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The role of 5-hydroxytryptamine and noradrenaline in the hyperthermic reaction induced by pethidine in rabbits pretreated with pargyline

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Summary

1. Inhibition of 5-hydroxytryptamine (5-HT) synthesis by *p*-chlorphenylalanine protected rabbits pretreated with pargyline from the fatal hyperthermic reaction which occurs on the intravenous injection of pethidine.

2. The development of tolerance to morphine did not protect against the fatal pargyline-pethidine hyperpyrexia. Moreover, the injection of nalorphine before or after pethidine conferred no protection.

3. Pethidine evoked a hyperpyrexia in rabbits pretreated with lithium sulphate or yohimbine.

4. Sodium diethyldithiocarbamate caused a fatal hyperpyrexia in rabbits pretreated with pargyline.

5. It is concluded that the pargyline-pethidine hyperthermic interaction might involve the relative concentrations of 5-HT and noradrenaline in the hypothalamus.

Introduction

The administration of pethidine to patients receiving monoamine oxidase (MAO) inhibitors has resulted in severe toxic reactions which included motor restlessness, excitement and hyperpyrexia (Mitchell, 1955 ; Sjoqvist, 1965 ; Stockley, 1969). Of all the potent analgesics used, only pethidine shows such an interaction. Recently, Penn & Rogers (1971) have shown that fatal hyperpyrexia developed when pethidine was injected intravenously into rabbits pretreated with pargyline. In addition, neither morphine nor pentazocine was found to elicit a pyrexic reaction in pargyline pretreated rabbits. These workers suggested that the febrile response to pethidine may be related to the increased concentration of cerebral monoamines, especially 5-hydroxytryptamine (5-HT), resulting from MAO inhibition.

The purpose of the present investigation was to find out if the pargyline–pethidine interaction could be modified by some drugs which interfere with the synthesis of

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the brain monoamines, and also if the interaction could be modified through induction of morphine tolerance in rabbits.

Methods

Rabbits of local strains and of either sex weighing between 1·5 and 2·5 kg were used. Treatment with pargyline was the same as that described by Penn & Rogers (1971), a dose of 25 mg/kg being injected subcutaneously on five successive days. Pethidine 5 mg/kg was slowly injected intravenously into a marginal ear vein 3 h after the last dose of pargyline. *p*-Chlorophenylalanine (PCPA) suspended in Tween 80 was administered orally by a stomach tube in a dose of 320 mg/kg on the first day followed by 100 mg/kg on both the third and fourth days. Lithium sulphate was injected intraperitoneally in a dose of 100 mg/kg daily for five successive days. Sodium diethyldithiocarbamate (DEDTC) was injected intraperitoneally in a single dose of 400 mg/kg. Yohimbine was injected intraperitoneally in a dose of 10 mg/kg daily for two successive days. Pethidine 5 mg/kg was injected intravenously 3 h after drug treatment in each case. Control animals received 0·9% w/v NaCl solution (saline). The rabbits were made tolerant to morphine by injecting gradually increasing doses of morphine starting with 10 mg/kg twice daily and ending with 150 mg/kg, over a period of 10 days. Rectal temperature was measured by electrical thermocouples (Ellab electric universal thermometer type T.E.3) inserted 5–7 cm into the rectum.

Drugs

The following drugs were used: lithium sulphate (B.D.H.), morphine hydrochloride (B.D.H.), nalorphine hydrochloride (Burroughs Welcome), *p*-chlorophenylalanine (Sigma), pargyline hydrochloride (Abbott laboratories), pethidine hydrochloride (B.D.H.), nalorphine hydrochloride (Burroughs Wellcome), *p*-chlorophenylchloride (Sigma). The doses given in the text refer to the salts.

Results

Rabbits treated with pargyline, lithium, *p*-chlorophenylalanine, yohimbine or sodium diethyldithiocarbamate alone did not show any significant change in their body temperature when compared with animals treated with saline (Table 1).

TABLE 1. *Effect of treatment with various drugs on the rectal temperature of rabbits*

Drug	Dose mg/kg	No. of animals	Mean rectal temperature (°C) Time from injection (min)					
			−30	0	+30	+60	+90	+120
Saline	—	4	39·3	39·4	39·4	39·5	39·4	39·3
Pargyline	25	4	39·8	39·8	39·9	40·0	40·0	40·0
Pethidine	5	4	38·7	38·6	38·6	38·4	38·3	38·3
Lithium	100	5	39·5	39·4	39·5	39·7	39·6	39·5
Yohimbine	10	4	38·9	39·0	38·9	38·9	38·8	38·8
Diethyldithiocarbamate	400	4	39·5	39·6	39·6	39·5	39·3	39·3
Parachlorophenylalanine	420	3	39·4	39·3	39·2	39·2	39·1	39·0

Rabbits pretreated with p-*chlorophenylalanine (PCPA)*

In these rabbits pargyline was injected daily in a dose of 25 mg/kg, s.c. starting on the third day of PCPA pretreatment and continuing until the fifth day. Pethidine 5 mg/kg was injected 3 h after the last dose of pargyline. There was only a small, but significant ($P<0.05$) increase in the temperature of the PCPA-pretreated rabbits and none of the rabbits pretreated with PCPA died in hyperpyrexia (Fig. 1). Thus

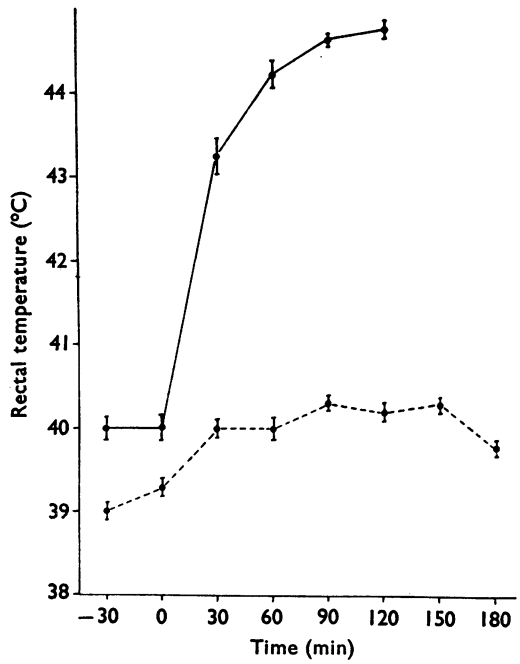

FIG. 1. Effect of *p*-chlorophenylalanine (PCPA) on the pargyline-pethidine hyperpyrexia. Pethidine (5 mg/kg) was injected i.v. at time zero into rabbits pretreated with pargyline (●——●) and rabbits pretreated with both pargyline and PCPA (●- - -●). Doses as in text. Each curve represents the mean response from four rabbits. The vertical lines indicate S.E.M. All the animals pretreated with pargyline died in hyperthermia while none of those treated with PCPA died.

PCPA completely protected the rabbits against the fatal hyperthermic interaction between pargyline and pethidine. However, it did not completely protect them against the motor restlessness and excitement.

Rabbits pretreated with lithium

Immediately after the injection of pethidine into rabbits pretreated with lithium there was restlessness, excitement and within 30 min, an average increase in temperature of 2·1° C over that of the control group (Fig. 2). The hyperpyrexia remained for more than 3 h after pethidine injection and one out of 6 rabbits died in hyperpyrexia.

Rabbits pretreated with yohimbine

The injection of pethidine into rabbits pretreated with yohimbine resulted in restlessness, convulsions and hyperpyrexia. The average increase in rectal temperature was 1·7° C (Fig. 3). None of the rabbits died.

Rabbits treated with sodium diethyldithiocarbamate (DEDTC)

DEDTC was injected intraperitoneally on the fifth day of treatment with pargyline in a dose of 400 mg/kg. This resulted in excitement, tremor and sometimes convul-

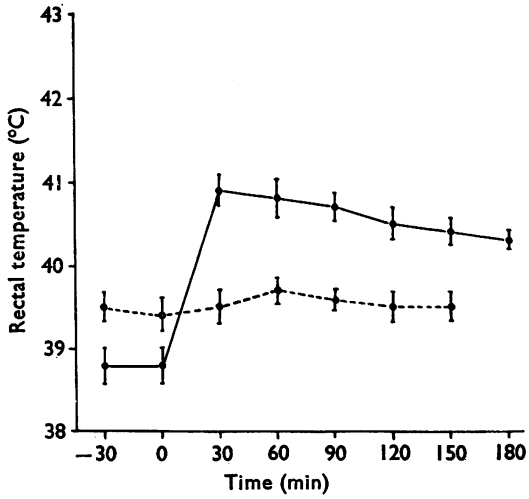

FIG. 2. Effect of pethidine on the rectal temperature of rabbits pretreated with lithium. Lithium sulphate (100 mg/kg) was injected i.p. daily for 5 days. Pethidine (5 mg/kg) was injected i.v. at time zero in one group of rabbits (●——●), the other group was injected with saline (●- - -●). Each curve represents the mean response from six rabbits. The vertical lines indicate S.E.M. One rabbit from the lithium-pethidine group died in hyperthermia.

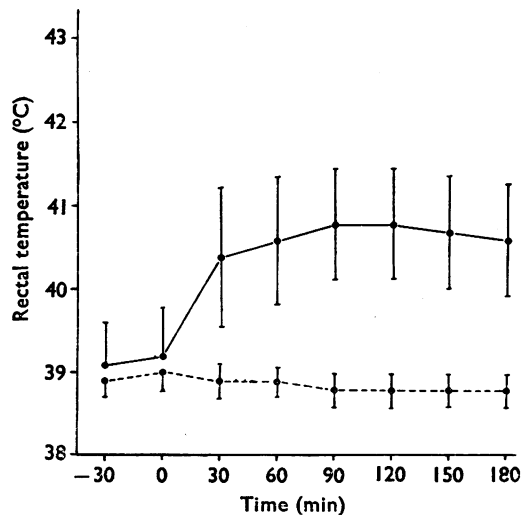

FIG. 3. Effect of pethidine on the rectal temperature of rabbits pretreated with yohimbine. Yohimbine HCl (10 mg/kg) was injected i.p. daily for 2 days. Pethidine (5 mg/kg) was injected i.v. at time zero in one group of rabbits (●——●), the other group was injected with saline (●- - -●). Each curve represents the mean response from four rabbits. The vertical lines indicate S.E.M.

sions. The rectal temperature rose steadily and all animals died in hyperpyrexia (Fig. 4).

Rabbits with chronic morphine tolerance

Chronic morphine tolerance did not confer any protection against the lethal pargyline–pethidine hyperpyrexia. Similarly, an injection of nalorphine 5 mg/kg intravenously either before or after pethidine did not modify the fatal hyperpyrexic interaction.

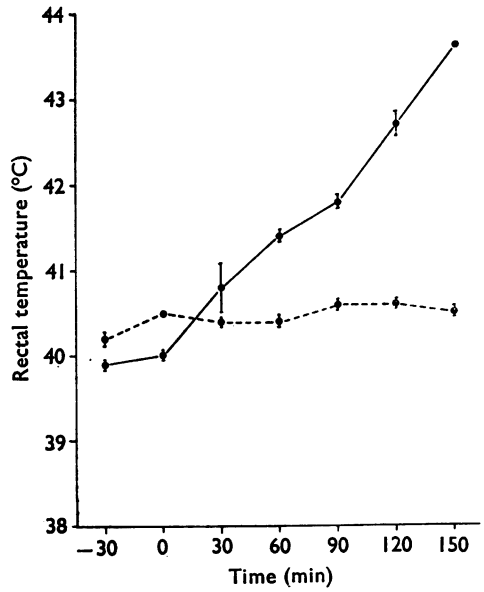

FIG. 4. Effect of sodium diethyldithiocarbamate (DEDTC) on the rectal temperature of rabbits pretreated with pargyline. Pargyline (25 mg/kg s.c. for 5 days) was injected in one group of rabbits (●——●), the other group was injected with saline (●- - -●). DEDTC (400 mg/kg) was injected i.p. at time zero. Each curve represents the mean response in four rabbits. The vertical lines indicate S.E.M. All rabbits pretreated with pargyline died in hyperthermia.

Discussion

The experimental results reported in this study showed that drugs which either inhibit or stimulate the synthesis of 5-hydroxytryptamine (5-HT) in the brain of rabbits can modify the hyperthermic interaction of pargyline and pethidine, or themselves can interact with pethidine.

Pretreatment of rabbits with PCPA, a drug that selectively depletes 5-HT in rat brain (Koe & Weissman, 1966), completely protected the animals against the otherwise fatal hyperthermic pargyline–pethidine interaction. On the other hand, the injection of sodium diethyldithiocarbamate, a compound that depletes noradrenaline in brain and other tissues through inhibition of the enzyme dopamine-β-hydroxylase (Carlsson, Lindqvist, Fuxe & Hökfelt, 1966; Aigner, Hornykiewicz, Lisch & Springer, 1967; Maj & Vetulani, 1970), produced a severe fatal hyperthermia in the pargyline-pretreated rabbits. Feldberg & Myers (1963) have suggested that the body temperature is regulated by the balance of noradrenaline and 5-HT in the hypothalamus.

Lithium has been used in the treatment of psychiatric disorders (Schou, 1968). Recently it has been reported that lithium significantly increases the rate of synthesis of brain 5-HT, possibly through an increase in the concentration of brain tryptophan (Sheard & Aghajanian, 1970 ; Cruet, Tagliamonte, Tagliamonte & Gessa, 1971). Pethidine caused a hyperthermic reaction when injected into rabbits pretreated with lithium. Yohimbine is another drug which has been shown to increase the concentration of brain 5-HT in rats (Papeschi, Sourkes & Youdim, 1971) possibly as a result of direct stimulation of 5-HT receptors on the postsynaptic cells or through blockade of the reuptake pump for 5-HT. Pethidine injection in the yohimbine-pretreated rabbits resulted in restlessness and hyperpyrexia.

It is known that tolerance is not easily acquired to pethidine (Osman, 1969), so rabbits were first made tolerant to morphine and it was assumed that they were cross-tolerant to pethidine. No protection was conferred against the fatal pargyline–pethidine interaction when the rabbits were made tolerant to morphine. Similarly no protection was achieved when nalorphine was injected before or after pethidine in another group of rabbits which had been pretreated with pargyline. This suggests that the pargyline–pethidine interaction occurs at sites in the brain other than those involved in analgesia and depression.

The results suggest that 5-HT is involved in the interaction occurring between pethidine and MAO inhibitors. Thus PCPA, by depleting brain 5-HT protected the rabbits against the otherwise fatal hyperpyrexia resulting from the pargyline–pethidine interaction. On the other hand, lithium and yohimbine, which increase 5-HT concentration in the brain, caused pethidine to provoke a hyperpyrexic response.

It has been shown by Spector, Hirsch & Brodie (1963) that there is a significant increase in the brain concentrations of noradrenaline and 5-HT in animals treated chronically with pargyline. DEDTC by upsetting the initial balance of the brain monoamines in favour of 5-HT in the pargyline pretreated rabbits, might produce a fatal hyperpyrexic reaction. Since pethidine has been shown to block the neuronal reuptake mechanism for cerebral 5-HT (Carlsson & Lindqvist, 1969), it is not surprising that a drug which increases the synthesis or delays the catabolism of 5-HT in the brain might produce a toxic interaction when combined with pethidine. Moreover, drugs like DEDTC might produce fatal hyperpyrexia in pargyline pretreated rabbits by depleting brain noradrenaline and thus precipitating a toxic interaction similar to that seen with pargyline and pethidine though the mechanism involved is different.

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