Comparative Study of Tiapride and Neuroleptics with Anti-Dopamine Activity on Convulsive Seizure in Mice

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Abstract—The effects of tiapride on the convulsive seizures induced by pentylenetetrazole, strychnine, picrotoxin and bemegride, and on electric seizure are reported and compared with those of sulpiride, chlorpromazine, haloperidol and reserpine. The number of deaths and intensity of convulsion increased dose-dependently and also with the increase in amplitude of electric shock. Tiapride and a similar compound, sulpiride, did not affect these seizures, whereas chlorpromazine potentiated strychnine-induced and electric seizure. Haloperidol and reserpine potentiated electric seizure, and chlorpromazine and reserpine tended to potentiate bemegride-induced seizure. Reserpine also tended to potentiate pentylenetetrazole-induced seizure. These results suggest that tiapride would be clinically safer than other drugs with anti-dopamine activity, except for sulpiride.

Tiapride, N-[2-(diethylamino)ethyl]-5-(methylsulfonyl)-o-anisamide, has a chemical structure and binding specificity to dopamine receptor similar to sulpiride, and it has been used to treat elderly patients with organic psychosis (1). Neuroleptics with anti-dopamine activity are also used in aged patients with organic psychosis, but these drugs occasionally induce seizure (2-4). Because the seizure-inducing potential of tiapride has not been examined, we studied its effect on the convulsion induced by pentylenetetrazole, strychnine, picrotoxin and bemegride as well as on electric seizure, and these effects were compared with those of sulpiride, chlorpromazine, haloperidol and reserpine.

Materials and Methods

Animals: Female ICR mice aged 6 weeks and weighing 17.2-30.0 g (Shizuoka Agricultural Cooperative Association for Laboratory Animals) were used.

Convulsants-induced seizure: Pentylene-

tetrazole, strychnine, picrotoxin and bemegride were used as convulsants. A preliminary experiment was conducted to determine the death-inducing threshold of the four convulsants. Animals were used in groups of 10 to 20. The number of animals that died within 1 hr after dosing with a convulsant was used to determine the death-inducing threshold of each compound. Each threshold dose of convulsant was given to 10 or 20 animals to examine the effect of the test drugs.

Electric seizure: Each dose of the test drugs was given to 10 animals. Electric current was increased 0.5 mA per sec. The amplitude of the current (mA) inducing clonic or tonic convulsion was measured, that is, each amplitude was expressed as the threshold of the respective convulsion.

Drugs: The test drugs were tiapride hydrochloride, sulpiride (Delagrange), chlorpromazine hydrochloride (synthesized at our Laboratories), haloperidol (Janssen) and reserpine (Serpasil® for injection, Takeda). Convulsants used in this study were pentylenetetrazole (Tokyo Kasei), strychnine

nitrate (Sigma), picrotoxin (Nakarai) and bemegride (Wako). All drugs except haloperidol and sulpiride were dissolved in saline or distilled water. Haloperidol and sulpiride were dissolved in a minimum amount of 20% acetic acid and 1N sulfuric acid, respectively, and the pH of the solution was adjusted to 7.0 with 1N sodium hydroxide. Reserpine was diluted with distilled water. All the convulsants were given i.p. The test drugs except for reserpine were given p.o. 1 hr before challenge. Reserpine was given i.p. 24 hr before challenge.

Statistics: Statistical significance was calculated by Student's *t*-test or Fisher's exact probability test (5).

Results

Death-inducing threshold of convulsants:

Table 1 shows the death-inducing threshold of each convulsant. All the convulsants caused death dose-dependently. The dose-effect curve of each convulsant was abrupt. The doses of convulsants used to examine the effects of the test drugs were as follows:

pentylentetrazole, 40 and 70 mg/kg; strychnine, 1.25 and 1.5 mg/kg; picrotoxin, 7 and 9 mg/kg; and bemegride, 20 and 30 mg/kg, i.p.

Effect of drugs on death: The effect of the test drugs on pentylentetrazole-induced seizure is shown in Table 2. Reserpine dose-dependently potentiated the death of animals treated with 40 mg/kg of pentylentetrazole. The other drugs had no effect.

The effect of the drugs on strychnine-induced seizure is shown in Table 3. Only chlorpromazine significantly potentiated the death-inducing effect of strychnine.

The effect of the drugs on picrotoxin-induced seizure is shown in Table 4. None of the drugs affected the seizure.

The effect of the drugs on bemegride-induced seizure is shown in Table 5. Chlorpromazine and reserpine slightly potentiated the effect of bemegride. The other drugs had no effect.

Effect of drugs on electric seizure: The effect of the test drugs on electric seizure is shown in Table 6. Chlorpromazine,

Table 1. Death-inducing effect of convulsants

Convulsant	Dose (mg/kg, i.p.)	Animals died Animals used
Pentylentetrazole	40	0/20
	50	2/20
	60	1/20
	70	6/20
	80	17/20
Strychnine	1	0/20
	1.25	3/20
	1.5	4/10
	1.7	15/20
	2	20/20
Picrotoxin	4	0/10
	8	3/20
	9	3/10
	10	6/10
	12	9/10
	16	10/10
Bemegride	20	0/20
	25	1/20
	30	5/20
	40	14/20
	50	20/20

Animals were observed for 1 hr after injection.

Table 2. Effect of drugs on pentylenetetrazole-induced seizure

Dose (mg/kg. p.o.)	Number of animals died/Number of animals used								
	Pentylenetetrazole 40 mg/kg (i.p.)				Pentylenetetrazole 70 mg/kg (i.p.)				
	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Reserpine
0	0/10	0/10	0/10	0/10	3/10	3/10	4/10	5/10	4/10
0.32	—	—	—	0/10	—	—	—	3/10	4/10
1	—	—	0/10	0/10	—	—	4/10	1/10	3/10
3.2	0/10	0/10	0/10	0/10	3/10	5/10	5/10	3/10	7/10
10	0/10	0/10	0/10	0/10	2/10	0/10	0/10	1/10	9/10
32	0/10	0/10	0/10	0/10	2/10	0/10	0/10	8/10	
100	0/10	0/10	0/10		1/10	3/10	5/10		
320	0/10	0/10			3/10	3/10			

All drugs except reserpine were given p.o. 1 hr before injection of pentylenetetrazole. Reserpine was given i.p. 24 hr before injection of pentylenetetrazole.

Table 3. Effect of drugs on strychnine-induced seizure

Dose (mg/kg. p.o.)	Number of animals died/Number of animals used								
	Strychnine 1.25 mg/kg (i.p.)				Strychnine 1.5 mg/kg (i.p.)				
	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Reserpine
0	1/10	1/10	0/10	0/10	7/10	5/10	2/10	4/10	5/20
0.32	—	—	—	0/10	—	—	—	1/10	0/10
1	—	—	1/10	0/10	—	—	1/10	0/10	0/10
3.2	0/10	0/10	2/10	2/10	3/10	2/10	3/10	4/10	1/10
10	1/10	0/10	3/10	1/10	4/10	5/10	6/10	3/10	1/10
32	0/10	0/10	1/10	0/10	4/10	1/10	4/10	3/10	
100	0/10	0/10	3/10		3/10	1/10	9/10*		
320	3/10	0/10			5/10	4/10			

All drugs except reserpine were given p.o. 1 hr before injection of strychnine. Reserpine was given i.p. 24 hr before injection of strychnine. *: $P < 0.05$

Table 4. Effect of drugs on picrotoxin-induced seizure

Dose (mg/kg. p.o.)	Number of animals died/Number of animals used								
	Picrotoxin 7 mg/kg (i.p.)				Picrotoxin 9 mg/kg (i.p.)				
	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Reserpine
0	0/10	0/10	4/20	0/10	2/10	6/20	8/20	8/20	3/10
0.32	—	—	—	0/10	—	—	—	1/10	1/10
1	—	—	1/10	0/10	—	—	0/10	1/10	1/10
3.2	0/10	0/10	0/10	1/10	2/10	0/10	2/10	0/10	4/10
10	0/10	0/10	0/10	0/10	1/10	2/10	3/10	1/10	2/10
32	0/10	0/10	0/10	0/10	2/10	4/10	4/10	3/10	
100	0/10	0/10	0/10		0/10	1/10	4/10		
320	0/10	0/10			3/10	3/10			

All drugs except reserpine were given p.o. 1 hr before injection of picrotoxin. Reserpine was given i.p. 24 hr before injection of picrotoxin.

Table 5. Effect of drugs on bemegride-induced seizure

Dose (mg/kg, p.o.)	Number of animals died/Number of animals used								
	Bemegride 20 mg/kg (i.p.)				Bemegride 30 mg/kg (i.p.)				Reserpine
	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	Tiapride	Sulpiride	Chlor- promazine	Halo- peridol	
0	0/20	0/10	0/10	0/10	3/10	10/20	3/10	4/10	5/20
0.32	—	—	—	0/10	—	—	—	2/10	2/10
1	—	—	0/10	0/10	—	—	6/10	2/10	3/10
3.2	0/10	0/10	0/10	0/10	3/10	6/10	6/10	5/10	6/10
10	0/10	0/10	0/10	0/10	1/10	5/10	8/10	2/10	6/10
32	0/10	0/10	0/10	1/10	2/10	8/10	7/10	5/10	
100	0/10	0/10	1/10		5/10	5/10	2/10		
320	0/10	0/10			1/10	4/10			

All drugs except reserpine were given p.o. 1 hr before injection of bemegride. Reserpine was given i.p. 24 hr before injection of bemegride.

Table 6. Effect of drugs on electric seizure

Drug	Dose (mg/kg, p.o.)	Threshold (mA)	
		Clonic	Tonic
Tiapride	0	2.5±0.1	4.8±0.2
	32	2.5±0.1	5.0±0.2
	100	2.6±0.1	5.0±0.2
	320	2.5±0.1	4.8±0.1
Sulpiride	0	2.3±0.1	4.2±0.1
	32	2.2±0.1	4.5±0.1
	100	2.4±0.0	4.7±0.1*
	320	2.2±0.1	4.4±0.1
Chlorpromazine	0	2.4±0.1	4.7±0.1
	1	2.3±0.01	5.2±0.6
	3.2	2.2±0.1*	4.3±0.2
	10	2.1±0.1*	5.1±0.8
	32	1.8±0.1*	3.5±0.2*
	100	1.6±0.1*	3.2±0.1*
Haloperidol	0	2.3±0.0	4.7±0.1
	1	2.6±0.1*	4.9±0.3
	3.2	2.3±0.1	4.5±0.2
	10	2.0±0.1*	4.0±0.2*
	32	1.8±0.1*	3.8±0.2*
	100	1.5±0.0*	3.3±0.1*
Reserpine	0	2.5±0.1	5.1±0.2
	1	2.6±0.1	4.8±0.2
	3.2	1.5±0.1*	2.7±0.2*
	10	1.5±0.1*	2.5±0.1*

All drugs except reserpine were given p.o. 1 hr before electric stimulation. Reserpine was given i.p. 24 hr before electric stimulation. Figures show the mean±S.E. *: P<0.05

haloperidol and reserpine potentiated the electric seizure, that is, these drugs lowered the amplitude inducing clonic and tonic

convulsion. Tiapride and sulpiride had no effect.

The effects of the test drugs on seizure are

Table 7. Summary of the effect of drugs on convulsant-induced and electric seizures

Drug	Seizure	Pentylene-tetrazol	Strychnine	Picrotoxin	Bemegride	Electric	
						Clonic	Tonic
Tiapride		→	→	→	→	→	→
Sulpiride		→	→	→	→	→	→
Chlorpromazine		→	↑	→	↗	↑	↑
Haloperidol		→	→	→	→	↑	↑
Reserpine		↗	→	→	↗	↑	↑

→ : No effect, ↑ : Potentiation, ↗ : Slight potentiation.

summarized in Table 7. Tiapride, like sulpiride, had no effect on any of these seizures, whereas chlorpromazine potentiated strychnine-induced and electric seizures. Haloperidol and reserpine also potentiated electric seizure, and chlorpromazine and reserpine slightly potentiated bemegride-induced seizure. Reserpine also slightly potentiated pentylenetetrazole-induced seizure.

Discussion

Reserpine, an amine depleter, lowers the seizure threshold in rodents (6). Clinically, neuroleptics with anti-dopamine activity occasionally induce convulsive seizure (2–4), and reserpine weakens the effect of anti-convulsants (7). Tiapride is a dopamine specific antagonist in the central nervous system (8). However, its effect on the seizure threshold has not been examined. In our experiments, tiapride had no effect on the seizure induced by any of the convulsants or on electric seizure.

Sulpiride, like tiapride, was also without effect, but haloperidol, chlorpromazine and reserpine potentiated or tended to potentiate the seizure in some experiments.

The mechanisms of the convulsants are not clear; however, amine neurons and some other neurons are supposed to be involved in drug-induced and electric seizures. Norepinephrine (9, 10), serotonin (9, 11, 12), GABA (13), acetylcholine (14) and adenosine (9) are supposed to be involved in pentylenetetrazole-induced convulsion. Glycine (15, 16) and GABA (17, 18) are involved in strychnine and picrotoxin-induced convulsions, respectively. GABA

and an unknown substance are reported to be involved in bemegride-induced convulsion (19). In electric seizure, such substances as norepinephrine, serotonin and adenosine are supposed to participate (9). In contrast, dopamine has little effect on pentylenetetrazole-induced and electric seizures (9).

Such neuroleptics as chlorpromazine block many amine receptors as well as the dopamine receptor (20, 21), and reserpine lowers the activity of norepinephrine, serotonin and dopamine on the receptor sites. Therefore, these drugs would potentiate the seizure, and this effect might correlate with the seizure-inducing effect in clinical use. In contrast, tiapride and sulpiride act only on the dopamine receptor (8). Therefore, the absence of an effect on seizure may be due to their selective blocking activity on the dopamine receptor. Sulpiride only poorly penetrates the blood-brain barrier (22), and further experiments are needed to confirm its effect on seizure in the case of intraventricular injection. However, the drug is safe for even schizophrenics with epileptic syndrome (23).

In conclusion, tiapride would be clinically safer than other anti-dopamine drugs except for sulpiride.

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