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Effect of *p*-chlorophenylalanine on the interaction between phenelzine and pethidine in conscious rabbits

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SERIOUS reactions have been reported after administration of pethidine to patients who were under treatment with monoamine oxidase (MAO) inhibitors.[1] Evidence from animal data indicates that biogenic amines may play a major role in this toxic interaction and an altered metabolism of pethidine a minor one. In rabbits, excitation, hyperthermia and hypertension result from the combined administration of MAO inhibitors and pethidine.[2–4] These symptoms are reduced by pretreatment of the animals with α-methyltyrosine and the hypertension is also lysed by phentolamine thus suggesting that these symptoms are mediated by the sympathetic system.[2] There is also evidence to indicate that 5-hydroxytryptamine (5HT) may be important for a more severe toxic interaction with lethal outcome in mice[5,6] and rabbits.[7] To further analyse the MAO inhibitor–pethidine induced toxic interaction in rabbits the present experiments were conducted.

In order to record blood pressure in conscious animals, rabbits weighing 2·5–3·5 kg were operated under ether anaesthesia.[2] Polyethylene catheters filled with heparinized saline were inserted into the femoral artery and vein up to the level of aortic bifurcation. The catheters were led under the skin to the back where they were protected by wire. A constant infusion of heparinized saline kept the catheters open until the animals were killed. Injections were made to the venous catheter and arterial pressures were recorded with a Statham P 23AC transducer and Grass polygraph. Rectal temperature was measured with a thermocouple. Since this type of operation tended to raise rectal temperature, intact rabbits were used for measurement of hyperthermia only.

Noradrenaline (NA) was measured from the hypothalamus according to Bertler *et al.*[8] and 5HT according to Bogdanski *et al.*[9]

Phenelzine and pethidine. Pethidine (1·25 mg/kg, i.v.) alone had no measureable effects on circulation, temperature or behaviour when compared to controls injected with saline. Pretreatment with phenelzine (5 mg/kg, s.c., 10 hr before pethidine) made the animals alert and increased the 5HT levels in hypothalamus by 120 per cent (Table 1). This treatment greatly modified the effect of pethidine (1·25 mg/kg, i.v.) which now raised the systolic blood pressure by 40 mm Hg (Fig. 1) and caused bradycardia. The animals were excited, tremor and jumping being the most prominent symptoms. The rectal temperature rose by 0·7° (Fig. 2). A larger dose of phenelzine (30 mg/kg, s.c., 10 hr

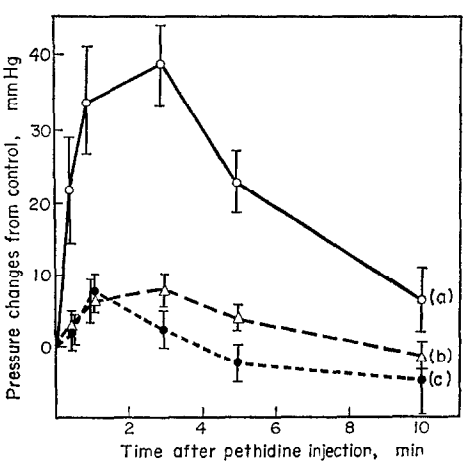

FIG. 1. Pressor responses to pethidine (1·25 mg/kg, i.v.) in rabbits pretreated with phenelzine (5 mg/kg, s.c., 10 hr before pethidine). (a) pretreatment with phenelzine only; (b) *p*-chlorophenylalanine plus phenelzine; (c) *p*-chlorophenylalanine+5-hydroxytryptophan+phenelzine. Mean±S.E. from four to five animals are given, for further details see text.

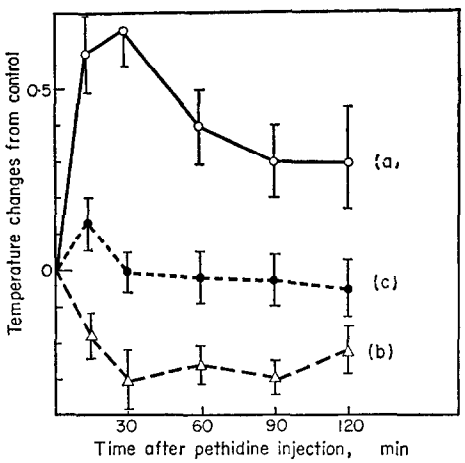

FIG. 2. Changes of rectal temperature after pethidine in rabbits pretreated with phenelzine. For symbols and details see Fig. 1 and text.

before pethidine) did not increase further the pressor and bradycardic effects of pethidine. But the animals now became more excited and more hyperthermic after pethidine than they were when using a smaller phenelzine dose.

Effect of p-chlorophenylalanine (pCPA). Pretreatment of rabbits with pCPA (150 mg/kg, s.c. on three successive days) made the animals restless and hungry. After phenelzine (5 mg/kg, s.c., 10 hr before pethidine) these animals became even more alert and sensitive to handling. This treatment lowered the hypothalamic 5HT levels to the levels measured in controls not treated with phenelzine (Table 1). Pethidine given to these animals rather than evoking excitation, sedated the animals instead. Further, blood pressure, heart rate and rectal temperature now remained largely unaltered (Figs. 1 and 2).

Effect of 5-hydroxytryptophan (5HTP). To restore the brain 5HT levels, 5HTP (50 mg/kg, s.c., on 3 successive days) was given along with pCPA (150 mg/kg, on 3 days) before the phenelzine injection (5 mg/kg, s.c. 10 hr before pethidine). 5HTP counteracted the fall of brain 5HT due to pCPA and even produced highest levels of hypothalamic 5HT measured (Table 1). No significant behavioural effect was seen after 5HTP plus pCPA, neither did phenelzine provoke any remarkable excitation. After phenelzine the response to pethidine (1·25 mg/kg, i.v.) in these animals was not reversed from that seen after pCPA plus phenelzine without 5HTP: no excitation symptoms, no pressor response, and no hyperthermia were seen (Figs. 1 and 2).

TABLE 1. LEVELS OF 5-HYDROXYTRYPTAMINE (5HT) AND OF NORADRENALINE (NA) IN THE HYPOTHALAMUS OF THE RABBIT PRETREATED WITH PHENELZINE, *p*-CHLOROPHENYLALANINE (pCPA) AND 5-HYDROXYTRYPTOPHAN (5HTP)

Pretreatment	Amine concn in hypothalamus (ng/g)	
	5HT	NA
Controls (4)	830±40	Not measured
Phenelzine (4)	1850±80	2250±480
pCPA+phenelzine (4)	810±130	2650±720
pCPA+5HTP+phenelzine (4)	2340±190	Not measured

For the details of pretreatment see text. Ten hr after the phenelzine administration, the animals were given pethidine (1·25 mg/kg, i.v.) and the animals were killed 2 hr thereafter. Number of animals are given in parentheses. Mean±S.E. are given.

Effect of phenylalanine. Since 5HTP did not counteract the effect of pCPA, the pCPA effect could result from mechanisms other than the blockade of the 5HT synthesis. pCPA is partly metabolized into *p*-chlorophenylethylamine,[10] and it could, e.g. block the formation, of phenylethylamine from phenylalanine. To provide excessive amounts of this precursor, phenylalanine (150 mg/kg, s.c. on 3 successive days) was added to the pretreatment with pCPA. But again, after phenelzine, pethidine did not provoke excitation or hyperthermia indicating that phenylalanine did not counteract pCPA. The hypothalamic 5HT levels after this treatment were similar to those seen after pCPA plus phenelzine.

In the present experiments pethidine was unable to cause excitation symptoms, hypertension, or hyperthermia in rabbits pretreated with pCPA and phenelzine. pCPA decreases the rate of synthesis of 5HT[10] and may also transiently decrease the rate of synthesis of NA.[11] The latter was probably not importantly involved in the present experiments since pCPA did not modify the hypothalamic NA levels elevated by phenelzine. Therefore, the protecting effect of pCPA against the toxic interaction of phenelzine and pethidine in rabbits might plausibly be related to lowered levels of brain 5HT as previously suggested.[7] On the other hand, treatment with 5HTP along with pCPA restored the brain 5HT levels without restoring the toxic symptoms to pethidine seen in the animals pretreated with phenelzine alone. It seems unlikely that the high levels of brain 5HT resulting from 5HTP given over 3 days would localize only in blood vessels and other sites of minor importance. Therefore, one must conclude that the protective effect of pCPA against the phenelzine–pethidine interaction is not directly dependent on the brain 5HT levels.

It seems to us that the timing of the 5HTP administration is of great importance. Gessner* has reversed the protective effect of pCPA against the toxic interaction of pethidine and MAO inhibitors by injecting 5HTP after the MAO inhibition. The same applies to our previous experiments with mice.[5] But we feel that those experiments can merely refer to the toxicity of 5HTP in the presence of MAO inhibition.

Phenylethylamine, a metabolite of phenylalanine, greatly augments the pressor response to pethidine in rabbits.[2] The pressor effects of phenylethylamine are enormously potentiated by MAO inhibitors both in anaesthetized and conscious rabbits.[12] On these grounds we have previously suggested that phenylethylamine could initiate the excitation symptoms caused by pethidine in rabbits pretreated with MAO inhibitors.[2] Our failure to counteract pCPA by giving concomitantly phenylalanine could be due to low doses of phenylalanine, too low to compete with pCPA. The effects of pCPA may be complex since it elevates the blood pressure in rats,[13] a phenomenon which we did not find in rabbits. Therefore its protecting effect on the pethidine–phenelzine interaction awaits further experiments with, e.g. measurements of brain phenylethylamine levels.

In conclusion, these results demonstrate that although pCPA abolishes the toxic interaction between phenelzine and pethidine, the restoring of brain 5HT levels by administration of 5HTP does not restore the toxic interaction.

Department of Pharmacology,
University of Helsinki,
Helsinki, Finland

MAURI J. MATTILA
ANTTI J. JOUNELA

REFERENCES

1. P. H. DENTON, V. M. BORRELLI and N. V. EDWARDS, *Br. med. J.* **2**, 1752 (1962).
2. A. J. JOUNELA, *Ann. Med. exp. Fenn.* **48**, 249 (1970).
3. M. NYMARK and I. MOLLER-NIELSEN, *Lancet* **2**, 525 (1963).
4. R. G. PENN and K. J. ROGERS, *Br. J. Pharmac.* **42**, 485 (1971).
5. A. J. JOUNELA, *Ann. Med. exp. Fenn.* **48**, 261 (1970).
6. K. J. ROGERS and J. A. THORNTON, *Br. J. Pharmac.* **36**, 470 (1969).
7. S. N. GONG and K. J. ROGERS, *Br. J. Pharmac.* **42**, 646P (1971).
8. Å. BERTLER, A. CARLSSON and E. ROSENGREN, *Acta physiol. scand.* **44**, 273 (1958).
9. D. F. BOGDANSKI, A. PLETSCHER, B. B. BRODIE and S. UDENFRIEND, *J. Pharmac. exp. Ther.* **117**, 82 (1956).
10. B. K. KOE and A. WEISSMAN, *J. Pharmac. exp. Ther.* **154**, 499 (1966).
11. F. P. MILLER, R. H. COX, JR., W. R. SNODGRASS and R. P. MAICKEL, *Biochem. Pharmac.* **19**, 435 (1970).
12. M. M. AIRAKSINEN, O. MUSTALA and P. TORSTI, *Ann. Med. exp. Fenn.* **44**, 376 (1966).
13. A. ITO and S. M. SCHANBERG, *J. Pharmac. exp. Ther.* **181**, 65 (1972).

* P. K. Gessner, personal communication.