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Antagonism of fenfluramine-induced hyperthermia in rats by some, but not all, selective inhibitors of 5-hydroxytryptamine uptake

M.F. Sugrue[1]

Centre de Recherche Merrell International, 16, rue d'Ankara, Strasbourg, France

1 The injection of fenfluramine (7.5 mg kg^{-1}, i.p.) to rats housed at 27–28°C was associated with an elevation of core body temperature which peaked at approximately 1 h post-injection.

2 One h pretreatment with citalopram (20 mg kg^{-1}, i.p.), chlorimipramine (10 mg kg^{-1}, i.p.), femoxetine (10 mg kg^{-1}, i.p.) and fluoxetine (20 mg kg^{-1}, i.p.) resulted in an attenuated response to fenfluramine. In contrast, Org 6582 (20 mg kg^{-1}) and zimelidine (20 mg kg^{-1}) were devoid of an effect on fenfluramine-induced hyperthermia. The response to fenfluramine was also blocked by i.p. injections of metergoline (0.2 mg kg^{-1}), methysergide (5 mg kg^{-1}) and mianserin (0.5 mg kg^{-1}). Rectal temperature was unaltered by both the 5-hydroxytryptamine (5-HT) uptake inhibitors and the 5-HT receptor antagonists.

3 The IC_{50} values (nM) for *in vitro* inhibition of [^{3}H]-5-HT uptake into rat hypothalamic synaptosomes were for citalopram 2.4, chlorimipramine 8.8, femoxetine 14, fluoxetine 16, Org 6582 75 and zimelidine 250. The injection of all six compounds (20 mg kg^{-1}, i.p.) 1 h before death was associated with an inhibition of [^{3}H]-5-HT uptake into rat hypothalamic synaptosomes which ranged from 47.2% for chlorimipramine to 83.3% for citalopram.

4 Rat hypothalamic 5-HT levels were decreased by approximately 50% 3 h after the injection of fenfluramine (15 mg kg^{-1}, i.p.). This effect was blocked by a 1 h pretreatment with fluoxetine, Org 6582 and zimelidine (all 20 mg kg^{-1}, i.p.).

5 K_i values for displacement of specifically bound [^{3}H]-5-HT (1 nM) to rat hypothalamic membranes were for metergoline 26 nM, methysergide 1.1 μM, mianserin 3.6 μM, chlorimipramine 9.2 μM and fluoxetine 32.7 μM. Values for citalopram, femoxetine, Org 6582 and zimelidine were in excess of 65.4 μM.

6 Fenfluramine-induced hyperthermia in rats is blocked by citalopram, chlorimipramine, femoxetine and fluoxetine but not by Org 6582 and zimelidine. This dichotomy cannot be explained in terms of differences in 5-HT uptake, storage and release mechanisms in the rat hypothalamus. Moreover, antagonism of fenfluramine-induced hyperthermia cannot be attributed to blockade of central, postsynaptic 5-HT receptors. The involvement of an indoleamine other than 5-HT is discussed.

Introduction

The administration of fenfluramine to rats housed at 20°C has little effect on body temperature. In contrast, the drug elicits hyperthermia when rats are kept in an environment of 25–28°C (Frey, 1975; Sulpizio *et al.*, 1978). Fenfluramine-induced hyperthermia is attributed to the drug being accumulated by central 5-hydroxytryptamine (5-HT) nerve terminals followed by the subsequent release of the monoamine. The response is attenuated in rats which have been depleted of central 5-HT or have been pretreated with 5-HT receptor antagonists capable of penetrating into the brain. Further evidence that the effect is indirectly mediated is the fact that it is blunted by the prior administration of chlorimipramine (Sulpizio *et al.*, 1978). This action of chlorimipramine is attributed to its ability to block 5-HT re-uptake.

[1] Present address: Centre de Recherche, Laboratoires Merck Sharp & Dohme-Chibret, 63 203 Riom-Cédex, France.

Zimelidine, when compared to chlorimipramine, is comparable in potency and is a more specific inhibitor of 5-HT re-uptake (Ross *et al.*, 1976). However, in contrast to chlorimipramine, zimelidine pretreatment is unable to attenuate fenfluramine-induced hyperthermia (Pawlowski *et al.*, 1980). The objective of this study was to determine if this lack of effect was common to other selective inhibitors of 5-HT re-uptake. The compounds studied were chlorimipramine, citalopram, femoxetine, fluoxetine, Org 6582 ((±)-8-chloro-11-antiamino-benzo-(b)-bicyclo-3.3.1-nona-3, 6a-(10a)-diene) and zimelidine. In addition to their effect on fenfluramine-induced hyperthermia, the compounds were subjected to several neurochemical studies: these were *in vitro* and *ex vivo* blockade of hypothalamic synaptosomal [^{3}H]-5-HT uptake, affinity for hypothalamic 5-HT_1 recognition sites and antagonism of the ability of fenfluramine to decrease hypothalamic 5-HT content. Some of these results have been presented to the British Pharmacological Society (Sugrue, 1981).

Methods

Animals

Male Sprague-Dawley rats (180–220 g) were used in all experiments.

Fenfluramine-induced hyperthermia

Rats were placed in a warm room (27–28°C) for 1 h before commencing the experiment. Each experiment consisted of four groups of six rats. The groups were vehicle-treated, fenfluramine alone, drug under study alone and the drug combination. Fenfluramine, 7.5 mg kg^{-1}, was injected i.p. and rectal temperature was recorded by means of an Ellab TE-3 thermometer immediately before and 0.5, 1, 2.5 and 3.5 h after fenfluramine injection. The body temperature of rats receiving vehicle (saline) was also recorded at these times. Results are expressed as the difference (mean ± s.e.mean) between post- and pre-fenfluramine readings. Drugs under study were injected intraperitoneally 1 h before fenfluramine.

Monoamine uptake

The *in vitro* inhibition of [^{3}H]-5-HT uptake into a synaptosome rich fraction of rat hypothalamus was determined as described in detail elsewhere (Goodlet *et al.*, 1977). Briefly, tissue was homogenized in 19 volumes of 0.32 M sucrose and the resultant homogenate centrifuged at 1,000 *g* for 10 min at 4°C. A 0.1 ml aliquot of the suspension, amount of tissue present was equivalent to 5 mg of original tissue, was added to beakers containing 2 ml of Krebs-Bicarbonate buffer to which had been added ascorbic acid (11 μM), pargyline (19 μM) and the test drug. After a 10 min preincubation at 37°C under an atmosphere of 95% O_2 plus 5% CO_2, [^{3}H]-5-HT was added in a volume of 0.1 ml to yield a final concentration of 26 nM. Incubation was continued for a further 5 min and was stopped by adding 5 ml ice-cold saline and by standing the beakers in ice for 10 min. The homogenate was separated from the medium by filtration under vacuum. The filter discs were dissolved in 10 ml of Filtersolv and samples were counted in a Beckman liquid scintillation counter with a counting efficiency of 55% for tritium. Incubations were carried out in the presence of four concentrations of the test drug, control at 37°C and control at 0°C. Each incubation was performed in quadruplicate. The concentration of [^{3}H]-5-HT taken up was calculated in terms of d.p.m. g^{-1} original tissue divided by d.p.m. ml^{-1} medium, correction having been made for diffusion at 0°C. The control tissue : medium ratio was approximately twenty. % inhibition of uptake was calculated for each concentration of drug tested and the molar concentration of drug required to inhibit uptake by 50% (IC_{50}) was obtained from log concentration/% inhibition regression curves constructed by the method of least squares.

Ex vivo uptake experiments were essentially conducted in a similar manner. Hypothalamic tissue was homogenized in 9 volumes of 0.32 M sucrose, 0.1 ml of supernatant was added to 0.95 ml buffer and [^{3}H]-5-HT was added in a volume of 50 μl after the preincubation. Results are expressed as % inhibition of uptake and each result is the mean of at least four determinations.

Ligand receptor binding

The method used was essentially that of Bennett & Snyder (1976). Hypothalamic tissue was homogenized in 40 volumes of 0.05 M Tris-HCl buffer, pH 7.4, and was centrifuged at 50,000 *g* for 10 min. The pellet was washed once by resuspension in cold Tris-HCl. The washed pellet was suspended in 100 volumes of Tris-HCl containing 0.1% ascorbic acid and 4 mM $CaCl_2$ and incubated at 37°C for 10 min to destroy endogenous 5-HT. A 2 ml aliquot of suspension, 20 mg of original tissue content, was transferred to each incubation tube followed by the addition of 10 μM pargyline before the inclusion of [^{3}H]-5-HT. Incubation lasted 10 min at 37°C. Assays were performed in sextuplicate with half the tubes containing 10 μM 5-HT. Specific binding was the difference in binding in the absence and in the presence of 5-HT and at a ligand concentration of 1 nM accounted for approximately 60% of total radioligand bound. The

radioligand concentrations used for saturation curves ranged from 0.5 to 20 nM. Drugs were studied at five concentrations and IC_{50} values were determined by log-probit analysis of the % displacement of specifically bound ligand. K_i values were determined using the equation $K_i = IC_{50}/(1 + C/K_d)$ (Cheng & Prusoff, 1973) where C is ligand concentration and the K_d value from saturation experiments was 1.9 nM.

Hypothalamic concentrations of 5-HT

Tissue levels of 5-HT were determined using the method of Earley & Leonard (1978). 5-HT was extracted using Sephadex G-10 columns and assayed spectrophotofluorometrically. Results are expressed as ng g^{-1} wet tissue and are corrected to 100% recovery based on concurrently run internal standards. Each result is the mean of at least four determinations.

Statistics

Statistical differences were determined using Student's *t* test (2-tailed).

Drugs

The following drugs were dissolved in saline (0.9% w/v NaCl): chlorimipramine HCl (Ciba-Geigy), citalopram HCl (Lundbeck), femoxetine HCl (Ferrosan), (±)-fenfluramine HCl (Servier), fluoxetine HCl (Lilly), methysergide bimaleate (Sandoz) and zimelidine HCl (Astra). Mianserin HCl and Org 6582 HCl (both Organon) were dissolved in distilled water. Metergoline (Farmitalia) was dissolved in distilled water containing ascorbic acid (10 mg ml^{-1}). Doses refer to the free base.

Results

Fenfluramine-induced hyperthermia

On the basis of preliminary experiments a dose of 7.5 mg kg^{-1} was used since the i.p. injection of this dose of fenfluramine to rats housed at 27–28°C elicited a reproducible elevation in body temperature which was invariably greater than 1°C. Gross behaviour was not affected by this dose. The temperature increase following fenfluramine administration peaked between 1 and 2 h and a 1 h time interval was selected for expression of results, although in all experiments temperature was recorded up to 3.5 h post-fenfluramine administration. Rectal temperature was unaltered by the injection of 5-HT uptake inhibitors or 5-HT receptor antagonists and for the sake of clarity this data is omitted from the text.

Table 1 Antagonism of fenfluramine-induced hyperthermia

Drug	Dose (mg kg^{-1})	Rectal temperature increase (°C) Fenfluramine	Combination
Citalopram	20	1.32±0.20	0.48±0.11**
Chlorimipramine	10	1.19±0.18	0.34±0.17**
Femoxetine	10	1.42±0.05	0.75±0.14**
Fluoxetine	20	1.38±0.22	0.68±0.16**
Org 6582	20	1.35±0.18	1.45±0.21
Zimelidine	20	1.18±0.16	1.01±0.14
Metergoline	0.2	0.93±0.21	0.04±0.03**
Methysergide	5	1.42±0.05	0.73±0.14**
Mianserin	0.5	0.93±0.21	0.34±0.11*

Rats were placed in a warm room (27–28°C) for 1 h before the start of the experiment. Drugs were injected i.p. 1 h before fenfluramine (7.5 mg kg^{-1}). Rectal temperature was measured immediately before and 1 h after fenfluramine administration. Results are expressed as the difference in rectal temperature and each result is the mean ± s.e.mean of 6 experiments. Different from fenfluramine: * $P < 0.05$, ** $P < 0.01$.

The effects of a 1 h pretreatment with the selected 5-HT uptake inhibitors are shown in Table 1. Fenfluramine-induced hyperthermia was attenuated by pretreatment with chlorimipramine (10 mg kg^{-1}), femoxetine (10 mg kg^{-1}), citalopram (20 mg kg^{-1}) and fluoxetine (20 mg kg^{-1}). The antagonism elicited by lower doses of these drugs was not statistically significant (data not shown). In contrast to these agents, both Org 6582 and zimelidine (20 mg kg^{-1}) were ineffective. Higher doses were not tested since 5-HT re-uptake is blocked by both compounds at this dose (see Discussion). For comparative purposes, the 5-HT receptor antagonists metergoline, methysergide and mianserin were studied. The minimum doses required for statistically significant antagonism were for metergoline, 0.2 mg kg^{-1}, methysergide, 5 mg kg^{-1} and mianserin, 0.5 mg kg^{-1}.

[^{3}H]-5-HT uptake

The *in vitro* uptake of [^{3}H]-5-HT into rat hypothalamic synaptosomes was inhibited by all six compounds studied (Table 2). The most potent inhibitor (IC_{50} in nM in brackets) was citalopram (2.4) followed by chlorimipramine (8.8), femoxetine (14), fluoxetine (16), Org 6582 (75) and zimelidine (250). The injection of all six compounds at a dose of 20 mg kg^{-1} (i.p.) 1 h before death was associated with an inhibition of [^{3}H]-5-HT uptake into rat hypothalamic synaptosomes which ranged from 47.2% for chlorimipramine to 83.3% for citalopram (Table 2).

Table 2 Inhibition of the uptake of [^{3}H]-5-HT into rat hypothalamic synaptosomes

Drug	In vitro *IC50* (nM)	Ex vivo *% inhibition of uptake (mean ± s.e.mean)*
Citalopram	2.4	83.3 ± 0.7
Chlorimipramine	8.8	47.2 ± 0.9
Femoxetine	14	69.7 ± 0.5
Fluoxetine	16	70.2 ± 1.3
Org 6582	75	79.8 ± 0.6
Zimelidine	250	67.0 ± 0.5

Rat hypothalamic synaptosomes were preincubated at 37°C for 10 min then [^{3}H]-5-HT (final concentration 26 nM) was added and the incubation continued for 5 min. For *in vitro* studies, drugs were added at the start of the 10 min preincubation. IC_{50} values were obtained from log concentration/% inhibition regression curves constructed by the method of least squares. Four drug concentrations were studied in quadruplicate. For *ex vivo* studies, drugs (20 mg kg^{-1}) were injected i.p. 1 h before death. Results are expressed as % inhibition of uptake and each result is the mean ± s.e.mean of 4 experiments.

[^{3}H]-5-HT binding studies

Scatchard analysis of [^{3}H]-5-HT binding to rat hypothalamic membranes was undertaken using six concentrations of ligand which ranged from 0.5 to 20 nM and revealed the presence of a single binding component. K_d and B_{max} values were 1.9 nM and 24.2 pmol g^{-1} tissue, respectively. Drug affinities obtained from displacement curves are listed in Table 3. The K_i value for 5-HT (1.3 nM) is close to the K_d. Metergoline was the only compound studied to possess a K_i less than 1 μM. K_i values of 9.2 and 32.7 μM were obtained for chlorimipramine and fluoxetine respectively. K_i values for femoxetine, citalopram, Org 6582 and zimelidine were in excess of 65.4 μM, i.e. the IC_{50} value was greater than 0.1 mM.

Table 3 Affinities of different drugs for rat hypothalamic [^{3}H]-5-HT binding sites

Drug	K_i (nM)
5-Hydroxytryptamine	1.3
Metergoline	26
Methysergide	1100
Mianserin	3600
Chlorimipramine	9200
Fluoxetine	32700
Citalopram	>65400
Femoxetine	>65400
Org 6582	>65400
Zimelidine	>65400

K_i values were determined using the equation $K_i = IC_{50}/(1 + C/K_d)$ were C is ligand concentration (1 nM) and the K_d obtained from saturation experiments is 1.9 nM. The IC_{50} value was determined by log/probit analysis of the % displacement of specifically bound ligand by five different concentrations in triplicate of each drug.

Table 4 Effect of various treatments on fenfluramine-induced depletion of rat hypothalamic 5-HT content

Treatment	*5-HT levels* (ng g^{-1})
Vehicle	905 ± 18
Fenfluramine	420 ± 13**
Fluoxetine	928 ± 22
Fluoxetine + fenfluramine	919 ± 31†
Org 6582	820 ± 62
Org 6582 + fenfluramine	786 ± 26†
Zimelidine	1091 ± 17*
Zimelidine + fenfluramine	1029 ± 5†

Drugs (20 mg kg^{-1}) were injected i.p. 30 min before fenfluramine (15 mg kg^{-1}) or 3.5 h before death. Rats were killed 3 h after fenfluramine injection. Hypothalamic 5-HT levels are expressed as ng g^{-1} tissue and each result is the mean ± s.e.mean of at least 4 experiments.
Different from vehicle-treated: * $P < 0.01$; ** $P < 0.001$
Different from fenfluramine-treated: † $P < 0.001$.

Depletion of hypothalamic 5-HT

For these experiments the dose of fenfluramine was increased to 15 mg kg^{-1} since this dose was necessary to achieve a significant and reproducible reduction in hypothalamic 5-HT content. Levels were approximately halved at 3 h after the injection of this dose (Table 4). 5-HT uptake blockers, all at 20 mg kg^{-1}, were injected i.p. 0.5 h before the administration of fenfluramine. All drugs profoundly blocked the fenfluramine-induced decrease in 5-HT levels. Hypothalamic steady-state levels of 5-HT were significantly increased 3.5 h after the injection of zimelidine. Levels were unaltered by Org 6582 and fluoxetine.

Discussion

The results of this study confirm the ineffectiveness of zimelidine at attenuating the ability of fenfluramine to raise the core temperature of rats housed in a warm environment (Pawlowski *et al.*,

1980) and reveal that Org 6582 is also devoid of this effect. In contrast, fenfluramine-induced hyperthermia is antagonized by the administration of citalopram, chlorimipramine, femoxetine and fluoxetine. These conclusions have been published in abstract form (Sugrue, 1981) and at approximately the same time Pawlowski (1981) independently reported on the ineffectiveness of Org 6582. This difference between the 5-HT uptake inhibitors was somewhat unexpected since in previous experiments it had been demonstrated that morphine-induced antinociception in rats is potentiated by citalopram, femoxetine, fluoxetine, Org 6582 and zimelidine and this was attributed to the ability of the drugs to block 5-HT re-uptake (Sugrue & McIndewar, 1976; Sugrue, 1979). There is strong evidence indicating that the hyperthermic response to fenfluramine is dependent upon the ability of the drug to release 5-HT from central nerve terminals (see Introduction). To achieve this it is generally accepted that fenfluramine gains access to 5-HT storage mechanisms by means of the so-called membrane amine pump mechanism. The observation that some, but not all, inhibitors of 5-HT re-uptake attenuate the response to fenfluramine is puzzling and a number of neurochemical experiments were undertaken in an attempt to resolve this dilemma.

All the drugs are potent inhibitors of the uptake of [^{3}H]-5-HT into rat hypothalamic synaptosomes, the IC_{50} values for citalopram, chlorimipramine, femoxetine and fluoxetine being less than 20 nM. At first sight it is of interest to note that Org 6582 and zimelidine are the least potent at blocking [^{3}H]-5-HT uptake and that these two agents failed to attenuate fenfluramine-induced hyperthermia. However, to invoke this as an explanation is untenable for several reasons. Firstly, zimelidine is demethylated *in vivo* to norzimelidine and it is this substance which accounts for 5-HT uptake inhibition *in vivo* (Ross & Renyi, 1977). Secondly, Org 6582 is an extremely effective inhibitor of 5-HT re-uptake *in vivo* (Sugrue *et al.*, 1976; 1978) and the lack of correlation between its ability to block 5-HT uptake *in vivo* and *in vitro* has been the subject of previous discussion (Sugrue *et al.*, 1976). Thirdly, the i.p. injection of 20 mg kg^{-1} of both Org 6582 and zimelidine markedly blocks the uptake of [^{3}H]-5-HT into rat hypothalamic synaptosomes, both agents possessing comparable activity to compounds which attenuate the fenfluramine-induced increase in body temperature. This result clearly demonstrates that the difference between the compounds in this experimental model cannot be attributed to a marked difference in their ability to block the hypothalamic 5-HT neuronal membrane carrier mechanism. Moreover, it is to be noted that chlorimipramine is the most effective of the uptake inhibitors studied at antagonizing fenfluramine-induced hyperthermia and yet it is the weakest inhibitor of [^{3}H]-5-HT uptake *ex vivo*.

Fenfluramine, in order to elicit hyperthermia, releases 5-HT from central stores. The possibility that Org 6582 and zimelidine prevent this action of the drug was investigated by studying their effect on the ability of fenfluramine to reduce hypothalamic 5-HT levels. Tissue content of 5-HT is decreased by approximately 50% 3 h after the i.p. injection of 15 mg kg^{-1} fenfluramine. This action of fenfluramine is markedly blocked by pretreatment with either Org 6582 or zimelidine, both 20 mg kg^{-1} i.p. Fluoxetine (20 mg kg^{-1}, i.p.) was also studied since it antagonizes fenfluramine-induced hyperthermia and a block of 5-HT depletion was also observed.

The inability of both Org 6582 and zimelidine to attenuate the elevation in core temperature elicited by fenfluramine cannot be rationalized on the basis of observed differences in effects on central presynaptic 5-HT nerve terminals. Blockade of postsynaptic 5-HT receptors is not a property unknown to 5-HT uptake inhibitors. For example, an antagonistic effect has been demonstrated for amitriptyline (Fuxe *et al.*, 1977; Tang & Seeman, 1980). Moreover, the temperature response to fenfluramine is blocked by metergoline, methysergide and mianserin. The affinity of the 5-HT uptake blockers for postsynaptic 5-HT receptors in the rat hypothalamus was assessed by determining their ability to displace [^{3}H]-5-HT binding. Metergoline, methysergide and mianserin were included for comparative purposes. Metergoline is the most potent displacer having a K_i of 26 nM. The K_i values for methysergide and mianserin are in the μM range. Of the uptake blockers studied, only chlorimipramine and fluoxetine possess a K_i of less than 65.4 μM. Both citalopram and femoxetine antagonize fenfluramine-induced hyperthermia yet both drugs have negligible affinity for 5-HT_1 binding sites. Radioligand binding studies indicate the heterogeneity of central postsynaptic 5-HT binding sites. Differential drug potencies in competing for [^{3}H]-5-HT and [^{3}H]-spiroperidol binding sites in rat cortical tissue suggest that the two radioligands label two distinct populations of recognition sites. The [^{3}H]-5-HT and [^{3}H]-spiroperidol binding sites have been termed 5-HT_1 and 5-HT_2 receptors respectively (Peroutka & Snyder, 1979; Seeman *et al.*, 1980). 5-HT_1 and 5-HT_2 binding sites are present in rat hypothalamus with the former being more abundant (Peroutka & Snyder, 1981; Leysen *et al.*, 1982). In general, agonists display higher affinities for 5-HT_1 while antagonists prefer 5-HT_2 sites (Peroutka *et al.*, 1981). The affinities of citalopram (Dumbrille-Ross *et al.*, 1981; Hyttel, 1982; Leysen *et al.*, 1982), fluoxetine (Peroutka & Snyder, 1980; Dumbrille-Ross *et al.*, 1981) and zimelidine (Hall & Ogren, 1981; Fuxe *et al.*, 1982) for rat cortical 5-HT_2 bind-

ing sites range from weak (i.e. μM range) to negligible (i.e. 100 μM range). Moreover, the affinity of chlorimipramine for 5-HT_2 recognition sites is appreciably greater than that of citalopram (Leysen *et al.*, 1982) or fluoxetine (Stolz *et al.*, 1983) and these differences are not manifested in the ability of the three drugs to attenuate fenfluramine-induced hyperthermia. Hence it would appear valid to conclude that the ability of certain 5-HT uptake blockers to antagonize fenfluramine-induced hyperthermia is not mediated by an antagonistic action on central 5-HT_1 and/or 5-HT_2 receptors. Germane to this concept is the total inability of citalopram to block responses in the rat which are considered to be indicative of central postsynaptic 5-HT receptor activation (Pawlowski *et al.*, 1981).

Of interest is the observation that zimelidine blocks the uptake of 5-HT, but not tryptamine, by rat cortical slices. In contrast, the uptake of both substances is blocked by fluoxetine (Jones & Broadbent, 1982). It is to be recalled that fluoxetine, but not zimelidine, antagonizes fenfluramine-induced hyperthermia. Intrahypothalamic injection of tryptamine raises the core temperature of rats and this effect is blocked both by the prior administration of 5-HT receptor antagonists and by the depletion of central 5-HT stores (Cox *et al.*, 1981). Both these procedures antagonize the response to fenfluramine and an intriguing possibility is the involvement of tryptamine in the hyperthermic response to fenfluramine. It is also to be noted that methergoline is a much more effective antagonist of tryptamine- than 5-HT-induced hyperthermia (Cox *et al.*, 1981) and that the drug is extremely effective in attenuating fenfluramine-induced hyperthermia. While the hypothesis implicating tryptamine is obviously speculative, there are strands of evidence in its favour.

In summary, the selective 5-HT uptake inhibitors Org 6582 and zimelidine do not share with chlorimipramine, citalopram, femoxetine and fluoxetine the ability to attenuate the rise in core temperature following the administration of fenfluramine to rats housed in a warm environment. All compounds are potent inhibitors of [^{3}H]-5-HT uptake and both Org 6582 and zimelidine prevent the fenfluramine-induced reduction in rat hypothalamic 5-HT content. Hence the qualitative difference between the uptake inhibitors cannot be attributed to differing actions on 5-HT uptake, storage and release mechanisms in the rat hypothalamus. Blockade of central postsynaptic 5-HT receptors is a most unlikely explanation for the attenuated response to fenfluramine in light of the very low affinities of the drugs for these binding sites. The possible involvement of an indoleamine other than 5-HT is discussed.

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