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# POSSIBLE INVOLVEMENT OF BRAIN SEROTONIN IN APOMORPHINE-INDUCED HYPOTHERMIA

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Apomorphine lowered body temperature in rats and mice and raised the brain 5-HIAA level. Hypothermia was inhibited by butyrophenones and LSD but not by methysergide and PCPA. LSD also inhibited the apomorphine-induced enhancement of 5-HIAA; this effect was similar to that previously described for butyrophenone. It was noted that apomorphine directly stimulated central dopamine receptors which indirectly increased 5-HT turnover, this latter action leading to hypothermia. The effectiveness of LSD resulted from its ability to stabilize 5-HT inside the neuron.

Apomorphine
LSD
Body temperature
Butyrophenones
Brain serotonin turnover

## 1. Introduction

Our experiments with apomorphine have revealed that this compound lowers the body temperature in rats (unpublished results) and in mice (Maj et al., 1972); apomorphine-induced hypothermia was also reported by other authors (Barnett et al., 1972; Lapin and Samsonova, 1968a,b; Schelkunov, 1968; Schelkunov and Stabrovsky, 1971). We have also found that apomorphine elevated the concentration of serotonin and its metabolite, 5-hydroxyindoleacetic acid, in the rat brain (Grabowska et al., 1973).

It was therefore of interest to determine whether or not apomorphine-induced hypothermia in both these species depended on the action of apomorphine on central serotoninergic processes.

## 2. Materials and methods

The experiments were carried out on male Albino Swiss mice, weighing 17–22 g, and on male Wistar rats, weighing 130–170 g. The rectal temperature was measured at 10-min intervals for 50 min after the s.c. injection of apomorphine, using an Ellab thermistor thermometer. Our pilot experiments have shown that the maximum effect appears after 15–30 min, and the hypothermia disappears 45–60 min after the injection. Each group consisted of 10 mice or 5 rats randomly assigned. The results are presented as the temperature difference ($\Delta t$) between the experimental and the control, saline-treated, group. The levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were determined in the same brain respectively with the method of Maickel et al. (1968) and Miller et al. (1970). Each group consisted of 7 animals.

The compounds were injected as solutions in saline (apomorphine, Ro 4-4602), from a commercially available ampoule (LSD), or as suspensions in 3% aqueous solutions of Tween 80 (methysergide, spiroperidol, pimozide, p-chlorophenylalanine, 5-hydroxytryptophan). LSD (i.p.) was given simultaneously with apomorphine, methysergide (i.p.) 10 min before apomorphine, spiroperidol (i.p.) 105 min, pimozide (i.p.) 210 min and p-chlorophenylalanine (PCPA) 24

or 72 hr before apomorphine. Ro 4-4602 was given i.p. 30 min before the i.p. injection of 5-HTP.

Statistical significance of the results was evaluated with Student's *t*-test.

The following compounds were used: apomorphine hydrochloride (McFarlane), methysergide hydrogen maleate (Sandoz), delysid (LSD-25, Sandoz), p-chlorophenylalanine (Sigma), spiroperidol (Janssen), pimozide (Janssen), Ro 4-4602 (seryltrihydroxybenzylhydrazine, Hoffmann–La Roche), L-5-hydroxytryptophan (Sigma).

Table 1
The influence of LSD and methysergide on apomorphine-induced hypothermia in rats and mice.
Each group consisted of 5 rats and 10 mice. The values are mean differences between the rectal temperature of the control and experimental groups (in °C) measured 20 (rats) or 30 (mice) min after apomorphine injection.

| Treatment (dose, mg/kg) | Δt (°C) ± S.E.M. Rats | Mice |
|---|---|---|
| Apomorphine (1.0)[a] | −1.2 ± 0.4 * | −3.5 ± 0.4 *** |
| Apomorphine (1.0)[b] + LSD (1.0) | +0.6 ± 0.2 ** | −1.0 ± 0.5 ** |
| Apomorphine (5.0)[a] | −2.2 ± 0.2 *** | −1.7 ± 0.2 *** |
| Apomorphine (5.0)[b] + LSD (1.0) | +1.0 ± 0.2 *** | 0 ± 0.4 |
| Apomorphine (25.0)[a] | −2.9 ± 0.3 *** | −2.2 ± 0.4 *** |
| Apomorphine (25.0)[b] + LSD (1.0) | +0.9 ± 0.6 *** | −0.7 ± 0.4 * |
| LSD (1.0)[a] | −0.1 ± 0.1 | −0.8 ± 0.1 ** |
| Apomorphine (1.0)[a] | −1.2 ± 0.4 * | −3.5 ± 0.6 *** |
| Apomorphine (1.0)[b] + methysergide (5.0) | −1.6 ± 0.2 | −2.7 ± 0.2 |
| Apomorphine (5.0)[a] | −2.2 ± 0.2 *** | −3.2 ± 0.4 *** |
| Apomorphine (5.0)[b] + methysergide (5.0) | −1.7 ± 0.4 | −1.8 ± 0.2 * |
| Apomorphine (25.0)[a] | −2.9 ± 0.3 *** | −3.8 ± 0.4 *** |
| Apomorphine (25.0)[b] + methysergide (5.0) | −2.8 ± 0.3 | −4.6 ± 0.7 |
| Methysergide (5.0)[a] | −1.0 ± 0.1 ** | −1.3 ± 0.2 |

[a] The significance of the difference from the saline-treated group.
[b] The significance of the difference from the respective apomorphine-treated group.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Student's *t*-test).

## 3. Results

### *3.1. The effect of apomorphine on body temperature*

#### *3.1.1. Rats*

Apomorphine transiently depressed body temperature (tables 1,2). Simultaneously there appeared stereotypy and a significant enhancement of locomotor activity.

#### *3.1.2. Mice*

Apomorphine, 1.0, 5.0 and 25.0 mg/kg, significantly depressed the body temperature (tables 1,2); the effect was stronger than in rats and was independent of the dose. In different experiments, the reaction of mice to the same dose of apomorphine was different.

The apomorphine-treated mice, particularly those which had been injected with higher doses of apomorphine, were excited, they sniffed intensively, and the frequency of 'rearing' increased. These symptoms,

Table 2
The influence of pimozide and spiroperidol on apomorphine-induced hypothermia in rats and mice.
Each group consisted of 5 rats and 10 mice. For further explanations and footnotes see table 1.

| Treatment (dose, mg/kg) | Δt (°C) ± S.E.M. Rats | Mice |
|---|---|---|
| Apomorphine (1.0)[a] | −2.6 ± 0.4 *** | −3.0 ± 0.4 *** |
| Apomorphine (1.0)[b] + pimozide (4.0) | −0.5 ± 0.2 ** | −0.6 ± 0.3 *** |
| Apomorphine (5.0)[a] | −2.6 ± 0.2 *** | −2.5 ± 0.3 *** |
| Apomorphine (5.0)[b] + pimozide (4.0) | −1.1 ± 0.3 ** | −0.8 ± 0.2 *** |
| Apomorphine (25.0)[a] | −2.7 ± 0.3 *** | −4.2 ± 0.3 *** |
| Apomorphine (25.0)[b] + pimozide (4.0) | −1.8 ± 0.2 | −3.6 ± 0.4 |
| Pimozide (4.0)[a] | −0.2 ± 0.2 | +0.1 ± 0.2 |
| Apomorphine (1.0)[a] | −2.3 ± 0.3 ** | −2.6 ± 0.3 *** |
| Apomorphine (1.0)[b] + spiroperidol (0.5) | −1.0 ± 0.2 * | +0.3 ± 0.3 *** |
| Apomorphine (5.0)[a] | −2.6 ± 0.3 *** | −2.7 ± 0.4 *** |
| Apomorphine (5.0)[b] + spiroperidol (0.5) | −1.1 ± 0.3 ** | −0.5 ± 0.3 *** |
| Apomorphine (25.0)[a] | −2.6 ± 0.3 *** | −2.6 ± 0.5 *** |
| Apomorphine (25.0)[b] + spiroperidol (0.5) | −1.8 ± 0.2 * | −2.1 ± 0.4 |
| Spiroperidol (0.5)[a] | −0.5 ± 0.1 | −0.3 ± 0.3 |

which were particularly marked directly after apomorphine had been injected, subsided after 30 min.

*3.2. The effect of LSD on apomorphine-induced hypothermia*

*3.2.1. Rats*

LSD, 1.0 mg/kg, completely protected against apomorphine-induced hypothermia irrespective of the dose of apomorphine (table 1), and the combined treatment produced a hyperthermic effect. LSD alone depressed body temperature within the range of 0.7°C between 40 and 50 min after injection. In rats LSD did not induce any significant changes in apomorphine stimulation.

*3.2.2. Mice*

Apomorphine-induced hypothermia was counteracted by LSD (table 1). Significant results were obtained using two lower doses of apomorphine. LSD slightly but significantly depressed the body temperature of mice in some experiments, but in others did not affect it at all. In mice no significant LSD-induced changes in apomorphine stimulation were noted.

*3.3. The effect of methysergide on apomorphine-induced hypothermia*

*3.3.1. Rats*

Methysergide, 5.0 mg/kg, did not affect the hypothermia (table 1) or stimulation induced by apomorphine. Methysergide alone depressed the body temperature by 0.3–1.3°C.

*3.3.2. Mice*

Methysergide alone depressed the body temperature of mice up to 1.6°C. Methysergide given 10 min before apomorphine did not affect apomorphine-induced hypothermia in a regular manner (table 1). Significant inhibition as well as potentiation of the hypothermia was observed at some intervals. Methysergide did not affect apomorphine-induced behaviour.

*3.4. The effect of pimozide and spiroperidol on apomorphine-induced hypothermia*

*3.4.1. Rats*

Pimozide (4 mg/kg) and spiroperidol (0.5 mg/kg) significantly counteracted the hypothermia produced by apomorphine, although the effect of the highest dose of apomorphine was less pronounced. Neither of the butyrophenones affected rat body temperature (table 2). Apomorphine-induced stereotypy and motor stimulation were abolished by spiroperidol and pimozide.

*3.4.2. Mice*

Spiroperidol (0.5 mg/kg) and pimozide (4.0 mg/kg) did not affect body temperature, but counteracted the hypothermia brought about by apomorphine 1.0 or 5.0 mg/kg, but not by 25 mg/kg (table 2). These two compounds prevented apomorphine-induced behavioural changes.

*3.5. The influence of PCPA on apomorphine-induced hypothermia*

*3.5.1. Rats*

PCPA administered 72 hr before apomorphine did not significantly alter apomorphine-induced hypothermia; PCPA itself was without effect on body temperature.

*3.5.2. Mice*

PCPA administered 24 or 72 hr before apomorphine did not significantly alter hypothermia induced by smaller doses of apomorphine; PCPA itself was without effect on body temperature. The action of the highest dose of apomorphine, 25.0 mg/kg, was potentiated by PCPA.

*3.6. The effect of 5-HTP (given together with Ro 4-4602) on the body temperature*

*3.6.1. Rats*

5-HTP given at doses of 50 and 100 mg/kg together with Ro 4-4602 (25 mg/kg) considerably depressed the rats' body temperature for the total observation time; the maximum effect appeared after 20 or 30 min (table 3). The higher dose of 5-HTP produced less hypothermia than the smaller one.

*3.6.2. Mice*

5-HTP given together with Ro 4-4602 produced a transient depression of body temperature (observed only at 10 min) (table 3).

Table 3
The changes of body temperature after treatment with Ro 4-4602 and 5-HTP.
Each group consisted of 10 mice and 5 rats respectively. The values are mean differences between the rectal temperature of the control and experimental groups (in °C) at a given interval after 5-HTP injections.

| Species | Treatment (mg/kg) | Time intervals (min) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 10 | 20 | 30 | 40 | 50 | 60 | 90 |
| Mouse | 5-HTP (50) | −1.08 * | +0.20 | +0.89 | +0.90 | +0.74 | +0.50 * | +0.03 |
| | 5-HTP (100) | −1.36 * | −0.25 | +0.12 | +0.39 | +0.42 | +0.28 | −0.23 |
| Rat | 5-HTP (50) | −2.90 * | −2.66*** | −3.60*** | −3.08*** | −3.00*** | −3.02*** | −2.84*** |
| | 5-HTP (100) | −1.24 | −1.86 | −1.78*** | −1.60 ** | −1.36 * | −1.50 * | −1.20 * |

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (the difference from the saline-treated group).

### *3.7. The influence of apomorphine on brain 5-HT and 5-HIAA concentrations*

#### *3.7.1. Rats*

Apomorphine at doses of 1.0 and 5.0 mg/kg significantly elevated brain 5-HT concentration; the significant increase of brain 5-HIAA content was produced only by the lowest dose, although the other doses tended to elevate it (table 4).

#### *3.7.2. Mice*

Low doses of apomorphine did not alter the brain 5-HT concentration, a dose of 25 mg/kg depressed it. All apomorphine doses significantly elevated the brain 5-HIAA content (table 5).

### *3.8. The influence of LSD on apomorphine-induced changes of brain 5-HT and 5-HIAA concentrations*

#### *3.8.1. Rats*

LSD did not alter the brain 5-HT concentration in apomorphine-treated rats (table 4), but significantly counteracted the apomorphine-induced increase in brain 5-HIAA concentration; the 5-HIAA concentration in these groups was lower than in the control rats

Table 4
Whole brain 5-HT and 5-HIAA contents in apomorphine and LSD-treated rats.
Each group consisted of 7 animals. Rats received apomorphine simultaneously with LSD and were killed 15 min later.

| Treatment (dose, mg/kg) | 5-HT (ng/g ± S.E.M.) | 5-HIAA (ng/g ± S.E.M.) |
|---|---|---|
| Saline | 655.5 ± 8.8 | 694.4 ± 28.5 |
| Apomorphine (1.0) [a] | 715.7 ± 27.8 * | 817.0 ± 34.6 * |
| Apomorphine (1.0) [b] + LSD (1.0) | 665.0 ± 9.4 | 616.7 ± 27.5 *** |
| Apomorphine (5.0) [a] | 711.1 ± 11.7 ** | 772.1 ± 33.5 |
| Apomorphine (5.0) [b] + LSD (1.0) | 743.7 ± 25.0 | 586.1 ± 15.0 *** |
| Apomorphine (25.0) [a] | 608.0 ± 25.1 | 800.6 ± 48.6 |
| Apomorphine (25.0) [b] + LSD (1.0) | 624.3 ± 54.0 | 588.0 ± 18.6 ** |
| LSD (1.0) [a] | 684.0 ± 21.1 | 610.0 ± 14.2 * |

For footnotes see table 1.

Table 5
Whole brain 5-HT and 5-HIAA contents in apomorphine- and LSD-treated mice.
Each group consisted of 7 animals. Mice received apomorphine simultaneously with LSD and were killed 15 min later.

| Treatment (dose mg/kg) | 5-HT (ng/g ± S.E.M.) | 5-HIAA (ng/g ± S.E.M.) |
|---|---|---|
| Saline | 619.7 ± 22.2 | 634.7 ± 34.4 |
| Apomorphine 1.0 [a] | 681.4 ± 19.0 | 782.0 ± 21.0 ** |
| Apomorphine 1.0 [b] + LSD 1.0 | 712.3 ± 21.1 | 573.1 ± 24.3 *** |
| Apomorphine 5.0 [a] | 579.0 ± 14.3 | 825.7 ± 29.8 *** |
| Apomorphine 5.0 [b] + LSD 1.0 | 653.3 ± 17.8 ** | 582.8 ± 32.0 *** |
| Apomorphine 25.0 [a] | 529.7 ± 14.0 ** | 898.6 ± 40.9 *** |
| Apomorphine 25.0 [b] + LSD 1.0 | 673.7 ± 17.3 *** | 563.4 ± 28.5 *** |
| LSD 1.0 [a] | 686.6 ± 11.3 * | 651.7 ± 37.1 |

For footnotes see table 1.

(table 4). LSD alone did not affect the brain content of 5-HT but depressed the 5-HIAA content.

### *3.8.2. Mice*

In the groups receiving apomorphine (5.0 or 25.0 mg/kg) together with LSD, the brain 5-HT concentration was higher, and 5-HIAA concentration was lower than in the groups receiving apomorphine alone (table 5). LSD alone significantly elevated the brain 5-HT content, but did not alter the 5-HIAA content of the mouse brain (table 5).

## 4. Discussion

The results of the experiments on the influence of pharmacological agents and a heat stress, as well as the effects of the administration of 5-HT or its precursor, 5-HTP, have shown 5-HT to be a hypothermic factor in rats in thermoregulative processes (Aghajanian and Weiss, 1968; Bruinvels, 1970; Bruinvels and Kemper, 1971; Corrodi et al., 1967; Feldberg and Lotti, 1967; Mantegazzini, 1966; Myers and Yaksh, 1968; Reid et al., 1968; Reid, 1970; Schmidt and Fähse, 1964; Winter, 1971). 5-HTP when administered together with a monoamine oxidase inhibitor does indeed induce hyperthermia (Bruinvels and Kemper, 1971; Mantegazza, 1965); however, a disturbed catabolism of other monoamines cannot be disregarded.

In our experiments, a considerable and long-lasting hypothermia was observed after both 5-HTP and an inhibitor of peripheral decarboxylase had been administered. In the experiments in which both 5-HT and its precursor were given, their possible interaction with the catecholaminergic system had been allowed for (Butcher et al., 1972; Johnson et al., 1968; Snyder, 1970).

In our previous experiments (Grabowska et al., 1973), apomorphine was found to enhance 5-HT and 5-HIAA concentrations in the rat brain. These changes are believed to have originated from an increased turnover of 5-HT; they caused an increased inflow of 5-HT to the serotonin receptor and were probably responsible for apomorphine-induced hypothermia in rats.

Administration of LSD inhibited the lowering of the rat body temperature by apomorphine. Although LSD had no significant effect on the apomorphine-induced enhancement of brain 5-HT concentration, it markedly inhibited the increase of 5-HIAA possibly indicating impairment of 5-HT release. LSD, sometimes regarded as a blocking agent (Berde et al., 1960; Boakes et al., 1970; Cerletti and Doepfner, 1958; Vane, 1962), sometimes as a serotonin receptor stimulant (Andén, 1968; Andén et al., 1968) has, as the literature indicates, a stabilizing influence on in-

terneuronal serotonin (Aghajanian and Weiss, 1968; Chase et al., 1967; Freedman, 1961; Lin et al., 1969; Rosecrans et al., 1967; Schubert et al., 1970; Tonge and Leonard, 1969). Thus a decreased inflow of 5-HT to the receptor may well be responsible for the blocking effect of LSD on apomorhine-induced hypothermia.

The assessement of the results however, ought not to be exclusively based on a serotoninergic mechanism for LSD but other mechanisms should also be considered; among these its possible interaction with the catecholaminergic system should be particularly noted (Costa and Zetler, 1959; Diaz et al., 1967; Dixon, 1968; Elder and Dille, 1962; Horita and Hamilton, 1969; Leonard and Tonge, 1969; Person, 1970; Tonge and Leonard, 1969).

In our experiments, the dopamine receptor blocking agents, spiroperidol and pimozide inhibited apomorphine-induced hypothermia.

We have previously found that spiroperidol and pimozide also inhibit apomorphine-induced changes in 5-HT and 5-HIAA in the rat brain (Grabowska et al., 1973). Therefore it seems that apomorphine-induced hypothermia does not result from a direct effect of apomorphine on serotonin neurons but results from an indirect, secondary response to stimulation of dopamine receptors.

Methysergide, like LSD, is believed to be a serotonin receptor blocking agent (Berde et al., 1960; Boakes et al., 1970;Chambers and Marshall, 1967); it counteracted the body temperature changes that resulted from 5-HT or 5-HTP (Mantegazza, 1965; Winter, 1971). The lack of influence of methysergide on apomorphine-induced hypothermia is in contrast with the suggested serotoninergic mechanism and cannot be explained at present. Dissimilar effects of LSD and methysergide have also been described by other authors (Corne and Pickering, 1967; Freedman, 1961; Freedman et al., 1970; Rosecrans et al., 1967; Tonge and Leonard, 1969, 1972).

The lack of effect of PCPA on apomorphine-induced hypothermia is obscure. However, in some brain structures of PCPA-treated rats, apomorphine has been found to raise the 5-HT and 5-HIAA concentrations, as it does in normal rats (Grabowska et al., 1973). In some structures PCPA has been found to partially inhibit the tryptophane hydroxylase activity (Knapp and Madell, 1972).

In mice, as in rats, 5-HT is believed to be the body temperature lowering factor (Kärjä et al., 1961; Lapin and Samsonowa, 1968b; Mantegazzini, 1966). In our experiments the administration of the 5-HT precursor, 5-HTP, together with the peripheral decarboxylase inhibitor (Ro 4-4602), caused a temporary hypothermia; an increase in body temperature that later became noticeable was probably due to the aforesaid interaction of 5-HTP and 5-HT formed with the catecholaminergic system.

The lowering of body temperature in mice by apomorphine has been described previously (Barnett et al., 1972; Lapin and Samsonova, 1968a,b; Schelkunov and Stabrovsky, 1971). The mechanism of the apomorphine-induced hypothermia in mice seems to be the same as in rats.

In mice, as in rats, the lack of effect of methysergide and PCPA on apomorphine-induced hypothermia is inexplicable; the lack of effect of PCPA may have resulted from the higher resistance of mice to PCPA (Koe and Weissman, 1966; Welch and Welch, 1967).

Barnett has suggested that the decrease of body temperature after the administration of apomorphine into mice is a result of a direct stimulation of dopamine receptors in the central nervous system. Indeed butyrophenones inhibit this hypothermia (Barnett et al., 1972; Schelkunov, 1968). However, butyrophenones are unable to inhibit hypothermia after both DPA and the peripheral dopa decarboxylase inhibitor Ro 4-4602 have been administered (Maj and Pawlowski, 1973). Although Barnett's suggestion implies their capability of inducing hyperthermia, butyrophenones alone do not bring about any siginificant changes in body temperature.

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