction of barbiturate binding sites with both the subtypes of GABA receptors leading to anticonvulsant effect. Baclofen has been reported to modify potassium conductance and to decrease the release of excitatory neurotransmitter [35]. It is apparent that the activation of $GABA_B$ receptors alone is not adequate to reverse the effect of various chemoconvulsants. However, ability of barbiturates to facilitate $GABA_A$ergic transmission, coupled with the ability of baclofen to inhibit the release of excitatory transmitters, could account for the enhanced anticonvulsant effect of barbiturates. Interestingly, pentobarbital, but not phenobarbital, enhanced the anticonvulsant effect of diazepam against various chemoconvulsants. This is consistent with the report that only pentobarbital enhances [^{3}H]benzodiazepine and [^{3}H]GABA binding [1, 12, 18, 30, 31, 34]. These studies raise the possibility that the interaction of pentobarbital, but not phenobarbital, with GABA and benzodiazepine sites may play a role in its anticonvulsant effect.

In conclusion, activation of $GABA_A$ receptors, and not $GABA_B$ receptors, provide protection against various chemoconvulsants which affect GABA receptor-complex or glycine receptors. However, the activation of either type of GABA receptors facilitate the anticonvulsant effect of barbiturates. Furthermore, only pentobarbital, and not phenobarbital, facilitates the anticonvulsant effect of diazepam against chemoconvulsants.

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