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Modulation of the Inhibitory Effect of Phenylethylamine on Spontaneous Motor Activity in Mice by CPP-(±)-3-(2-Carboxypiperazin-4-YL)-Propyl-1-Phosphonic Acid

I. P. LAPIN*[1] AND A. YUWILER†[2]

*Neuronal Excitability Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892
†Neurobiochemistry Research Laboratory, Veterans Administration Medical Center, West Los Angeles, Los Angeles, CA, 90073

LAPIN, I. P. AND A. YUWILER. *Modulation of the Inhibitory Effect of Phenylethylamine on Spontaneous Motor Activity in Mice by CPP-(±)-3-(2-Carboxypiperazin-4-YL)-Propyl-1-Phosphonic Acid.* PHARMACOL BIOCHEM BEHAV **56**(2), 199–204, 1997.—β-phenyl-ethylamine (PEA) at dose of 50 mg/kg inhibits spontaneous motor activity in mice. CPP-(±)-3-(2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid, a selective and competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, in doses of 0.2–10 mg/kg dose-dependently antagonizes this inhibitory effect of PEA. This effect of CPP appeared to be selective because the inhibitory action of PEA was not altered by pretreament with noncompetitive antagonists of NMDA receptors, such as dizocilpine (MK-801), phencyclidine (PCP), 1-phenylcyclohexylamine (PCA) or by antagonists of other behavioral effects of PEA such as haloperidol, baclofen and phenibut (β-phenyl-GABA). CPP failed to antagonize the inhibitory effect of other tested drugs such as diazepam, haloperidol, baclofen and phenibut. Intracerebroventricularly administered NMDA (0.2 μM), an agonist of NMDA receptors, suppressed the antagonistic effects of CPP against PEA. This suggests that anti-PEA effect of CPP is related to NMDA receptors. Anti-PEA effect of CPP is not due to accelerated deamination of PEA in CPP-treated mice. When small doses of PEA (5 and 10 mg/kg) and CPP (0.2 and 1 mg/kg) were used, the synergism of two drugs was observed. CPP (1 mg/kg) and deprenyl (0.5 mg/kg), an inhibitor monoamine oxidase of B type (MAO-B), had additive effects on PEA-induced inhibition of locomotion. This effect was not associated with any further inhibition of activity of brain MAO-B (over the inhibition induced by deprenyl alone—by 65%) under high (80 μM) or low (4.3 μM) concentration of PEA as a substrate in the medium. Mechanism of the interaction of CPP and PEA, two drugs belonging to different groups of biologically active compounds, deserves further studies. **Copyright © 1997 Elsevier Science Inc.**

Phenylethylamine CPP Antagonists of NMDA receptors MAO-B Spontaneous motor activity Mice

BOTH competitive and non-competitive antagonists of NMDA receptors have an anxiolytic effect in animal models of anxiety (5). PEA (β-phenyl-ethylamine) has been recently described (3) as an anxiety-inducing (anxiogenic) compound. It seemed, therefore, intriguing to ask whether antagonists of NMDA receptors antagonize PEA. Because animal models of anxiety are based on alterations of motor activity of animals, it was necessary first to control first of all the interaction of anxiogenic and anxiolytic drugs on the level of motor activity. For this purpose we began this study as a preliminary series of control experiments prior to examination of interaction of antagonists of NMDA receptors and PEA in animal models of anxiety. In one of the models of anxiety we use now, an elevated plus maze in mice, total number of arms, closed and open, entered by a mouse is generally considered as a measure of the action of a tested drug on the general motor activity. However, we have observed that this procedure does not reliably evaluate the effect of drugs and their combinations on motor performance because a mouse can show very high locomotor activity within a closed or, less often, an open arm,

[1] Present address: Berhterev Psychoneurological Research Institute, St. Petersburg, 193019, Russia.
[2] Requests for reprints should be addressed to Dr. A. Yuwiler, Veterans Administration Medical Center, West Los Angeles, CA 90073.

TABLE 1

ANTAGONISM OF CPP TO PEA-INDUCED INHIBITION OF LOCOMOTION

	Treatment (IP), Dose (mg/kg)			Locomotion			
	I	II	*n*	Horizontal	Total Distance (cm)	Number of Movements	Movement Time (s)
1	Saline	Saline	22	936 ± 65	688 ± 57	70 ± 3	58 ± 4
2	Saline	PEA, 25	18	701 ± 105*	808 ± 137	45 ± 6*	58 ± 15
3	Saline	PEA, 50	30	614 ± 78*	306 ± 82*	50 ± 5*	38 ± 5*
4	Saline	PEA, 200	8	560 ± 95*	38 ± 11*	14 ± 6*	4 ± 1*
5	CPP, 10	Saline	10	942 ± 38	810 ± 45	74 ± 3	76 ± 4
6	CPP, 10	PEA, 50	18	824 ± 36†	862 ± 90†	70 ± 5†	69 ± 4†

Statistically significant differences ($p < 0.05$): *—with Group 1, †—with Group 3.

without traveling between arms. As a result it seemed necessary to measure also spontaneous motor activity with a motor activity monitor in order to establish whether a combination of drugs, like an anxiogen and an anxiolytic, alters the motor activity. During those control experiments we have made, by chance, an observation that one of the tested drugs, namely CPP-(±)-3-(2-Carboxypiperazin-4-yl)-propyl)-propyl-1-phosphonic acid, a selective and competitive antagonist of NMDA receptors, appeared to be the only drug which selectively antagonizes PEA. This intriguing finding of an interaction between two drugs belonging to far distant groups of bioogically active compounds became the subject of our more detailed study. The purpose of the present article is describe interactions between CPP and PEA in detail.

METHODS

Animals

Male NIH-Swiss 5–6-wk old mice weighing 20–22 g were used. The animals were housed in groups of five in plastic cages (25 × 14 × 12 cm) with ad lib access to standard food and water under controlled environmental conditions (ambient temperature, 23–24°C; humidity 50–60%; 12/12 h light/dark cycle). The same conditions were during the experiment in the laboratory. Animals were used in only one experiment.

Drugs

Dizocilpine hydrogen maleate (MK-801), (±)-3-(2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), (±)baclofen, haloperidol, diazepam, R(-)deprenyl hydrochloride were from Research Biochemical Inc. (Natick, MA), β-phenyl-ethylamine (PEA) and *N*-methyl-D-aspartate (NMDA) from Sigma Chemical Co. (St. Louis, MO), phencylidine hydrochloride (PCP) from the Research Technology Branch, National Institute on Drug Abuse (Research Triangle Park, NC), 1-phenylcyclohexylamine (PCA) and (±)-5-aminocarbonyl-10, 11-dihydro-5H-dibenzo/a,d/cyclohepteb-5, 10imine (ADCI) from Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, phenibut (β-phenyl-gamma-aminobutyric acid HCL) from the Bekhterev Psychoneurological Research Institute, St. Petersburg, Russia. MK-801, CPP, PCP, ADCI, baclofen, phenibut, deprenyl were dissolved in physiological saline. Haloperidol was dissolved in two drops of glacial acetic acid diluted with saline and neutralized with 1N NaOH. Diazepam was suspended in 10% of propylene glycol. Drugs were injected intrapertitoneally (IP) or subcutaneously (SC) in a volume equal to one per cent of body weight. To test interactions with PEA, drugs were taken in maximal doses not altering spontaneous motor activity by themselves. All NMDA antagonists in higher doses (than mentioned below) induced hypermotility.

Behavioral Testing

A Digiscan Animal Activity Monitor (Model RXYZCM-16, Omnitech Electronics, Inc. Columbus, OH) was used to measure 11 parameters of spontaneous motor activity: horizontal activity, total distance (cm), number of movements,

TABLE 2

ANTAGONISM OF CPP TO PEA-INDUCED INHIBITION OF VERTICAL MOVEMENTS

	Treatment (i.p.) Dose (mg/kg)		Vertical Activity		
	I	II	Vertical Activity	Number of Vertical Movements	Vertical Time (s)
1	Saline	Saline	43.0 ± 4.5	21.5 ± 1.4	15.4 ± 1.7
2	Saline	PEA, 10	30.2 ± 6.1	16.7 ± 1.8*	11.8 ± 2.0
3	Saline	PEA, 25	2.4 ± 1.3*	1.5 ± 0.6*	0.8 ± 0.7*
4	Saline	PEA, 50	2.8 ± 1.4*	1.6 ± 0.6*	0.5 ± 0.3*
5	Saline	PEA, 100	0.8 ± 0.7*	0.8 ± 0.4	0.1 ± 0
6	CPP, 10	Saline	14.7 ± 3.3*	7.2 ± 2.1*	5.1 ± 2.0*
7	CPP, 10	PEA, 50	7.4 ± 2.7†	5.7 ± 1.9†	2.5 ± 1.0†

Statistically significant differences ($p < 0.05$): *—with Group 1, †—with Group 4.

TABLE 3

DOSE-DEPENDENT ANTAGONISTIC EFFECT OF CPP AGAINST INHIBITORY ACTION OF PEA ON SPONTANEOUS MOTOR ACTIVITY

Dose of CPP (mg/kg, IP)	Total Number of Inhibitory Effects of PEA (50 mg/kg, IP)	Number of Inhibitory Effects of PEA Which Are Statistically Significantly Antagonized by CPP	Parameters of Behavior in Which Antagonism Was Observed
0.2	9	2	II, IV
1.0	9	5	I–IV, XI
5.0	9	6	I–IV, XI, XII
10.0	9	9	I–IV, V–VII, XI, XII

Recorded parameters of behavior: I = horizontal activity, II = total distance (cm), III = number of movements, IV = movement time (s), V = vertical activity, VI = number of vertical movements, VII = vertical time (s), VIII–X = stereotypies (not changed by PEA), XI = clockwise revolutions, XII = anticlockwise revolutions, XII and XIV = time (s) spent resp. at center and in corners (both parameters were not changed by PEA); groups of 16 mice.

movement time (s), vertical activity, number of vertical movements, vertical time (s), clockwise revolutions, anticlockwise revolutions, center time (s), time spent in corners (s). The behavior of two mice, each in an acrylic chamber (internal dimensions 40.5 × 40.5 × 30 cm) was quantified simultaneously. Test episodes were 5 min in duration. Experiments were performed from 10 a.m. to 3 p.m. Activity was determined with infrared sensors. Mice were allowed 15–20 s to adjust to the test chamber before data accumulation. This time was sufficient for travel from the center of the chamber to its margins. Illumination inside the chambers was 80–100 luxes in the center and 50–60 luxes in corners.

Activity of brain monoamine oxidase of B type (MAO-B) was assayed by a modification of the radiometric procedure of Wurtman and Axelrod (6) using 14 C-phenylethylamine (80 μM, 2.3 Ci/mole and 4.3 μM, 46 Ci/mole) as substrate and extacting the oxidized products of the reaction mixture into 10 volumes of toluene. The lower concentration of substrate was used so as to be able to detect any competetive inhibition of MAO B by CPP. Tissue was homogenized in 100 volumes of water. The reaction mixture consisted of 40 μL water, 20 μL 0.5 phosphate buffer ph 7.4, 20 μL homogenate, 20 μL substrate. Tubes were briefly spun to mix and the mixture incubated at 37°C for 30 min. The reaction was stopped with 20 μL of 6 N HCL and product extracted into 2.0 mL of toluene. 0.6 mL of the toluene was taken and counted.

Procedure

Pretreatments were made 30 min prior to PEA. Deprenyl was administered 2 h prior to PEA. Motor activity was measured 5 min after administration of PEA. This interval has been found earlier as an optimal for observing the behavioral effects of PEA (Lapin, 1990). After diazepam, haloperidol, phenibut, and baclofen motor activity was measured in 30 min. After a session in the monitor, mice were returned to their cage, and the next mouse was taken in about a minute. Thus each mouse was taken for recording of motor activity from a group of the same size (usually a group consisted of 8 or 10 mice).

Statistical Analysis

Behavioral data are expressed as the mean ± SEM. The statistical significance of behavioral differences among the

TABLE 4

FAILURE OF CPP TO ANTAGONIZE THE INHIBITORY EFFECT OF VARIOUS PSYCHOTROPIC DRUGS ON LOCOMOTION

	Treatment (IP), Dose (mg/kg)		Locomotion			
	I	II	Horizontal Activity	Total Distance (cm)	Number of Movements	Movement Time (s)
1	Saline	Vehicle	907 ± 66	710 ± 77	73 ± 2	62 ± 3
2	Saline	Diazepam, 2	702 ± 41*	320 ± 27*	55 ± 3*	42 ± 4*
3	CPP, 10	Diazepam, 2	624 ± 53	277 ± 23	48 ± 4	40 ± 4
4	Saline	Haloperidol, 0.5	692 ± 61*	438 ± 32*	53 ± 4*	39 ± 2*
5	CPP, 10	Haloperidol, 0.5	407 ± 44†	307 ± 32†	33 ± 3†	30 ± 3†
6	Saline	Phenibut, 80	645 ± 75*	425 ± 51*	50 ± 5*	55 ± 5
7	CPP, 10	Phenibut, 80	452 ± 60	270 ± 64	37 ± 6	38 ± 7
8	Saline	Baclofen, 4	441 ± 65*	420 ± 52*	40 ± 4*	40 ± 6*
9	CPP, 10	Baclofen, 4	515 ± 73	439 ± 48	46 ± 5	46 ± 4

CPP in a dose of 10 mg/kg did not alter any parameter of locomotion (see also Table 1). Statistically significant differences ($p < 0.05$): *—with Group 1, †—with the respective group of Treatment II. Groups of 10 mice; group 1 consists of 20 mice.

TABLE 5

LACK OF ANTAGONISM OR SYNERGISM OF SMALLER DOSES OF CPP AND PEA

	Treatment (IP) mg/kg		Vertical Activity		
	I	II	Vertical Activity	Number of Vertical Movements	Vertical Time (s)
1	Saline	Saline	51.2 ± 8	23.4 ± 4	23.2 ± 3
2	Saline	PEA, 10	34.6 ± 6	16.7 ± 3	18.4 ± 3
3	CPP, 5	Saline	18.1 ± 4*	13.3 ± 2*	8.6 ± 2
4	CPP, 5	PEA, 10	18.4 ± 4	11.1 ± 2	0.8 ± 0.3†
5	Saline	Saline	88.8 ± 9	34.3 ± 3	38.2 ± 3
6	Saline	PEA, 5	64.5 ± 5*	33.1 ± 3	26.1 ± 3*
7	CPP, 1	Saline	78.7 ± 8	32.7 ± 4	34.3 ± 5
8	CPP, 1	PEA, 5	26.2 ± 5†	22.9 ± 3†	21.3 ± 3
9	CPP, 0.2	Saline	86.4 ± 6	33.3 ± 4	36.1 ± 4
10	CPP, 0.2	PEA, 5	42.6 ± 4†	24.8 ± 2†	25.7 ± 2†

Groups of 10 mice. Statistically significant differences: *—with Group 1 or 5, resp., †—with Group 2 or 6 resp.

group means was determined with the Mann–Whitney U-test. To simplify data presentation, MAO-B activities are pooled normalized values of samples assayed at the 2 substrate levels. Samples are normalized to the rates at 80 μM by using the mean ratio of rates obtained from 6 samples concurrently assayed at both substrate levels.

RESULTS

Antagonism of CPP to PEA-induced Inhibition of Spontaneous Motor Activity

PEA at doses of 25–100 mg/kg inhibited locomotor activity (Table 1). A dose of 10 mg/kg was sufficient to inhibit vertical activity (Table 2). Stimulation of spontaneous motor activity was not observed after doses of 25, 50 and 100 mg/kg tested 5, 15 and 30 min after IP administration. There were only two exceptions, however, a statistically significant increase in total distance and in clockwise revolutions seen 15 m in after IP injection of 50 mg/kg of PEA.

Inhibition of horizontal and vertical components of spontaneous motor activity was dose-dependent (Tables 1 and 2).

CPP appeared to be the only drug among antagonists of NMDA receptors to antagonize the inhibitory effect of PEA, compounds such as dizocilpine (MK-801, 0.01 mg/kg), PCP (0.1 mg/kg), PCA (0.5 mg/kg), ADCI (5 mg/kg) did not. Haloperidol (0.1 mg/kg), phenibut (20 mg/kg) and baclofen (2 mg/kg) also failed to antagonize the effect of PEA. Diazepam (0.125 mg/kg) enhanced the inhibitory effect of PEA on all four parameters of locomotion.

CPP antagonism of the inhibitory action of PEA was dose-dependent (Table 3). The threshold dose of CPP was 0.2 mg/kg (Table 3) and a dose of 10 mg/kg statistically significantly antagonized all 9 inhibitory effects of PEA (Table 3). At the same time, maximally effect dose of 10 mg/kg CPP failed to diminish the inhibitory action of various psychotropic drugs, diazepam (2 mg/kg), haloperidol (0.5 mg/kg), phenibut (80 mg/kg), baclofen (4 mg/kg) on locomotion (Table 4).

Subcutaneously (SC) administered CPP (10 mg/kg) had the same antagonistic effect towards PEA as IP administered CPP.

Synergism of CPP with Small Doses of PEA

Subthreshold doses of PEA (5 and 10 mg/kg) and CPP (0.2, 1 and 5 mg/kg) were synergistic when these two drugs were given together (Table 5). This synergism occurred under doses which do not change the motor activity by themselves.

Additive Effect of CPP and Deprenyl on PEA-induced Inhibition of Locomotion

Subthreshold doses of deprenyl (0.5 mg/kg) and CPP (1 mg/kg) which alone did not affect motor activity and did not

TABLE 6

ADDITIVE EFFECT OF CPP AND DEPRENYL ON PEA-INDUCED INHIBITION OF LOCOMOTION

	Treatment (IP) Dose (mg/kg)			Locomotion			
	I	II	III	Horizontal Activity	Total Distance (cm)	Number of Movements	Movement Time (s)
1	Saline	Saline	Saline	1020 ±30	742 ± 36	71 ± 3	62 ± 4
2	Deprenyl, 0.5	Saline	Saline	896 ± 63	615 ± 56	65 ± 3	53 ± 4
3	Saline	CPP, 1	Saline	911 ± 58	636 ± 49	69 ± 3	57 ± 4
4	Saline	Saline	PEA, 10	1060 ± 68	838 ± 85	60 ± 4	65 ± 6
5	Deprenyl, 0.5	Saline	PEA, 10	992 ± 69	898 ± 93	62 ± 3*	69 ± 9
6	Deprenyl, 0.5	CPP, 1	PEA, 10	508 ± 58*†	355 ± 97*†	34 ± 6*†	28 ± 9*†

Groups of 8 mice. Statistically significant differences: *—with Group 1, †—with Group 5.

TABLE 7

SUPPRESSION OF ANTI-PEA EFFECT OF CPP BY ICV ADMINISTERED NMDA

	Treatment			Locomotion	
	I IP mg/kg	II ICV nM	III IP mg/kg	Horizontal	Total Distance (cm)
1	Saline	Saline	Saline	924 ± 63	692 ± 54
2	Saline	Saline	PEA, 50	540 ± 34*	343 ± 37*
3	CPP, 10	Saline	Saline	792 ± 52	620 ± 87
4	Saline	NMDA, 0.2	Saline	718 ± 46	608 ± 73
5	CPP, 10	NMDA, 0.2	Saline	618 ± 121	542 ± 134
6	Saline	NMDA, 0.2	PEA, 50	555 ±40	360 ± 35
7	CPP, 10	Saline	PEA, 50	1043 ± 80†	766 ± 129†
8	CPP, 10	NMDA, 0.2	PEA, 50	564 ± 54‡	467 ± 71‡

Groups of 24–30 mice. Statistical significance of the differences ($p < 0.05$): *—with Group 1, †—with Group 2, ‡—with Group 7.

alter the action of small doses of PEA (10 mg/kg), did potentiated the sedative effect of a subtreshold dose of PEA when given together (Table 6).

Suppression of Anti-PEA Effect of CPP by i.c.v. Administered NMDA

NMDA (0.2 nM, i.c.v.) alone did not alter neither spontaneous locomotion nor inhibition induced by PEA (Table 7). Administration of NMDA after CPP suppressed the anti-PEA of the latter.

Effect of Deprenyl, PEA, CPP and Their Combinations on the Activity of Brain Monoamine Oxidase B Activity

Neither CPP nor PEA altered activity of brain MAO-B (Table 8). A combination of CPP and PEA also did not alter the activity. Deprenyl (0.5 mg/kg) inhibited MAO-B activity by 68% (Table 8). Combination of deprenyl and PEA (50 or 10 mg/kg) had the same effect.

DISCUSSION

In the present study PEA at doses of 10–100 mg/kg inhibited spontaneous motor activity in mice. This contrasts with our previous observations (1,2) that PEA at doses of 50 mg/kg or more induces locomotor hyperactivity. The two studies did not differ in the source for PEA (Sigma) or in the time between i.p. injection of PEA and measurement of motor activity (5 min) which in our previous experiments was optimal for observing PEA-induced stimulation. The two studies did differ in the strain of Swiss albino mice, NIH-Swiss vs SHR (Swiss-Hradec-Rappolovo), in housing conditions (35–40/group vs 5/group), dietary supplement (milk vs water) and in room temperature (19–20°C vs 23–24°C). In addition, motor activity was measured with animals in a $20 \times 15 \times 10$ cm i.d. chamber in early studies and in a $40.5 \times 40.5 \times 30$ cm chamber in the present one. The effect of any of these changes on the differences in results is not known.

The most striking finding of this study is a "double selectivity" of the interaction of CPP with PEA: CPP appeared to be the only compound among these tested which antagonized PEA, and PEA was the only inhibitory compound whose action was antagonized by CPP. Drugs previously found (1,2) to be antagonists of PEA-induced behaviors (e.g., haloperidol, phenibut and baclofen) were ineffective against PEA in the present study (Table 4). Both IP and SC administration of CPP antagonized PEA which makes it unlikely that the antagonism is somehow related an effect of CPP on the absorption

TABLE 8

MAO-B ACTIVITY OF MOUSE BRAIN

	Treatments (IP), mg/kg			MAO-B Activity			
	I	II	*n*	nmol/h/mg tissue	%	nmol/h/g protein	%
1	Saline	Saline	7	2.26 ± 0.34	100	12.9 ± 0.7	100
2	CPP, 10	Saline	7	1.79 ± 0.19	79.2	12.8 ± 1.0	99.2
3	Saline	PEA, 50	6	2.16 ± 0.21	95.6	14.2 ± 2.0	110
4	CPP, 10	PEA, 50	7	2.13 ± 0.17	94.2	13.0 ± 1.1	100.8
5	Saline	PEA, 10	6	1.94 ± 0.17	86	12.2 ± 0.7	94.6
6	CPP, 10	PEA, 10	7	2.12 ± 0.14	93.8	12.2 ± 1.1	94.6
7	Saline	Saline	8	2.31 ± 0.29	100	13.0 ± 1.4	100
8	Deprenyl, 0.5	Saline	8	0.74 ± 0.11*	32	4.6 ± 0.7*	35.4
9	Deprenyl, 0.5	PEA, 50	8	0.81 ± 0.10*	35	4.5 ± 0.6	34.6
10	Deprenyl, 0.5	PEA, 10	8	0.80 ± 0.12*	34.6	4.4 ± 0.7	33.8
11	CPP, 1	PEA, 10	8	2.04 ± 0.15	88	12.8 ± 1.0	98.5

*Difference with Group 7 is statistically significant ($p < 0.001$).

or distribution of PEA. Degradation of PEA (MAO-B) was not accelerated by CPP (Table 8). CPP antagonism of PEA actions could occur at the level of PEA receptors or on PEA-triggered neural mechanisms that modulate the spontaneous motor activity.

Because the anti-PEA effect of CPP was suppressed by an agonist of NMDA receptors, NMDA, one may suppose the this effect of CPP is mediated via NMDA receptors. The noncompetitive antagonists of NMDA receptors, MK-801, PCP, PCA and ADCI, taken at maximal doses which would itself alter motor activity did not antagonize PEA in our study. CPP also differs from the other NMDA antagonists used in not stimulating motor activity in mice (unpublished observations). Whether these differences are somehow related to that unique antagonistic effect of CPP against PEA remains absolutely unclear.

The mechanism of synergism between small doses of CPP and PEA is equally puzzling. An additive effect of CPP and deprenyl on PEA-induced inhibition of locomotion (Table 6) suggested that CPP might inhibit MAO-B deaminating PEA or potentiate the inhibitory action of deprenyl. Direct assay of MAO-B activity did not support this possibility (Table 8). Although substrate levels in the MAO assay were reduced so as to detect a competitive inhibition, it is possible, albeit unlikely, that the Ki for CPP was not too low to permit detection in the assay (Table 8).

In conclusion, we suggest that interactions between CPP and PEA in the level of spontaneous motor activity have to be taken into account in experiments dealing with the activity of CPP and PEA in animal models of anxiety.

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