*School of Studies in Pharmacology,*
*University of Bradford,*
*Bradford, 7, Yorks, U.K.*
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G. M. DREW
J. R. FOZARD*
S. N. HOOD
G. D. H. LEACH

* Present address: Department of Pharmacology, University of Manchester.

# Antagonism by methysergide of the 5-hydroxytryptamine-like action of toxic doses of fenfluramine in dogs

Fenfluramine produces anorexia in experimental animals and in man, but does not stimulate the central nervous system (Le Douarec, Schmitt & Laubie, 1966; Colmore & Moore, 1968). It has been reported to cause depletion of catecholamines both centrally and peripherally (Ziance & Kunnard, 1968; Duce & Gessa, 1966) and in contrast to amphetamine to release brain 5-hydroxytryptamine (Opitz, 1967; Duhault & Verdavainne, 1967). Also in contrast to amphetamine it lowers body temperature in experimental animals (Jespersen, Bonaccorsi & Garattini, 1969; Bizzi, Bonaccorsi & others 1969).

The effect of fenfluramine alone and in combination with methysergide (a specific 5-HT antagonist) was studied in 5 male beagle dogs by recording the rectal temperature and observing gross behaviour. (±)-Fenfluramine hydrochloride or saline was given subcutaneously after recording of the basic temperature, and 2½ h later methysergide bimaleate was administered intraveneously. Each dog was tested 3 times at 7–10 day intervals.

Fenfluramine causes hypothermia in dogs—as in other species—with maximum effect 2½ h after injection. Methysergide given alone does not influence body temperature at the dose tested, but when given 2½ h after fenfluramine a clear-cut and statistically significant antagonism of the fenfluramine-induced hypothermia was revealed. [$P < 0{\cdot}05$, $P < 0{\cdot}01$ and $P < 0{\cdot}01$ at 3, 3½ and 4 h respectively (Student's *t*-test)].

Fenfluramine caused changes in behaviour similar to those reported by Bogdanski, Weissbach & Udenfriend (1958) after injection to dogs of 5-HTP, a 5-HT precursor, which at decarboxylation raises the brain level of 5-HT up to 10 times (Udenfriend, Weissbach & Bogdanski, 1957). The fenfluramine-induced reactions were: sedation, mydriasis, apparent blindness, whining by petting, diarrhoea and unwillingness to keep still during measurement of rectal temperature. All these symptoms were more or less improved after methysergide. Two of the dogs behaved quite normally half an hour after the injection, while the other 2 dogs were still partially sedated. The fenfluramine controls continuously showed the mentioned symptoms up to 5–6 h after administration.

Some evidence was obtained that methysergide also antagonized the fenfluramine-induced anorexia, because when food was presented 1 h after the administration of methysergide or saline, none of the 4 dogs treated with fenfluramine + saline showed any interest in the food, while 2 of the 4 dogs treated with the combination ate with fairly good appetite, and 1 dog showed interest without eating.

The antagonism of subcutaneously administered methysergide (0·05 mg/kg) to the fenfluramine sedation and discomfort was confirmed in an experiment with 4 female beagles. The antagonism judged on gross behaviour observations was evident in 3 of these dogs which had received 2·5, 5 or 20 mg/kg fenfluramine subcutaneously about 3 h before. The behaviour of 1 dog given fenfluramine 5 mg/kg was not improved by methysergide.

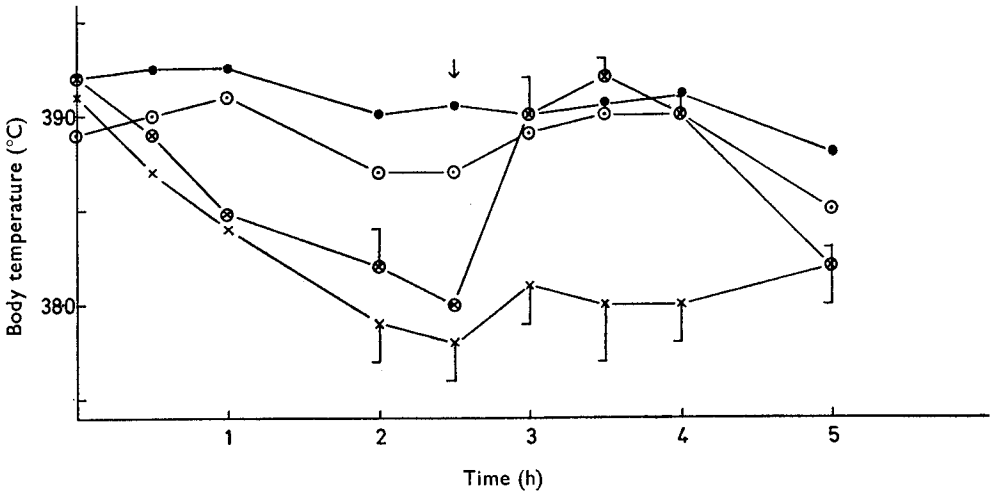


FIG. 1. The effect of fenfluramine alone or in combination with methysergide on the temperature in dogs

| *At 0 h subc.* | *At 2½ h i.v.* | |
|---|---|---|
| Saline | Saline | —·— (4 dogs) |
| Saline | Methysergide 0·05 mg/kg | —⊙— (3 dogs |
| Fenfluramine 20 mg/kg | Saline | —×— (4 dogs) |
| Fenfluramine 20 mg/kg | Methysergide 0·05 mg/kg | —⊗— (4 dogs) |

At ↓ methysergide or saline was injected. Vertical bars indicate standard error of the mean.

In summary a large dose of fenfluramine given to dogs caused symptoms which were grossly similar to those reported after administration of 5-HTP, indicating that 5-HT plays an important role in the reactions. The symptoms improved after administration of the 5-HT antagonist methysergide, which also seemed to antagonize the fenfluramine-induced anorexia.

Methysergide might be of value in the treatment of fenfluramine overdosage.

*Department of Pharmacology,*
*Alfred Benzon Ltd.,*
*29, Halmtorvet,*
*DK-1700 Copenhagen V.*
SUNE JESPERSEN

*Department E,*
*Sct. Hans Hospital,*
*DK-4000 Roskilde, Denmark.*
J. SCHEEL-KRÜGER

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