quaternary ganglionic blocking agent chlorisondamine, which does not cross the blood-brain barrier, have shown that the increased norepinephrine turnover in the heart of the hypertensive animals can be normalized, whereas the delayed turnover in medulla oblongata and hypothalamus persists.

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EFFECTS OF p-CHLOROPHENYLALANINE, A SEROTONIN DEPLETOR, ON SIDMAN AVOIDANCE RESPONSE IN RATS

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Koe and Weissman (1) have demonstrated that p-chlorophenylalanine (p-CPA)* is a potent and selective depletor of brain serotonin in experimental animals. Administration of p-CPA strongly inhibits both tryptophan and phenylalanine hydroxylase activities. Several investigators have presented the studies regarding the behavioral effects of p-CPA. The drug was found to decrease spontaneous motor activity of rats (2-4) and to reduce aggressive behavior of mice (5). On the other hand, administration of p-CPA induced sexual excitation in rats (6) and cats (7) and caused an increased rate of acquisition of the conditioned avoidance response in rats (2, 4). The present experiment was designed to study the effects of p-CPA on Sidman-type avoidance response in rats.

Male rats of Wistar strain, weighing about 230 g (3 months old), served as the subjects. They were housed in an individual cage. The daily-intake of a commercial diet (CLEA CA-1) was restricted to 15 g/animal allowing free access to drinking water. Sidman-type avoidance apparatus (Kyoto Keisoku Co.) was used. The rat was placed in a box for 30 minutes every day, and frequencies of lever-presses and electroshock performances were recorded. The avoidance response-shock interval was 40 seconds, the shock-shock interval was 10 seconds, and the shock duration was 1 second. The rats which had received the training trials more than 20 sessions were maintained on the diet containing 0.1% p-CPA for 12 days. In another series of experiment, single doses of 100 and 300 mg/kg of p-CPA were administered orally in the

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* p-CPA was kindly supplied by Carles Pfizer and Co. Groton, Conn., U.S.A.

rats which had received the training trials. A more detailed description of the experimental procedures may be found in the previous paper (8). The statistical significance of the data was determined by Student's *t*-test.

The body weight of rats was gradually reduced during the addition of p-CPA to the diet, and the mean body weight was decreased by 31.1 g (*n*=10) after 12 days of this diet. No obvious alteration in the gross behavior was observed, apart from increased irritability on handling. As shown in Table 1-A, a

TABLE 1. Effects of p-CPA on Sidman avoidance response.

A) Addition of 0.1% p-CPA to the diet for 12 days (*n*=10)

	Avoidance response (% change)	Shock (% change)
Before	100%	100%
1st day	111.4±10.5	94.8±13.2
2nd "	150.7±27.0	77.9±11.7
3rd "	136.9±11.0**	88.0± 6.6
4th "	166.4±20.3**	70.9±10.9*
5th "	143.8±17.9*	98.1±10.0
7th "	143.7±18.2*	90.8±15.8
10th "	147.6±11.6**	81.6± 6.8*
11th " (5-HTP, 50 mg/kg i.p.)	78.5±10.7	119.6±14.6
12th "	132.8±14.7*	86.4±12.2
After discontinuation of the p-CPA diet		
5th "	124.1±21.1	108.6±14.6
10th "	92.2± 7.3	105.2± 9.1

B) Single oral administration of p-CPA (*n*=8)

p-CPA (mg/kg) (24 hr before the 1st day-testing)	100	300	300+5-HTP (50 mg/kg i.p., 1 hr before the 1st day-testing)
Avoidance response (% change)			
Before	100%	100%	100%
1st day	142.5±24.5	172.9±14.1**	118.4±10.5
2nd "	—	195.7±27.6**	178.3±28.8**
3rd "	173.2±32.6*	189.9±21.1**	176.7±24.0**
4th "	114.8±14.2	223.2±36.5**	175.2±24.1**
5th "	136.0±19.1	231.1±35.2**	179.5±29.9*
7th "	123.3±12.2	149.7±29.5	148.9±22.0*
10th "	121.9±22.1	122.9±15.1	112.7±12.6
Shock (% change)			
Before	100%	100%	100%
1st day	87.0± 7.2	76.9± 7.5**	106.4± 4.7
2nd "	—	76.1± 8.9*	73.2±12.2*
3rd "	77.3± 7.0**	65.1± 9.2**	68.5± 8.1**
4th "	95.4± 9.6	87.8±10.2	53.7± 7.3**
5th "	96.9± 7.2	71.9± 7.1**	67.4±12.0*
7th "	87.3± 9.6	92.7±13.3	100.9±14.2
10th "	98.9± 7.5	96.0±17.9	96.6±12.9

Mean±S.E.

Significant increase: ***P*<0.01, **P*<0.05.Significant decrease: ***P*<0.01, **P*<0.05.

significant increase ($P=0.01$ or 0.05) in the avoidance response rate with a decrease in the number of shocks was found from the 3rd day of the p-CPA diet. These changes in the avoidance responses and shocks were completely antagonized by 5-hydroxytryptophan (5-HTP; 50 mg/kg i.p.) administered 1 hour before the testing at the 11th day. These two parameters of the avoidance behavior were restored to the control level 7 to 10 days after discontinuation of the 12-day feeding of p-CPA. As shown in Table 1-B, single administration of p-CPA also enhanced the frequency of avoidance response and decreased the number of shocks. A significant increase ($P=0.01$) in the avoidance response rate was obtained from 1 to 5 days after 300 mg/kg of p-CPA, and it recovered to the control level at 10 days after the administration. The responses of the avoidance behavior to p-CPA were abolished by treatment of the animals with 5-HTP (50 mg/kg i.p.) 1 hour before the 1st day-testing after p-CPA, but the time-course of changes in these two parameters later than the 2nd day was almost similar to that in the animals treated with p-CPA alone. Single intraperitoneal injection of 5-HTP (50 mg/kg) did not affect the number of avoidance responses and shocks.

There are three possible explanation of the present behavioral changes caused by p-CPA: 1) direct action of p-CPA, 2) increase in phenylalanine level, and 3) serotonin depletion in the brain. After the administration of p-CPA, the level of p-CPA itself in the brain increased quickly, and then little p-CPA was present 3 days after the administration (1, 9). Brain phenylalanine level increased to the maximum level at the 2nd day and returned to the control in about 4 days. However, serotonin content in the brain decreased markedly for several days after the administration of p-CPA, and slowly returned to the normal level over a period of 10 days (1, 9). Therefore, an excellent correlation between the degree of facilitation of the Sidman avoidance performance and serotonin depletion caused by p-CPA indicates the concept that this drastic decrease in the brain serotonin is probably the critical event for facilitation of the avoidance behavior. This conclusion was also supported by the present results that an increase in the avoidance response rate induced by p-CPA was reversed by the supplement of 5-HTP. The effects of α -methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, on the Sidman avoidance response will be reported elsewhere.

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