phospholipase pathway (DPPD, SDDC). Thus, these three antioxidants could act to reduce peroxide levels and inhibit PGE synthesis by different mechanisms. It is possible that the differences may be related to differing modes of antioxidative action depending on the type of antioxidants.

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Amitriptyline and femoxetine, but not clomipramine or citalopram, antagonize hyperthermia induced by directly acting 5-hydroxytryptamine-like drugs in heat adapted rats

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5-HT uptake inhibitors and pirenperone (a 5-HT_2 receptor antagonist), which in previous experiments antagonized fenfluramine (5-HT releaser)-induced hyperthermia in heat adapted rats, were tested against hyperthermia induced by the directly acting 5-HT agonist—*m*-CPP and quipazine. Pirenperone and—to a lesser degree—amitriptyline and femoxetine antagonized the hyperthermia. Citalopram and clomipramine were inactive. It is concluded that hyperthermia induced by 5-HT-like drugs in rats is due to the stimulation of the 5-HT_2 receptor and that the antagonistic effect of citalopram and clomipramine against fenfluramine-induced hyperthermia might be connected with their effect on the uptake of 5-HT.

5-Hydroxytryptamine (5-HT) uptake inhibitors, amitriptyline, clomipramine, femoxetine and citalopram, prevent hyperthermia induced by the 5-HT releasing agent, fenfluramine, in rats housed at 26–28 °C (Frey 1975; Sulpizio et al 1978; Pawłowski 1981; Sugrue 1981; Maj et al 1982). This hyperthermia is central in origin and has been proved to be mediated by 5-HT (Sulpizio et al 1978). Therefore, the above fact is in agreement with the view that 5-HT uptake inhibitors can block the entrance of fenfluramine into the 5-HT-ergic neurons (via inactivation of the neuronal membrane carrier system) and in this way prevent the pharmacological action of this drug (Ghezzi et al 1973; Frey 1975; Sulpizio et al 1978). However, there is a poor correlation between degree of the inhibition of the 5-HT uptake and the protection against the fenfluramine-induced hyperthermia for the 5-HT uptake inhibitors (Sugrue 1981; Maj et al 1982). Moreover, some potent 5-HT uptake inhibitors (e.g. zimelidine and Org 6582) do not prevent fenfluramine-induced hyperthermia (Pawłowski et al 1980; Pawłowski 1981; Sugrue 1981). Therefore, it could be suggested that the antagonistic action of amitriptyline, clomipramine, femoxetine and citalopram is due to a mechanism different from 5-HT uptake inhibition, i.e. the blockade of the carrier system for 5-HT and fenfluramine. Indeed, the anti-5-HT action of amitriptyline has been observed in many other pharmacological tests (Fuxe et al 1977; Maj et al 1979; Kwiatek et al 1980; Hall & Ögren 1981), and femoxetine can antagonize the 5-HT receptor in the blood vessels (Petersen et al 1979). So far, the central anti-5-HT action of clomipramine cannot be excluded (Hall & Ögren 1981) and only citalopram has never been suggested to possess central or peripheral anti-5-HT properties (Hyttel 1982). In this context, it seemed interesting to investigate the effects of amitriptyline, clomipramine, femoxetine and citalopram upon the hyperthermia induced by the directly acting 5-HT-mimetics, 1-(m-chlorophenyl)-piperazine (m-CPP) and quipazine (Maj & Lewandowska 1980). Pirenperone dihydrochloride (R 50 656), a new potent 5-HT (5-HT_2) receptor blocking agent (Colpaert & Leysen 1981; Colpaert et al 1982; Krstić & Katušić 1982; Leysen et al 1982), which in the preliminary experiments (Pawłowski, to be published), in low doses

(0·00625–0·4 mg kg^{-1}), dose-dependently counteracted the hyperthermia induced by 5-HT releasers (fenfluramine, *p*-chloroamphetamine), served as a reference compound.

Methods

The experiments were on male Wistar rats (175–225 g) having had free access to food and water until the beginning of the experiment. Before the experiment, the rats were adapted for 2 h to the conditions (temp. 28 ± 1 °C, humidity 40–45%). The oesophageal body temperature was measured with an Ellab T-3 thermometer. The inhibitors of the 5-HT uptake and pirenperone were administered 1 h before m-CPP or quipazine. Exceptionally, in an additional experiment (Table 3), the 5-HT uptake inhibitors, amitriptyline and femoxetine were given 30 min before quipazine. Each group consisted of 6–12 rats. The statistical evaluation was performed using Student's *t*-test.

Drugs given were: amitriptyline hydrochloride (Polfa), citalopram hydrobromide (Lundbeck), clomipramine hydrochloride (Ciba-Geigy), femoxetine hydrochloride (Ferrosan), 1-(*m*-chlorophenyl)-piperazine hydrochloride (*m*-CPP) (Angelini Francesco), pirenperone (R 47 465) dihydrochloride (R 50 656, Janssen Pharmaceutica), quipazine maleate (Miles Laboratories). Doses refer to the salts given. Drugs were dissolved in 0·9% NaCl (saline) and injected i.p. (5-HT uptake inhibitors, 5-HT agonists) in a volume of 4 ml kg^{-1} or s.c. (pirenperone) in a volume of 2 ml kg^{-1}.

Table 1. Effect of selective inhibitors of the 5-HT uptake and pirenperone (given 1 h before) upon 1-(*m*-chlorophenyl)-piperazine (*m*-CPP)-induced hyperthermia in rats kept at the ambient temperature of 28 ± 1 °C.

Treatment (mg kg^{-1})	Change from baseline oesophageal temperature at time (min) after challenge (°C ± s.e.m.)				
	30	60	90	120	150
Saline	0·2 ± 0·09	0·2 ± 0·08	0·2 ± 0·09	0·2 ± 0·12	0·3 ± 0·08
m-CPP (5)	1·4 ± 0·22	1·5 ± 0·23	1·5 ± 0·29	1·2 ± 0·25	0·8 ± 0·25
Amitriptyline (5) + *m*-CPP (5)	1·0 ± 0·21	0·9 ± 0·19	0·9 ± 0·24	0·8 ± 0·25	0·6 ± 0·23
Amitriptyline (10) + *m*-CPP (5)	0·4 ± 0·05***	0·5 ± 0·10**	0·5 ± 0·10**	0·6 ± 0·15	0·4 ± 0·18
Citalopram (20) + *m*-CPP (5)	1·1 ± 0·06	1·3 ± 0·06	1·4 ± 0·15	1·5 ± 0·21	1·4 ± 0·27
Clomipramine (20) + *m*-CPP (5)	1·5 ± 0·21	1·5 ± 0·20	1·4 ± 0·26	1·1 ± 0·35	0·9 ± 0·35
Femoxetine (10) + *m*-CPP (5)	1·1 ± 0·12	1·4 ± 0·20	1·3 ± 0·22	1·2 ± 0·17	0·9 ± 0·20
Femoxetine (20) + *m*-CPP (5)	0·5 ± 0·20**	0·6 ± 0·23*	0·7 ± 0·24	0·7 ± 0·18	0·7 ± 0·19
Pirenperone (0·1) + *m*-CPP (5)	0·4 ± 0·25*	0·4 ± 0·19**	0·3 ± 0·20**	0·2 ± 0·12**	0·2 ± 0·13*

Each experimental group consisted of 6 rats.
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$ (difference from group receiving *m*-CPP alone; Student's *t*-test).

Results and discussion

The 5-HT uptake inhibitors (used in doses ranging from 5–20 mg kg^{-1}) and pirenperone (0·025–0·4 mg kg^{-1}) did not change the basal body temperature of rats kept at 28 °C (data not shown).

Of the 5-HT uptake inhibitors only amitriptyline (10 mg kg^{-1}) and femoxetine (20 mg kg^{-1}) attenuated the hyperthermia induced by *m*-CPP (Table 1) and quipazine (Tables 2, 3). Their action was, therefore, similar—although much weaker—to that exerted by the 5-HT$_2$ (but not 5-HT$_1$) receptor antagonist, pirenperone (Colpaert & Leysen 1981; Colpaert et al 1982; Krstić & Katušić 1982; Leysen et al 1982), which at a dose of 0·1 mg kg^{-1} completely abolished the *m*-CPP- and quipazine-induced hyperthermia (Tables 1, 2). These findings suggest that the hyperthermia induced by 5-HT agonists in rats is due to the stimulation of the 5-HT$_2$ receptors (and not 5-HT$_1$ receptors) and that amitriptyline and femoxetine can be regarded as weak antagonists of the 5-HT$_2$ receptors. Indeed, amitriptyline and femoxetine, as well as pirenperone, have already been reported to antagonize the cardiovascular responses to 5-HT (Petersen et al 1979; Kwiatek et al 1980; Krstić & Katušić 1982), which—according to the most recent data—are mediated exclusively via stimulation of the 5-HT$_2$ receptors (Van Nueten et al 1982). It is also worth noting that cyproheptadine, a known antagonist of 5-HT receptors, which strongly inhibits the hyperthermia induced by fenfluramine, *p*-chloroamphetamine, *m*-CPP and quipazine (Frey 1975; Sulpizio et al 1978; Maj & Lewandowska 1980) as well as the cardiovascular responses to 5-HT (Kwiatek et al 1980; Krstić & Katušić 1982), has recently been identified as a blocker of mainly 5-HT$_2$ receptors while it has only a

Table 2. Effect of selective inhibitors of the 5-HT uptake and pirenperone (given 1 h before) upon quipazine-induced hyperthermia in rats kept at the ambient temperature of 28 ± 1 °C.

Treatment (mg kg^{-1})	Change from baseline oesophageal temperature at time (min) after challenge (°C ± s.e.m.)				
	30	60	90	120	150
Saline	0·1 ± 0·10	0·3 ± 0·11	0·2 ± 0·09	0·1 ± 0·07	0·2 ± 0·10
Quipazine (5)	1·9 ± 0·22	2·3 ± 0·19	2·4 ± 0·17	2·4 ± 0·21	1·9 ± 0·28
Amitriptyline (5) + quipazine (5)	1·4 ± 0·24	2·2 ± 0·18	2·1 ± 0·11	2·0 ± 0·11	1·6 ± 0·15
Amitriptyline (10) + quipazine (5)	1·3 ± 0·17*	1·7 ± 0·15*	1·6 ± 0·16*	1·6 ± 0·19*	1·3 ± 0·19
Citalopram (20) + quipazine (5)	1·8 ± 0·16	2·3 ± 0·18	2·2 ± 0·16	2·5 ± 0·19	2·7 ± 0·28
Clomipramine (20) + quipazine (5)	2·0 ± 0·21	2·5 ± 0·22	2·7 ± 0·28	2·6 ± 0·23	2·3 ± 0·23
Femoxetine (20) + quipazine (5)	1·2 ± 0·20*	1·8 ± 0·21	2·0 ± 0·14	2·0 ± 0·14	1·7 ± 0·22
Pirenperone (0·1) + quipazine (5)	0·2 ± 0·20***	0·4 ± 0·19***	0·5 ± 0·19***	0·4 ± 0·20***	0·2 ± 0·14***

Each experimental group consisted of 12 rats.
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$ (difference from group receiving quipazine alone; Student's *t*-test.

Table 3. The effect of amitriptyline and femoxetine (given 30 min before) upon quipazine-induced hyperthermia in rats kept at the ambient temperature of 28 ± 1 °C.

Treatment (mg kg^{-1})	Change from baseline oesophageal temperature at time (min) after challenge (°C ± s.e.m.)				
	30	60	90	120	150
Saline	0·2 ± 0·17	0·4 ± 0·19	0·3 ± 0·19	0·2 ± 0·18	0·2 ± 0·16
Quipazine (5)	1·8 ± 0·19	2·5 ± 0·18	2·4 ± 0·08	2·2 ± 0·14	2·0 ± 0·24
Amitriptyline (10) + quipazine (5)	1·5 ± 0·19	1·8 ± 0·19*	1·8 ± 0·20*	1·5 ± 0·21**	1·3 ± 0·23
Femoxetine (20) + quipazine (5)	1·4 ± 0·11	1·8 ± 0·18*	1·9 ± 0·14*	1·8 ± 0·15	1·6 ± 0·17

Each experimental group consisted of 6 rats.
*$P < 0.05$; **$P < 0.01$ (difference from group receiving quipazine alone; Student's t-test).

weak effect on 5-HT$_1$ receptors (Peroutka et al 1981).

Clomipramine (20 mg kg^{-1}) and citalopram (20 mg kg^{-1}), used in the dose in which they are potent antagonists of the hyperthermia induced by the 5-HT releasers, fenfluramine and *p*-chloroamphetamine (Pawłowski 1981), did not affect at all the hyperthermia induced by the directly acting 5-HT-mimetics (Tables 1, 2). This excludes the possibility of their blocking action on the 5-HT receptors, at least those whose stimulation produces hyperthermia in rats kept at 28 °C.

The results obtained in this study indicate that the antagonistic effect of—at least—clomipramine and citalopram towards the fenfluramine-induced hyperthermia (Frey 1975; Sulpizio et al 1978; Pawłowski 1981; Sugrue 1981) cannot be explained by their blocking action on the central 5-HT (5-HT$_2$) receptors. Therefore, it should be concluded that the antagonistic action of these drugs is connected somehow with their ability to inhibit the uptake of 5-HT. Why zimelidine and Org 6582 do not prevent the hyperthermia induced by fenfluramine (Pawłowski et al 1980; Pawłowski 1981; Sugrue 1981) remains to be elucidated.

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