Effect of Zotepine on Fenfluramine-Induced Hyperthermia in Rats

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Zotepine, 2-chloro-11-(2-dimethyl-amino-ethoxy)dibenzo [b, f]thiepin, is a new neuroleptic structurally different from known neuroleptics. The drug is reported to have potent and broad effects in clinical use. The drug is characterized by almost the same anti-hallucinatory effect as haloperidol, fewer extrapyramidal symptoms than known neuroleptics, and unlike chlorpromazine, the absence of overdepression of consciousness (1-3). In animal models, zotepine is also reported to have a potent anti-serotonergic as well as anti-dopaminergic activity (4, 5).

Fenfluramine is known to induce hyperthermia in rats by mediation of central serotonin in a warm environment (25-28°C) (5-9). In the present study, rats with fenfluramine-induced hyperthermia were used to investigate the anti-serotonergic activity of zotepine, and it was compared with clozapine, spiroperidol and oxypertine which are reported to have potent anti-serotonergic activity rather than anti-dopaminergic activity (9-11).

Male Sprague-Dawley rats, weighing 158-226 g, were used in groups of five to ten animals. All experiments were performed at an ambient temperature of 26-28°C. Rats were housed five per cage and placed in a warm room at least 1 hr before the test. Rectal temperature was measured using a thermometer (Thermo-Finer TF-DN, Terumo) 1, 2 and 3 hr after dosing with the drugs. In the case of fenfluramine (13 mg/kg)-induced hyperthermia, the drugs were given 1 hr before dosing with fenfluramine, and the rectal temperature was measured 1 and 2 hr thereafter.

Drugs used were zotepine (Fujisawa), clozapine, fenfluramine hydrochloride (synthesized in our research laboratories), spiro-

peridol (Spiropitan® for injection, Eisai) and oxypertine (extracted from Forit®, Daiichi). Zotepine and clozapine were dissolved in an equivalent amount of 1N hydrochloric acid. Spiroperidol was diluted with saline, and oxypertine was suspended in 0.5% methylcellulose-saline solution. Fenfluramine was dissolved in saline. The test drugs were given p.o. and fenfluramine was given i.p. ED₅₀ values were calculated according to the method of Litchfield-Wilcoxon, and statistical significance was analyzed by Student's *t*-test or the Cochran-Cox method.

Fenfluramine induced hyperthermia in a range of 1.02-1.64 and 1.47-2.32°C, 1 and 2 hr after injection, respectively. Zotepine in doses of 0.032 mg/kg and more significantly inhibited the fenfluramine-induced hyperthermia. Clozapine significantly inhibited the hyperthermia in a dose of 1.0 mg/kg. Spiroperidol and oxypertine also showed inhibitory effects in doses of 1.0 mg/kg and more and 32 mg/kg, respectively. On the basis of the ED₅₀, zotepine was at least 20 times more potent than clozapine, spiroperidol and oxypertine as shown in Table 1, the rank in order of activity being zotepine >> spiroperidol ≈ clozapine > oxypertine.

The effects of the drugs on the rectal temperature of intact rats was tested to determine whether the drugs inhibited hyperthermia, and especially whether they antagonized the effect of fenfluramine, as shown in Table 2. Zotepine, clozapine and spiroperidol had no effect on rectal temperature in the doses used. On the other hand, the effect of oxypertine was non-specific. In any case, zotepine had a more potent anti-serotonergic activity than clozapine, spiroperidol or oxypertine which are reported

Table 1. Effects of the drugs on fenfluramine-induced hyperthermia in rats

Drug	N*	ED50 (mg/kg, p.o.), (95% confidence limit)	
		60 min	120 min
Zotepine	10	0.078 (0.039–0.157)	0.065 (0.025–0.172)
Clozapine	5	3.14 (1.49–6.63)	2.69 (1.30–5.55)
Spiroperidol	5	1.56 (0.47–5.16)	4.70 (1.16–19.04)
Oxypertine	5	10<ED50<32	33.87 (9.14–125.51)

The ED50 values of the drugs were calculated according to the ability to antagonize fenfluramine-induced hyperthermia. *: Number of animals per group.

Table 2. Effects of the drugs on rectal temperature of intact rats

Drug	Dose p.o., (mg/kg)	Rectal temperature (°C)			
		0	hr		
			1	2	3
Zotepine	0	37.7±0.1	37.6±0.1	37.7±0.1	37.5±0.1
	0.1	37.7±0.1	37.6±0.2	37.6±0.1	37.6±0.1
	1.0	37.8±0.1	37.5±0.1	37.4±0.1	37.4±0.1
Clozapine	0	37.3±0.1	37.6±0.1	37.3±0.1	37.5±0.1
	1.0	37.3±0.1	37.4±0.1	37.2±0.1	37.5±0.1
	3.2	37.2±0.1	37.2±0.1	37.1±0.1	37.3±0.1
	10	37.3±0.1	37.2±0.1*	37.1±0.1	37.3±0.1
Spiroperidol	0	37.3±0.2	37.5±0.1	37.4±0.1	37.4±0.1
	0.1	37.4±0.1	37.5±0.1	37.5±0.1	37.4±0.2
	0.32	37.4±0.2	37.8±0.1*	37.4±0.1	37.6±0.6
	1.0	37.3±0.3	37.5±0.1	37.5±0.1	37.6±0.1
	3.2	37.4±0.2	37.2±0.1	37.3±0.1	37.3±0.02
Oxypertine	0	37.5±0.1	37.5±0.1	37.4±0.1	37.4±0.2
	1.0	37.5±0.1	37.6±0.3	37.5±0.3	37.6±0.2
	3.2	37.5±0.2	37.3±0.1	37.2±0.1	37.6±0.1
	10	37.5±0.1	37.4±0.1	37.2±0.1	37.0±0.1
	32	37.5±0.2	37.1±0.04**	36.8±0.1**	36.8±0.2*

Control group was given saline. Each group included five animals. Each value represents the mean±S.E.

*P<0.05 **P<0.01: significantly different from the corresponding control group.

to have more potent anti-serotonergic activity than known neuroleptics or to be more anti-serotonergic than anti-dopaminergic (9–11). In addition to the present results and those of our previous report (5), it is clear that zotepine has the most potent anti-serotonergic activity of the known neuroleptics. Clozapine is reported to cause fewer extrapyramidal symptoms (9), and spiroperidol and oxypertine are reported to be effective on syndromes on which haloperidol is ineffective (12). These effects are presumed to be due

to their potent central anti-serotonergic activity rather than anti-dopaminergic activity (9, 12). The potent central anti-serotonergic activity of zotepine as compared with its anti-dopaminergic activity (4) entertains the hope that it will provide unique effects in clinical use.

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