On the anti-apomorphine effect of fenfluramine

Fenfluramine is an anorexic drug which resembles amphetamine in chemical structure. Both compounds affect the dopaminergic mechanism in the striatum and both increase the striatum homovanillic acid concentrations (Jori & Bernardi, 1969) although the mechanism of these effects may be different.

We have investigated the influence of (+)-fenfluramine on the effects of apomorphine, which are believed to result from the stimulation of dopamine receptors. These effects have been recorded by the measurement, in rats, of stereotypy (Andén, Rubenson & others, 1967; Ernst, 1967), locomotor stimulation (Maj, Grabowska & Gajda, 1972; Thomas, 1970) and hypothermia (Grabowska, Michaluk & Antkiewicz, 1973; Kruk, 1972).

Male Wistar rats (130–170 g) were used to measure the intensity of stereotypy according to a 3 point scale (Janssen, Niemegeers & others, 1967). Two independent observers noted effects and the mean result was calculated. Locomotor activity of individual animals was measured using photocell cages; body temperature was measured rectally using an "Ellab" thermometer.

Fenfluramine (10·0 mg kg^{-1}, i.p.) significantly attenuated the apomorphine-induced stereotypy (Fig. 1). Apomorphine (1·0 and 5·0 mg kg^{-1}, s.c.) increased the motor

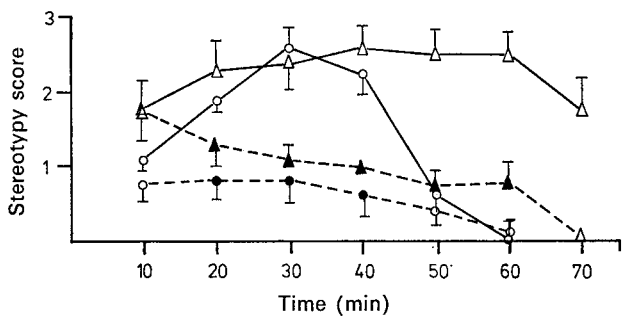

FIG. 1. The influence of fenfluramine (10 mg kg^{-1}, i.p. broken lines) on the stereotypy induced by apomorphine (s.c.) at doses 1·0 (○——○) and 5·0 (△——△) mg kg^{-1}. Solid symbols indicate statistical significance $P<$ (Student's *t*-test). Each group consisted of 6 rats. Fenfluramine was administered 3 h before the test.

activity of rats. The stimulatory action of the lower dose of apomorphine was abolished in the rats pretreated with fenfluramine and the effect of higher dose was significantly decreased (Fig. 2). Fenfluramine, alone, did not significantly affect

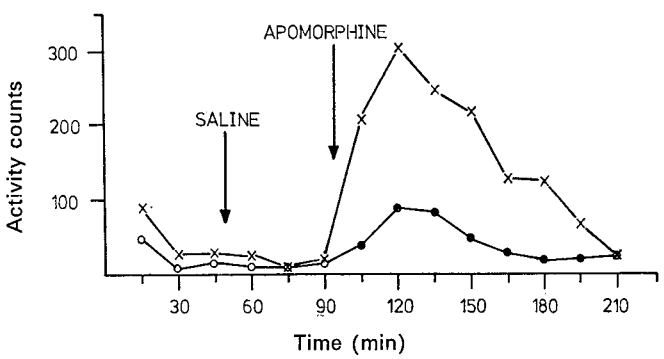

FIG. 2. The influence of fenfluramine (10·0 mg kg^{-1}, i.p.) on the stimulation of locomotor activity induced by apomorphine (5·0 mg kg^{-1}, s.c.). Fenfluramine was injected 2 h before the time 0. Solid circles indicate statistical significance (Wilcoxon two sample test). Each group consisted of 10 rats.

Table 1. *The influence of fenfluramine on the apomorphine-induced hypothermia in rats.*

Drug treatment mg kg^{-1}	Body temperature in °C ± s.e. Initial[A]	After apomorphine 15 min	30 min	45 min
Control	36·72 ± 0·11	37·15 ± 0·25	37·23 ± 0·21	37·25 ± 0·45
Apomorphine, 5·0[1] ..	37·09 ± 0·10	35·10 ± 0·25***	35·30 ± 0·28***	35·56 ± 0·23**
Fenfluramine, 10·0[2] + apomorphine, 5·0 ..	36·87 ± 0·10	36·35 ± 0·20**	36·25 ± 0·28*	36·38 ± 0·28*
Fenfluramine, 10·0[1] ..	36·88 ± 0·15	37·28 ± 0·29	37·38 ± 0·24	37·40 ± 0·26

[A] Initial temperature was mean body temperature calculated from three determinations made at 15 min intervals before apomorphine administration.
Statistical significance was evaluated with Student's *t*-test
[1] Significance in comparison with saline-treated group
[2] Significance in comparison with apomorphine-treated group

$^{*}P < 0.05$
$^{**}P < 0.01$
$^{***}P < 0.001$

locomotor activity, although decreased activity was seen in some rats as has previously been described (Boissier, Simon & others, 1965; Le Douarec & Neveu, 1970).

Fenfluramine 4 h before the test had no effect on body temperature but significantly moderated the apomorphine-induced hypothermia (Table 1).

These results show that fenfluramine attenuates those effects of apomorphine that result from the stimulation of dopamine receptors, i.e. stereotypy, locomotor stimulation and hypothermia. Similar anti-apomorphine effects have been described for neuroleptics (Grabowska & others, 1973; Janssen & others, 1967; Kruk, 1972; Maj & others, 1972; Thomas, 1970).

After higher doses of fenfluramine (20 mg kg^{-1}), we observed an initial period (2 h) of excitation and hyperirritability. Later the animals became quiet and after 5 h, two out of five rats showed full catalepsy, evaluated by the method of Delini-Stula & Morpurgo (1968).

Our results together with the anti-amphetamine effect of fenfluramine (Berger, Brown & Kranz, 1973; Bizzi, Bonaccorsi & others, 1970) suggest that fenfluramine may have a depressive effect on dopaminergic systems, but other modes of action of this compound (Costa, Groppetti & Revuelta, 1971; Le Douarec & Neveu, 1970) should not be disregarded.

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The effect of bronchodilators upon pulmonary resistance and compliance in the anaesthetized guinea-pig

Laboratory methods for the evaluation of bronchodilator drugs in animals almost invariably depend upon inhibition of an induced bronchospasm (Dixon & Brodie, 1903; Konzett & Rössler, 1940) and reflect changes in pulmonary compliance rather than resistance (Widdicombe, 1966). However, clinical assessments usually measure changes in ventilatory function such as forced expiratory volume, vital capacity or more recently, a change in pulmonary resistance (Comroe, 1965). This latter technique is the only clinical method directly applicable to laboratory animals. Pulmonary resistance and compliance changes have been used to show bronchoconstriction and bronchodilation in the conscious guinea-pig (Douglas, Dennis & others, 1972) but quantitative measurements of the actions of several bronchodilator drugs do not appear to have been made. Some such experiments are now reported.

Male albino guinea-pigs, 350–500 g, after overnight starving were anaesthetized by the intraperitoneal injection of allobarbitone (Dial, Ciba), 130 mg kg^{-1}, for pulmonary resistance and compliance measurement which required simultaneous and continuous recording of transpulmonary pressure, air flow and volume change. Transpulmonary pressure was determined by means of a differential pressure transducer connected to both an intrapleural and a tracheal cannula. Tracheal air flow was determined with the aid of a Fleisch tube and integration of this signal provided information on volume change (Daly, Farmer & Levy, 1971). Spontaneously respiring guinea-pigs were used since it was found that artificial ventilation obscured the bronchodilator response. Recordings were made until pulmonary resistance and compliance were constant. An infusion of test compound was then begun into the jugular vein and continued for 5 min. Two higher concentrations of drug were infused at 30 min intervals. Effects on pulmonary resistance and compliance were calculated as change from the starting level and as % of the maximum response obtainable to isoprenaline. The maximum response to isoprenaline, determined in a separate group of 10 animals, occurred with a total infused dose of 15 $\mu g\ kg^{-1}$. ED50 values were calculated (Table 1).

Relatively small but statistically significant changes (up to 30%) in pulmonary resistance and compliance were obtained. All the drugs tested were capable of achieving the same maximum response as isoprenaline while the doses used and relative activities are comparable with those of Carney, Daly & others (1971) for the guinea-pig tracheal chain and Konzett-Rössler preparations.

Because we have shown that some drugs cause similar changes in pulmonary compliance and resistance, techniques such as the Konzett-Rössler preparation (which depend on changes in compliance) may be thought of as satisfactory in the evaluation of bronchodilator drugs. However, there could be advantages when investigating novel drugs in using a method which distinguishes possible sites of