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Effects of Apomorphine and Piribedil on Pentylenetetrazol-Induced Seizures in Mice

William H. Riffee[1], Richard E. Wilcox[1], Cheng-Pei Li Goldman[1], and Robert V. Smith[2]

[1] Department of Pharmacology, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA
[2] Drug Dynamics Institute, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, USA

Abstract. Based on previous work examining the effects of dextroamphetamine on pentylenetetrazol (PTZ)-induced clonic seizure threshold, the objective of the present study was to determine the effects of two other dopamine agonists, apomorphine (AP) and piribedil, on PTZ seizures. TD_{50} and LD_{50} values for CD-1 mice were determined initially for the two drugs. Subsequently, dose- and time-response analyses established that AP decreased PTZ seizure threshold 15 min after administration, but increased the threshold at 60 min. Piribedil elevated the seizure threshold, but like AP, did not exhibit a clear dose-response relationship. Subsequent blocker studies with phentolamine, (−)sotalol, pimozide, and atropine suggested the possible neurotransmitter systems involved in the modulation of the PTZ-induced seizures by AP and piribedil. Pimozide blocked the changes in seizure threshold induced by both drugs. Atropine also decreased the AP-induced increase in threshold at 60 min. The pattern of inhibition of seizure threshold changes induced by the neurotransmitter blockers suggested that piribedil blocked seizures by means of indirect actions on several neurotransmitters.

Key words: Pentylenetetrazol – Seizures – Apomorphine – Piribedil – Receptor blockers

Apomorphine (AP) has been used to treat Parkinson's disease because of direct stimulation of central dopamine (DA) receptors (Vernier and Unna 1951; Asper et al. 1973). Furthermore, AP has been suggested as a potentially useful antidyskinetic drug (DiChiara et al. 1978), presumably through selective stimulation of dopaminergic autoreceptors (Carlsson 1975; Roth 1979).

Piribedil (ET 495), a DA agonist introduced in 1971 by Corrodi et al., also has been used orally in the treatment of Parkinson's disease (Chase et al. 1974). ET 495, as a dopaminergic receptor stimulant, differs from AP in that it is less potent and it has a much longer duration of action (Vakil et al. 1973; Butterworth et al. 1975).

Pentylenetetrazol (PTZ)-induced clonic seizure threshold has been found to be useful in examining effects of drugs on CNS excitability (Riffee and Gerald 1977a, b). In earlier studies, we have shown that another DA agonist, (+)amphetamine, produced alterations in chemoconvulsive threshold. With the potential clinical use of AP and possibly piribedil, it was of interest to determine the possible effects of these two drugs on seizure threshold and compare them to the changes induced by (+)amphetamine (cf., Riffee and Gerald 1976). In addition, since the toxic and lethal doses of AP and piribedil had not yet been established in the strain of mice used here, we first established the TD_{50} and LD_{50} of the drugs. The study using PTZ seizure threshold was then related to the toxic effects of AP and piribedil in mice.

Offprint requests to: Richard E. Wilcox

Materials and Methods

Male albino CD-1 mice (Charles River, Wilmington, MA), weighing 17–30 g, were used. The animals were housed in groups of ten per cage (17.5 × 6.5 inch), except during experimentation when they were housed in isolation cages (8.9 × 11.4 × 14.0 cm). The mice were permitted free access to food (Wayne Lab Blox) and water. All animals were allowed to acclimate to the laboratory environment for at least 24–48 h prior to the start of experimentation.

Drugs. The following drugs were used: AP HCl hemihydrate (MacFarland Smith, Edinburgh, Scotland), piribedil methane sulfonate (ET 495, Les Laboratories, Servier, Orleans, France), phentolamine HCl (Ciba-Geigy, Summit, NJ), (−)sotalol HCl (Mead-Johnson, Evansville, IN), pimozide (Janssen Pharmaceutica, Beerse, Belgium), and atropine sulfate (City Chemical, New York, NY).

All drug solutions were freshly made immediately before the start of experimentation. Drugs were dissolved in distilled water, with the exception of pimozide which was dissolved in tartaric acid (1.25 mg/ml), and all drugs were administered IP in a constant volume of 10 ml/kg.

Pentylenetetrazol (1,5-pentamethylenetetrazole) (Aldrich Chemical, Milwaukee, WI) was dissolved in distilled water and administered IV via a syringe infusion pump (model 341, Sage Instruments, Davison Orion Research Inc.) into the lateral tail vein of each mouse.

Toxicity Studies. The dosage that would produce toxic effects in 50% of the test animals (TD_{50}) was determined for AP and piribedil.

A rolling rotor designed for mice was used to test for neurologic deficiency induced by the drugs. The deficiency was defined as the failure of the animal to remain on the rotor rod for a 1-min period (each mouse was given three trials). The TD_{50} was calculated by the method of Litchfield and Wilcoxon (1949).

AP and piribedil were tested for their lethal effects upon mice. The test consisted of observing the number of animals

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Table 1. Time- and dose-response of acute apomorphine and ET495 (peribedil) administration on PTZ-induced clonic seizure threshold in CD-1 mice. Drugs were administered IP at the time indicated prior to PTZ infusion

Apomorphine					ET495				
Dose (mg/kg)	Percent of control (95% confidence intervals)				Dose (mg/kg)	Percent of control (95% confidence intervals)			
	Time after drug administration					Time after drug administration			
	15 min	30 min	45 min	60 min		15 min	30 min	45 min	60 min
50	77[a] (69–87)	97 (86–110)	106 (92–122)	120[a] (105–136)	50	106 (93–120)	119[a] (104–134)	120 (104–139)	99 (87–113)
60	79[a] (71–88)	111 (91–133)	118 (91–146)	126[a] (113–139)	100	110 (99–124)	113[a] (102–125)	120[a] (103–142)	99 (87–113)
70	91[a] (84–98)	104 (95–114)	114[a] (104–125)	120[a] (110–131)	150	98 (88–109)	117[a] (101–137)	121[a] (105–140)	98 (89–109)
80	90 (72–109)	105 (81–130)	120[a] (107–135)	129[a] (115–145)	200	91 (82–101)	118[a] (106–131)	141[a] (118–170)	111[a] (100–123)
90	91 (77–105)	110 (99–122)	135[a] (117–154)	143[a] (126–161)	300	103 (89–119)	124[a] (111–138)	127[a] (112–147)	115[a] (102–131)

[a] Statistically significant difference from control at $P < 0.05$ using the confidence interval of a ratio test (Goldstein 1969)

that survived at the end of a 60-min period following several appropriate dosages of the drug administered to groups of eight mice. The LD_{50} of the drug was also calculated according to the method of Litchfield and Wilcoxon (1949).

Seizure Threshold Studies. The clonic seizure was defined as the occurrence of 3 s of jerking movements of the ears and jaws with purposeless running movements of the forelimbs (Gerald and Riffee 1973; Riffee and Gerald 1977a, b).

PTZ was used to induce clonic seizure activity in groups of 10–15 mice, each group being used only once. The procedure used was a modification of that described by Orloff (1949). The test animal was briefly restrained while a 0.5% solution of PTZ was infused into a lateral tail vein at a constant rate of 0.51 or 0.57 ml/min with a syringe pump.

The time (seconds) required to elicit a clonic seizure, and the body weight of the mouse were used to calculate the PTZ dose required to induce the seizure. The results are expressed as percent response of the saline (control) groups.

The time- and dose-response relationships for AP- and piribedil-induced changes in PTZ seizure threshold following acute administration of the drugs were established.

Receptor Blocker Studies. This experiment was designed to provide some initial insights concerning the neurotransmitter system(s) involved in the alterations of PTZ-induced clonic seizure threshold produced by AP and piribedil. Phentolamine (5 mg/kg), an α-adrenergic receptor blocker, (–)sotalol (5 mg/kg), a β-adrenergic blocker, pimozide (2.5 mg/kg), a dopaminergic receptor blocker, and atropine (10 mg/kg), a cholinergic receptor blocker, were selected as the antagonists for this initial study (Riffee and Gerald 1976).

Phentolamine, (–)sotalol, pimozide, and atropine were administered IP at 10, 30, 60, and 120 min, respectively, prior to an injection of AP or piribedil. None of these compounds produced changes in seizure thresholds when administered alone.

Results

Toxicity Studies. TD_{50} and LD_{50} doses were as follows: AP TD_{50}, 70–100 mg/kg depending on the time of neurological testing; piribedil TD_{50}, 235 mg/kg; AP LD_{50}, 128 mg/kg; piribedil LD_{50}, 510 mg/kg.

Seizure Threshold Studies. The alterations of PTZ-induced clonic seizure susceptibility induced by AP were recorded at 15, 30, 45, and 60 min after drug administration. Within the dose range of 50 to 90 mg/kg, AP exhibited a biphasic time-response relationship by first decreasing and later increasing the seizure threshold (Table 1). Fifteen minutes following administration of AP (all doses), seizure threshold was decreased 10–23%. However, the seizure threshold was unchanged by AP at 30 min after drug administration. At 45 and 60 min after drug administration, AP produced its greatest effect in that it elicited a 15–43% increase of seizure threshold ($P < 0.05$, Table 1).

In contrast, piribedil produced its greatest response 45 min after administration (Table 1). The seizure threshold was significantly increased 20–42% ($P < 0.05$) in doses ranging from 50–300 mg/kg (Table 1). With piribedil, as with AP, a clear dose-response relationship was not demonstrated.

Receptor Blocker Studies. The time of peak effect for alteration of seizure threshold (TPE) induced by piribedil was 45 min. AP was found to exhibit two times of peak effect, 15 and 60 min (Table 1), producing the greatest susceptibility and the greatest resistance to PTZ-induced clonic seizures, respectively. Subsequent studies of the ability of the various neurotransmitter blockers to alter DA agonist-induced changes in seizure threshold were conducted at the TPE of 45 min for piribedil and at the two TPE times 15 and 60 min for AP.

Pimozide (2.5 mg/kg) successfully blocked the decrease in seizure threshold induced by AP (i.e., at 15 min postinjection),

Table 2. Effects of pretreatment with noradrenergic, dopaminergic, and cholinergic blockers on PTZ-induced clonic seizure susceptibility in CD-1 mice after acute administration (IP) of apomorphine (AP). Phentolamine, (–)sotalol, pimozide, and atropine were administered IP at 10, 30, 60, and 120 min prior to an injection of AP. The PTZ seizure threshold was determined 15 min or 60 min following administration

Dose (mg/kg)	Percent of control (95% confidence interval) 15 min after AP injection					Percent of control (95% confidence interval) 60 min after AP injection				
	AP + no pretreatment	AP + phentolamine (5 mg/kg)	AP + (–)sotalol (5 mg/kg)	AP + pimozide (2.5 mg/kg)	AP + atropine (10 mg/kg)	AP + no pretreatment	AP + phentolamine (5 mg/kg)	AP + (–)sotalol (5 mg/kg)	AP + pimozide (2.5 mg/kg)	AP + atropine (10 mg/kg)
50	77[a] (69–87)	80[a] (66–94)	91 (82–102)	105 (90–121)	92 (76–110)	120[a] (105–136)	115 (96–136)	114[a] (103–125)	106 (94–119)	90 (74–108)
60	79[a] (71–88)	86[a] (74–99)	84[a] (75–93)	108 (98–118)	76[a] (68–87)	126[a] (113–139)	106 (93–120)	113 (93–136)	108 (93–125)	97 (85–132)
70	91[a] (84–98)	88 (75–102)	83[a] (75–92)	97 (82–112)	84[a] (71–98)	120[a] (110–131)	121[a] (102–144)	119[a] (104–135)	109 (89–133)	107 (84–132)
80	90 (72–109)	90 (80–103)	80[a] (74–87)	97 (82–114)	79[a] (63–95)	129[a] (115–145)	120[a] (105–137)	108 (93–126)	116[a] (100–135)	106 (88–126)
90	91 (77–105)	92 (81–105)	79[a] (68–90)	100 (88–113)	84[a] (70–100)	143[a] (126–161)	122[a] (103–146)	107 (87–130)	108 (95–124)	103 (92–117)

[a] Statistically significant difference from control at $P < 0.05$ using the confidence interval of a ratio test (Goldstein 1969)

Table 3. Effects of pretreatment with noradrenergic, dopaminergic, and cholinergic blockers on PTZ-induced clonic seizure susceptibility in CD-1 mice after acute administration (IP) of ET 495. Phentolamine, (–)sotalol, pimozide, and atropine were injected IP 10, 30, 60, and 120 min, respectively, prior to administration of ET 495 (IP), which was 45 min prior to PTZ infusion

Dose (mg/kg)	Percent of control (95% confidence interval)				
	ET 495 + no pretreatment	ET 495 + phentolamine (5 mg/kg)	ET 495 + (–)sotalol (5 mg/kg)	ET 495 + pimozide (2.5 mg/kg)	ET 495 + atropine (10 mg/kg)
50	120[a] (104–139)	98 (86–113)	99 (86–115)	103[a] (90–118)	100 (89–112)
100	120[a] (103–142)	100 (89–113)	93 (81–108)	100 (88–114)	95 (82–118)
150	121[a] (105–140)	98 (88–109)	108 (93–127)	107 (95–121)	95 (82–109)
200	141[a] (118–170)	106 (88–125)	108 (96–121)	107 (96–118)	108 (94–125)
300	127[a] (112–147)	98 (81–116)	116[a] (105–129)	115[a] (104–128)	106 (94–120)

[a] Statistically significant difference from control at $P < 0.05$ using the confidence interval of a ratio test (Goldstein 1969)

restoring seizure threshold to near the control values (Table 2). (–)Sotalol and atropine weakly inhibited the AP (50 mg/kg)-induced decrease in seizure threshold, but had no affect at higher doses. Phentolamine (5 mg/kg) failed to block the AP-induced decreases in the seizure threshold.

Phentolamine, however, did effectively inhibit AP-induced increases in seizure threshold (60 min postinjection AP) produced by 50 and 60 mg/kg AP, but not at the 70 mg/kg to 90 mg/kg doses. (–)Sotalol exhibited inconsistent inhibition of AP-induced increases of seizures threshold, since it blocked the effect induced by 60, 80, and 90 mg/kg AP, but not that produced by 50 and 70 mg/kg (Table 3). The increased seizure threshold induced by AP at all dosages, with the exception of the 80 mg/kg dose (Table 2), was blocked by pretreatment with pimozide (2.5 mg/kg). Atropine successfully reduced the increase in seizure threshold induced by all dosages of (50–90 mg/kg) AP (Table 2). Each of the neurotransmitter blocking agents, when administered prior to piribedil, was successful in inhibiting the seizure threshold alterations elicited by that drug (Table 3).

Discussion

The present data are the first concerning TD_{50} and LD_{50} of AP and ET 495 administered to mice of the CD-1 strain. The TD_{50} of AP is 70 mg/kg and ranging up to 102 mg/kg depending on the time of neurological testing. The LD_{50} of AP is 128 mg/kg. The range of TD_{50} may reflect the contribution of a lowered seizure threshold at the earlier time

period (15 min) and the protection from seizure at the later time periods (60 min). However, the fact that the confidence limits of the LD_{50} value for AP overlap those for the 60 min TD_{50} value for the drug indicates that the apparent increase in the threshold for seizures was not sufficient to protect the animal from the lethal effects of the drug.

The LD_{50} and its confidence limits for AP are somewhat lower than those calculated by McKenzie and Soroko (1972) for CDI mice (165 mg/kg), although the latter was determined using SC administration versus the IP injection used in this study. This is of interest, since the literature reveals that the SC route requires two- to ten-fold less AP than the IP route to induce stereotypic behavior (Protais et al. 1976; Riffee et al. 1979; Riffee and Wilcox, data in preparation). This suggests that the lethality of AP is not determined exclusively by the dopaminergic agonist activity of the drug. In addition, it might also indicate the possible involvement of metabolites in the overall toxicity.

Biphasic changes occurred in PTZ-induced clonic seizure threshold in response to AP. At 15 min, AP induced a decreased seizure threshold and, at 60 min, AP produced an increased seizure threshold (Table 1). Thus, AP may produce proconvulsant, as well as anticonvulsant effects on PTZ-induced clonic seizures in CD-1 mice. An absence of anticonvulsant activity induced by AP in mice has been reported by McKenzie and Soroko (1972). Two factors, however, may account for these contradictory findings; the strain of mice used in the study (CD-1 versus CDI mice) and the procedures employed to induce seizure (PTZ versus electroshock).

The increase in chemoconvulsive threshold observed 60 min after AP administration suggests two possibilities: (1) The effect is secondary to the direct dopaminergic effects of AP, i.e., the seizure threshold changes were reflecting changes in neuronal systems other than those directly affected by AP; (2) the effect was due to metabolites of AP. The partial inhibition of the AP-induced changes by atropine (Table 2) supports the first possibility. The second possibility is supported by the bioavailability studies done in our laboratory (Smith et al. 1979, 1981), which indicate that AP enters the brain rapidly and reaches its peak concentration at or before 15 min postinjection. Thus, the parent compound could not be producing the effect directly.

AP selectively stimulated dopaminergic receptors to decrease the threshold for PTZ-induced seizures 15 min after AP injection. Our observations that AP has a specific action on stimulation of DA receptors is consistent with previous reports (Andén et al. 1967; Corrodi et al. 1971; Protais et al. 1976). It remains puzzling that such large doses of AP are necessary to elicit what appears to be a DA-specific action. Perhaps PTZ nonselectively stimulates multiple neuronal systems, and treatment with high doses of the dopaminergic agonist are required to effectively nullify the behavioral expression of seizures produced by the other, non-dopaminergic systems.

The effect of AP might usefully be compared with a similar effect produced by (+)amphetamine (Riffee and Gerald 1976). Like AP, (+)-amphetamine produces a biphasic effect on PTZ clonic seizure threshold. However, the biphasic effect produced by (+)amphetamine is dose-dependent, rather than being time-dependent (as with AP). AP is similar to (+)-amphetamine in that doses producing the lowering of seizure threshold are close to those doses that produce toxicity in this strain of mice. In contrast, pimozide is the only receptor blocker that completely abolishes the AP-induced lowering of seizure threshold, whereas the (+)amphetamine-induced proconvulsant effect apparently involves α- and β-adrenergic components (Riffee and Gerald 1976). Noradrenergic and cholinergic systems are probably not involved in the decrease in seizures induced by AP.

In contrast, our blocker data showed that the increase in seizure threshold induced by AP (at 60 min postinjection) probably involves noradrenergic, cholinergic, and dopaminergic systems. One might suspect that the nonspecific effects of AP were due to the dosages used in this study. That is, the doses were high enough to cause general toxic effects, and other neurotransmitter systems besides the dopaminergic system were affected. This is supported by the literature, which shows the interaction of AP with other nondopaminergic neuronal systems (Persson and Waldeck 1970; Stadler et al. 1973; Guyenet et al. 1975). Therefore, the anticonvulsant activity induced by AP may be due to the complex actions of AP and/or its metabolites on the noradrenergic, cholinergic, and dopaminergic systems.

Piribedil, like AP, has been found to reduce DA turnover in the striatum (Corrodi et al. 1971). In behavioral studies, ET 495, in a manner similar to AP, produces motor asymmetries in rats with unilaterally lesioned nigrostriatal pathways. These authors have suggested that the mode of action of ET 495 is by a direct DA receptor stimulation. However, in the present study, a clear dose-response relationship of ET 495-induced anticonvulsant activity was not demonstrated. Similar results using a stereotyped behavior model have been reported by Costall and Naylor (1973). Our receptor blocker data suggest that the mechanism by which ET 495 alters seizure threshold appears not to be simply a direct DA receptor stimulation. This is supported by the observations that ET 495 interacts with adrenergic and cholinergic systems within the CNS (Consolo et al. 1975).

The absence of the proconvulsant activity after ET 495 administration, as observed in the AP experiments, seems to suggest that, although the drugs are similar in some respects, this alteration of seizure threshold is a dopaminergic function that is not shared by these two compounds. Other dopaminergically controlled behaviors (e.g., cage-climbing) have also been shown to be affected by AP and not ET 495 (Protais et al. 1976).

These studies demonstrate the ability of AP to decrease the PTZ-induced clonic seizure threshold due to a specific stimulation of DA receptors, in spite of the relatively large doses used. In other studies (Riffee et al., unpublished data) we have demonstrated a modulation of this AP-induced effect on PTZ-seizures by low doses of ascorbate. Taken together, these data suggest that AP-induced lowering of PTZ seizure threshold may offer a behavioral model with unique responsiveness to subtle changes in DA receptor sensitivity in vivo. We are continuing to study this possibility.

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