# Mechanism of hyperthermia in the interaction between pethidine or imipramine and monoamine oxidase inhibitors

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IN PATIENTS RECEIVING treatment with monoamine oxidase (MAO) inhibitors, normal therapeutic doses of pethidine or tricyclic antidepressant have caused severe and often fatal toxic reactions characterised by symptoms which include excitement and a pronounced hyperthermia (Taylor, 1962). Similar hyperthermic reactions occur in rabbits given these drug combinations (Loveless and Maxwell, 1965).

These interactions have been attributed to a decreased breakdown of the pethidine or imipramine since monoamine oxidase inhibitors are known to inhibit detoxifying enzyme systems in the liver (London and Milne, 1962). However, the symptoms evoked in humans by the pethidine/MAO inhibitor interaction suggest central stimulation rather than the depression which occurs when detoxication of pethidine is impaired (Rogers and Thornton, 1969). Moreover, the onset of toxic symptoms occurs within a few minutes of pethidine administration to patients receiving monoamine oxidase inhibitors, whereas in patients with hepatic dysfunction the toxic effects of pethidine develop slowly and only after repeated doses (Dundee and Tinckler, 1952). In view of the atypical features of the reactions, it seems more likely that it may arise as a consequence of raised level of brain monoamines as there is evidence that the integrity of hypothalamic monoamine stores is associated with the maintenance of body temperature (Feldberg and Myers, 1963).

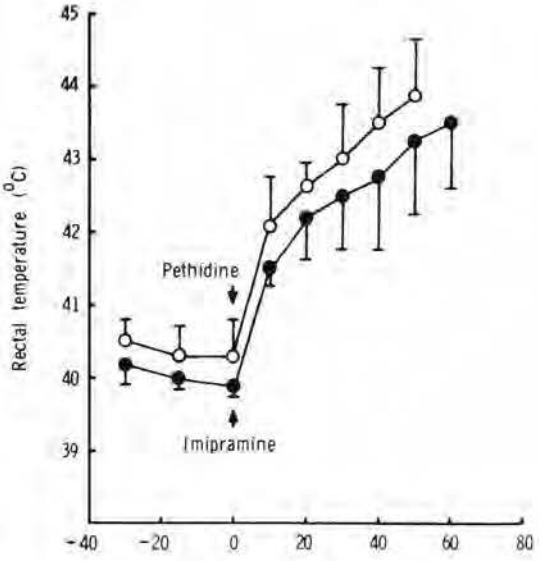


Fig. 1
**Effect of pethidine and imipramine on the body temperature of rabbits pretreated with pargyline.**

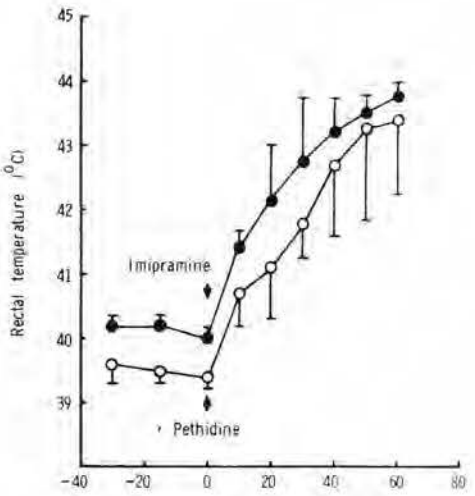


Fig. 2
**Effect of pethidine and imipramine on the body temperature of rabbits pretreated with reserpine and pargyline.**

We, therefore, investigated the role of the brain monoamines in hyperthermia induced by pethidine of imipramine in rabbits pretreated with pargyline with drugs that selectively alter the concentration of brain monoamines.

## Methods

The experiments were performed on male Californian rabbits weighing between 1½ and 2½ kg. Rabbits were pretreated with two daily doses of monoamine oxidase inhibitor, pargyline (25 mg/kg s.c.). Preliminary studies showed that such a regime was a suitable pretreatment as subsequent injection of pethidine or imipramine at a dose of 5 mg/kg invariably evoked a hyperthermic response.

On the day of the experiment, the rabbits were placed in head stocks for the recording of rectal temperature. A period of 30 minutes was allowed for the rabbits to settle in the stocks before pethidine or imipramine was infused slowly into the marginal ear vein at a rate of 1 mgm/kg/minute. Three rabbits were used in each group.

Drugs used and their dosage schedules were: reserpine (0.5 mg/kg) intraperitoneally (I/P) for two days prior to pargyline pretreatment, alpha-methyl paratyrosine (80 mg/kg) (I/P) 12 hourly for two days in combination with pargyline and p-chlorophenylalanine (125 mg/kg) daily (I/P) for three days prior to pargyline pretreatment. The drugs were dissolved in sterile apyrogenic solution.

Brain monoamines were measured in rabbits given the above drug dosage schedules. Control and drug-treated animals were killed by air embolism. The brains were rapidly removed from the skull and the cortex and cerebellum were dissected off and discarded. The brainstem was frozen in liquid nitrogen until used for assay. Following butanol-heptane extraction, the concentrations of noradrenaline, dopamine and 5 hydroxytryptamine were measured fluorimetrically.

## Results

In the rabbits pretreated with pargyline, the injection of either pethidine or imipramine rapidly evoked a marked hyperthermia (Figure 1). This was accompanied by bouts of shivering, motor restlessness and profuse salivation. The animals died in hyperthermia some 50-60 minutes after injection.

Pretreatment with reserpine or alpha-methyl paratyrosine failed to antagonise the drug-drug interaction (Figs. 2 and 3) but pretreating with

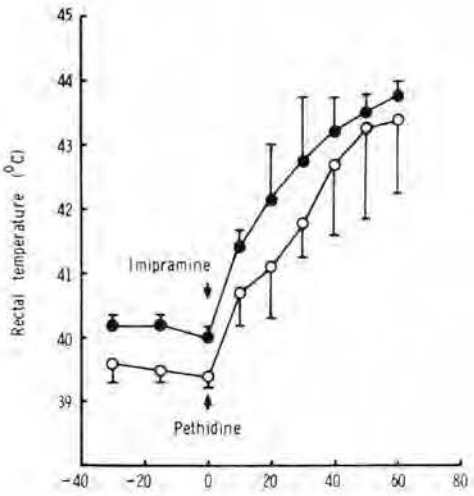


Fig. 3
**Effect of pethidine and imipramine on the body temperature of rabbits pretreated with alpha-MT and pargyline.**

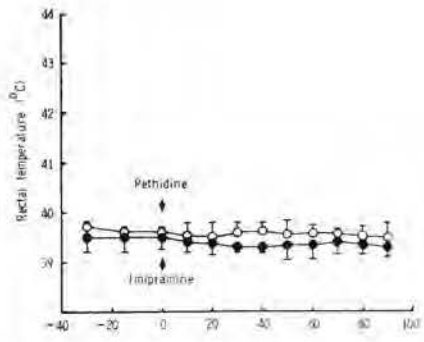


Fig. 4
**Effect of pethidine and imipramine on the body temperature of rabbits pretreated with PCPA and pargyline.**

p-chlorophenylalanine completely antagonised it (Fig. 4).

Figs. 5 to 7 show the changes in the concentration of the brain monoamines given the drug dosage schedules as described. The results are expressed as percentage change. Pargyline caused increases in the concentration of all cerebral monoamines (Fig. 5) while reserpine caused a marked fall of all the amine levels and the combination of the two drugs caused a rise only in 5 hydroxytryptamine (Fig. 6). Alpha-methyl paratyrosine alone depleted noradrenaline and dopamine without affecting 5 hydroxytryptamine (5HT) but when combined with pargyline, the 5 hydroxytryptamine level was increased (Fig. 7). P-chlorophenylalanine selectively depleted the 5HT level and it remained low even when combined pretreatment with pargyline (Fig. 8).

## Discussion

In the present study, the role of brain monoamines in hyperthermia induced by pethidine or imipramine in rabbits pretreated with pargyline was investigated with drugs that selectively alter the concentration of brain monoamines. The drugs used were reserpine which depletes the stores of catecholamines and 5 hydroxyteryptamine, alpha-methyl paratyrosine (a tyrosine hydroxylase inhibitor) inhibits the synthesis of catecholamines and P-chlorophenylalanine (a trytophan hydroxylase inhibitor) prevents the synthesis of 5 hydroxytryptamine.

The overall results show that reserpine and alpha-methyl p-tyrosine failed to antagonise the interaction between pethidine or imipramine with monoamine inhibitors and they failed to prevent the rise in cerebral 5 hydroxytryptamine following monoamine oxidase inhibition. On the other hand, pretreatment with p-chlorophenylalanine completely antagonised it. This drug blocked the rise in 5

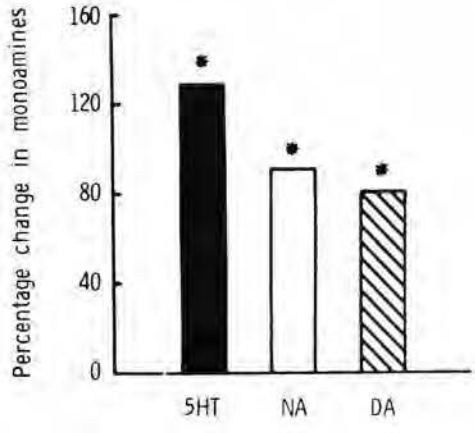


Fig. 5
**Effect of pargyline on the concentration of monoamines in the rabbit brainstem.**

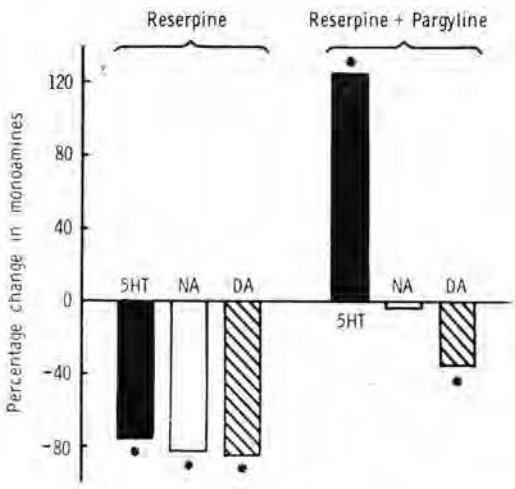


**Fig. 6**
**Effect of reserpine and reserpine and pargyline on the concentration of monoamines in the rabbit brainstem.**

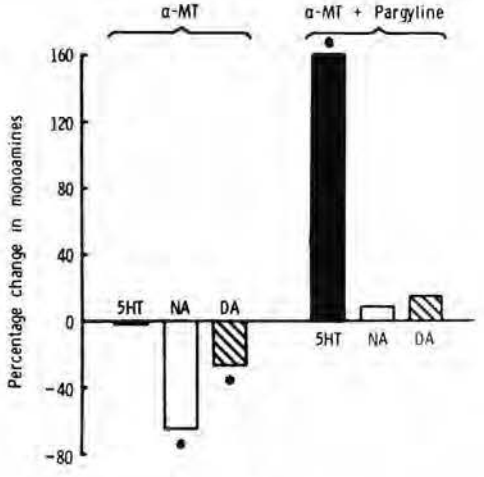


**Fig. 7**
**Effect of alpha-MT and pargyline on the concentration of monoamines in the rabbit brainstem.**

hydroxytryptamine without preventing the rise in catecholamines.

The results indicate, therefore, that the interaction between pethidine or imipramine and monoamine oxidase inhibitors can take place only in the presence of raised levels of cerebral 5 hydroxytryptamine.

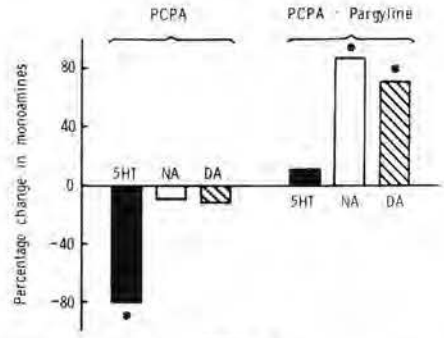


**Fig. 8**
**Effect of PCPA and PCPA and pargyline on the concentration of monoamines in the rabbit brainstem.**

Rogers and Thornton (1969) have shown that acute toxicity (LDSO) of pethidine is increased in mice pretreated with the monoamine oxidase inhibitor and this only occurs when the 5 hydroxytryptamine content of the brain is 60% above control values. Hence it is tempting to postulate that pethidine/monoamine oxidase inhibitor interaction occurs when pethidine causes a rapid release of 5 hydroxytryptamine content (Burke and Long, 1967) in the brain to a critical level.

## Summary

The administration of pethidine or imipramine to rabbits pretreated with pargyline evoked a hyperpyrexial reaction. This drug-drug interaction was not antagonised by reserpine or alpha-methyl p-tyrosine but completely antagonised by p-chlorophenylalanine. Changes in the concentration of pethidine or imipramine and monoamine oxidase inhibitors can take place only in the presence of raised levels of 5 hydroxytryptamine content of the brain.

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