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MODIFICATION OF APOMORPHINE HYPOTHERMIA BY DRUGS AFFECTING BRAIN 5-HYDROXYTRYPTAMINE FUNCTION

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Intraperitoneal administration of apomorphine caused hypothermia in mice. Pretreatment with the serotonin (5-HT) receptor antagonists methysergide (3 mg/kg), cinanserin (10 mg/kg) or brom-LSD (3 mg/kg) potentiated this response of apomorphine. Brain 5-HT depletion by p-chlorophenylalanine caused similar modification. On the contrary, the 5-HT receptor agonists quipazine (3 mg/kg) and MK-212 (3 mg/kg), significantly blocked apomorphine hypothermia. It was concluded that 5-HT modulates the dopamine (DA)-mediated body temperature changes and that drug-induced alterations in the brain 5-HT function modify apomorphine-induced hypothermia in a predictable manner. One mg/kg dose of lysergic acid diethylamide (LSD) blocked apomorphine hypothermia. The apomorphine-blocking effect of both quipazine and LSD developed tolerance. Moreover, LSD showed cross tolerance with quipazine. It was concluded that the hypothermia-blocking property of LSD resides on its ability to activate the hypothalamic 5-HT receptors.

Serotonin agonists and antagonists Temperature regulation Apomorphine Hypothermia Dopamine Serotonin Serotonin depletion LSD

1. Introduction

Apomorphine produces hypothermia in both laboratory animals (for references, see reviews by Colpaert et al., 1976; Di Chiara and Gessa, 1978) and humans (Cutler et al., 1979). It has been established that this response of apomorphine depends on its dopamine (DA) receptor agonistic effect (for references, see Colpaert et al., 1976; Di Chiara and Gessa, 1978). Several studies also have indicated that serotonin (5-HT) plays a major role in the regulation of body temperature (for review, see Myers and Waller, 1977). Hence, investigation on the influence of drugs affecting the serotonergic system on apomorphine hypothermia is of interest. However, only relatively few studies have examined the effect of 5-HT antagonists on this response of apomorphine (Grabowska et al., 1973; Cox and Lee, 1979). It seems no such studies have been made on the interaction between apomorphine and the more recently introduced 5-HT agonists such as quipazine (for references, see Lansdown et al., 1980) and 6-chloro-2-(1-piperazinyl)pyrazine (Clineschmidt and McGuffin, 1978; Fuller et al., 1978). So experiments were performed to investigate the influence of both 5-HT antagonists and agonists as well as brain 5-HT depletion on the hypothermic response of apomorphine.

It has been reported that lysergic acid diethylamide (LSD), which activates both the 5-HT (Trulson et al., 1976) and DA (for references, see Menon et al., 1977) systems antagonize apomorphine hypothermia (Grabowska et al., 1973). In the present study this property of LSD was compared with that of quipazine.

2. Materials and methods

Male Swiss mice (23–28 g, Hilltop Laboratories, Scottdale, Pennsylvania) were used. Experiments

were performed at a room temperature of 22 ± 1°C. The animals were placed in individual cages before the experiment and their rectal temperatures were measured by inserting a thermistor probe 2.5 cm into the colon. The temperature was read on a digital thermometer. The animals were not restrained and the probe was inserted only at intervals when the temperature was measured. Drugs were then administered and the temperature was again recorded at intervals of 10, 30, 60, 90 and 120 min.

Drugs used in this study were apomorphine HCl (Merck, Sharp and Dohme, New Jersey), methysergide maleate (Sandoz, New Jersey), cinanserin (Squibb, New Jersey), quipazine maleate (Miles, Indianapolis), 6-chloro-2-(1-piperazinyl)-pyrazine HCl (MK-212, Merck, Sharp and Dohme, Philadelphia), lysergic acid diethylamide tartrate and brom-LSD (both from National Institute on Drug Abuse, Baltimore), and p-chlorophenylalanine methylester HCl (PCPA, Astra, Sodertalje, Sweden). Solutions of these drugs were prepared just before the experiment and were injected intraperitoneally in a volume of 0.01 ml/g body weight. The doses of drugs represent the free base.

Expect PCPA, all the pretreatments were made 10 min before apomorphine. Our experience showed that these drugs were able to exert their expected responses within this time. PCPA was administered in a dose of 100 mg/kg daily for 3 consecutive days and the animals were used 24 h after the last dose. Control experiments were performed simultaneously in animals treated with distilled water.

Our initial studies on the dose-response relationship of apomorphine showed that a dose of 0.5 mg/kg did not alter rectal temperature and doses of 1.0, 3.0, 10.0 and 20.0 mg/kg caused dose-dependent lowering of rectal temperatures. The responses produced by 1.0 and 3.0 mg/kg doses showed day to day variation. However, a 10 mg/kg dose produced highly reproducible hypothermic effects of a sufficient degree with minimal day to day fluctuation (see Results). Hence this dose was selected for drug interaction studies. In order to investigate the effect of repeated doses of quipazine or LSD on apomorphine hypothermia, different groups of mice were treated with six doses of either quipazine or LSD (9 a.m., 1 p.m., and 4 p.m. on days 1 and 2). On the third day, after recording their rectal temperature, the effect of an acute dose of either quipazine or LSD on apomorphine was investigated as before. For investigating the probable existence of a cross-tolerance between quipazine and LSD, in one study, the influence of an acute dose of LSD on mice receiving 6 doses of quipazine was also studied. Mice pretreated with six doses of distilled water in the above schedule served as simultaneous controls.

3. Results

3.1. Effect of apomorphine on the rectal temperature of mice

A 10 mg/kg dose of apomorphine produced a consistent and highly reproducible fall in the rectal temperature of mice pretreated 10 min prior with

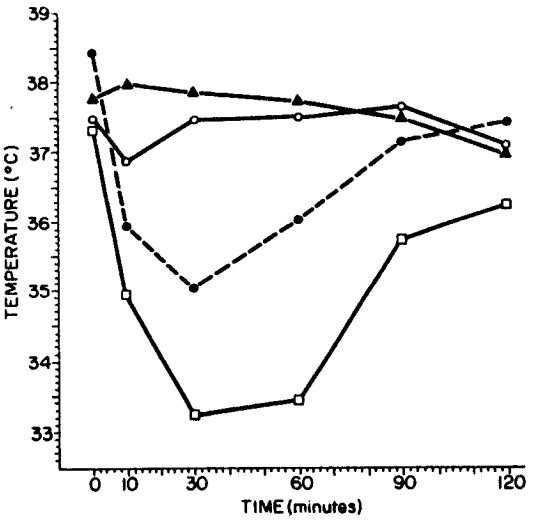

Fig. 1. Effect of methysergide (3 mg/kg) pretreatment on apomorphine (10 mg/kg) hypothermia in mice. ▲ $H_2O + H_2O$; ○ methysergide + H_2O; ● H_2O + apomorphine; □ methysergide + apomorphine. The second treatment was given 10 min after the first. H_2O + apomorphine n = 18, other groups n = 6. Temperature was recorded immediately before the first injection (zero time), then at 10, 30, 60, 90 and 120 min after the second injection. Methysergide + H_2O vs. methysergide + apomorphine $P < 0.005$ at 30, 60, 90 and 120 min. Student's t-test was used for statistical evaluation.

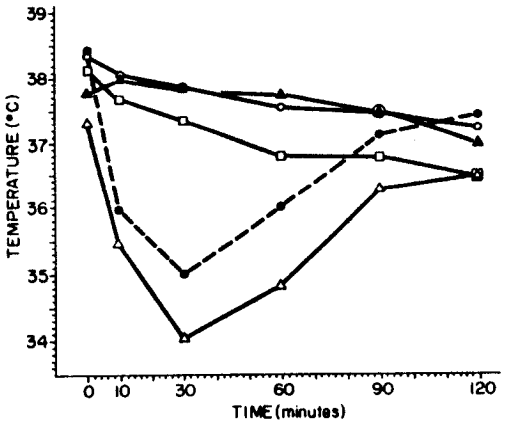

Fig. 2. Effect of quipazine on apomorphine hypothermia in mice. ▲ H_2O+H_2O, ○ quipazine $3.0+H_2O$, ● H_2O+ apomorphine, △ quipazine 1.0+apomorphine, □ quipazine 3.0+apomorphine. Quipazine $3.0+H_2O$ vs. quipazine 3.0+ apomorphine, N.S. at all time intervals which demonstrates complete blockade of apomorphine response. H_2O+ apomorphine vs. quipazine 1.0+apomorphine, N.S. at 30 min, <0.05 at 60 min and <0.001 at 90 and 120 min. See also fig. 1 legend.

distilled water. On three different days, the mean temperature changes (°C ± S.E.) observed at 30 min in groups of 6 mice were -3.9 ± 0.79, -3.15 ± 0.68 and -3.1 ± 0.4. The pooled data on these 18 mice are represented in figs. 1 and 2.

3.2. Effects of 5-HT antagonists and 5-HT depletion on apomorphine hypothermia

The results on the influence of methysergide pretreatment on apomorphine hypothermia are given in fig. 1. While methysergide alone did not alter rectal temperature significantly, it potentiated and prolonged apomorphine-induced fall in temperature. The results obtained in mice treated with brom-LSD, cinanserin or PCPA were comparable to that of methysergide.

3.3. Effects of 5-HT agonists on apomorphine hypothermia

While pretreatment with 1 mg/kg dose of quipazine potentiated apomorphine-induced lowering of rectal temperature, a 3 mg/kg dose almost completely abolished the temperature fall (fig. 2).

Unlike quipazine, MK-212 by itself lowered the rectal temperature, which made it difficult to interpret the data. However, since a 3 mg/kg dose of MK-212 did not produce hypothermia until 60 min, it was possible to compare its influence on apomorphine at 30 min. At this time, the rectal temperature fall seen in mice treated with MK-212 and apomorphine were significantly lower ($P < 0.05$) than that of water pretreated mice receiving apomorphine. Because a 5 mg/kg dose of MK-212 lowered rectal temperature even at 30 min, a dose-response relationship on its apomorphine antagonism could not be obtained.

3.4. Effect of LSD on apomorphine hypothermia and cross-tolerance between LSD and quipazine

A 1 mg/kg dose of LSD significantly blocked apomorphine hypothermia (fig. 3). Repeated administration of LSD led to tolerance development to the hypothermia-blocking effect of an acute dose of LSD (table 1). Similar tolerance develop-

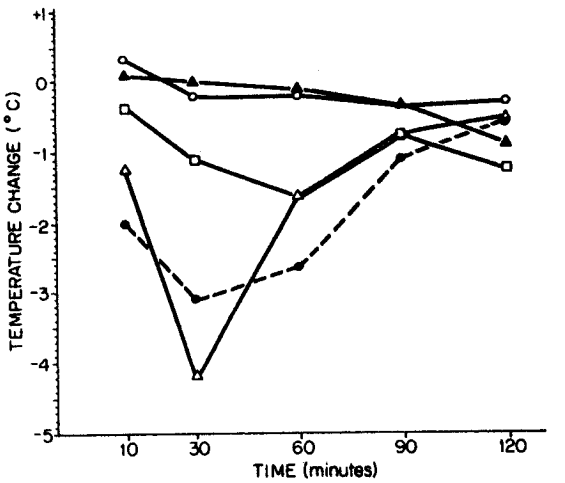

Fig. 3. Effect of LSD on apomorphine (10 mg/kg) hypothermia in mice. ▲ H_2O+H_2O; ○ LSD $1.0+H_2O$; ● H_2O+ apomorphine; △ LSD 0.3+apomorphine; □ LSD 1.0+ apomorphine. LSD 0.3+apomorphine vs. H_2O+apomorphine, N.S. at all time intervals. LSD 1.0+apo vs. H_2O+apo $P<0.001$ at 10 and 30 min and N.S. at other time intervals. See also fig. 1 legend.

TABLE I

Effects of acute and subacute treatments with either LSD or quipazine on apomorphine-induced hypothermia in mice.

Treatment [1]	No. mice	Rectal temperature changes seen at 30 min after apomorphine (°C ± S.E.) [2]	Significance [3]
Acute			
(1) H_2O + Apo 10.0 (control)	6	−3.10 ± 0.40	
(2) LSD 1.0 + Apo 10.0	12	−1.10 ± 0.23	P < 0.001
(3) Quip 3.0 + Apo 10.0	6	−0.92 ± 0.36	P < 0.001
Subacute			
(4) Subacute H_2O + Apo 10.06 (control)	6	−3.62 ± 0.11	
(5) Subacute H_2O + LSD 1.0 + Apo 10.0	6	−0.27 ± 0.26	
(6) Subacute LSD + LSD 1.0 + Apo 10.0	6	−2.12 ± 0.19	P < 0.001
(7) Subacute H_2O + Quip 3.0 + Apo 10.0	6	−0.45 ± 0.30	
(8) Subacute Quip + Quip 3.0 + Apo 10.0	6	−2.3 ± 0.27	P < 0.001
(9) Subacute Quip + LSD 1.0 + Apo 10.0	6	−1.95 ± 0.38	P < 0.01

[1] Subacute treatment consisted of injecting either LSD (1 mg/kg) or quipazine, 3 doses each day for 2 consecutive days. Temperature studies were performed 20 h after the last dose.

[2] The values represent the differences in the rectal temperature seen immediately before and 30 min after apomorphine.

[3] Probability was calculated using Student's t-test. 2 and 3 were compared with 1; 6 with 5; 7 with 8, and 9 with 5.

ment was also seen to an acute dose of quipazine in animals receiving 6 doses of quipazine. Moreover, in these subacutely quipazine-pretreated mice, a 1 mg/kg dose of LSD failed to block apomorphine hypothermia (table 1).

4. Discussion

Direct administration of apomorphine into the various areas in the brains of rats has shown that this DA agonist acts on the preoptic anterior hypothalamus to elicit its hypothermic response (Cox and Lee, 1977). The lowering of body temperature caused by centrally injected apomorphine is blocked by centrally or peripherally administered DA antagonists (for review, see Cox, 1979). Hence, it may be inferred that the interaction of peripherally administered drugs with apomorphine occurs at the central site.

The present study shows that decreasing the activity of the central serotonergic system by the administration of 5-HT antagonists potentiates apomorphine hypothermia. This result is in agreement with that of Grabowska et al. (1973). In addition, we also observed that brain 5-HT depletion also potentiated this response of apomorphine. Our finding that the 5-HT agonists block apomorphine hypothermia clearly shows that serotonergic drugs influence this response in a predictable manner and that such interaction studies are useful in the evaluation of drugs acting on the central serotonergic system. These findings also provide evidence for the modulatory roles for both DA and 5-HT in the regulation of body temperature.

The blockade of apomorphine hypothermia by LSD has been reported earlier (Grabowska et al., 1973). The present results show that 1 mg/kg dose of LSD significantly blocked the apomorphine-induced temperature fall. We also observed that this response of LSD as well as that of quipazine, a 5-HT agonist (for references see Introduction) develop tolerance. Moreover, a cross-tolerance between quipazine and LSD was also found to occur. These results indicate that, in these doses, these drugs stimulate the same 5-HT receptor sites located in the anterior hypothalamus where apomorphine acts. It may be pointed out that a behavioral study also has demonstrated that LSD and quipazine elicit identical responses (Winter, 1981). The demonstration that repeated treatments

of LSD to rats resulted in a decrease in the binding of both LSD and 5-HT to their specific binding sites in brain (Trulson and Jacobs, 1979), as well as the report that repeated quipazine treatment produced a decrease in the 5-HT binding to the cerebral cortex of rats (Savage et al., 1980) show that both these drugs stimulate 5-HT receptors.

In summary, these drug interaction studies revealed that treatments which depress the function of the central serotonergic neurons potentiate apomorphine hypothermia. This temperature response of apomorphine could be antagonized by drugs which either block DA receptors or stimulate 5-HT receptors. LSD, though activating the DA receptor sites, does not cause hypothermia, possibly because of its built-in 5-HT receptor agonistic property. The latter effect of LSD is most likely responsible for its blockade of apomorphine hypothermia.

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