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Effects of New Neuroleptics, Isofloxythepin and Zotepine, on Post-Decapitation Convulsions and Prolactin Secretion in Rats

KATSUSHI YAMADA,[1] NAOHIRO MATSUO, TOSHIHIRO MATSUDA, MARIKO TANAKA,* TATSUO FURUKAWA

*Department of Pharmacology, *Research Laboratory of Biodynamics, School of Medicine Fukuoka University, Fukuoka 814-01, Japan*

TAKESHI KOJA AND TAKEO FUKUDA

Department of Pharmacology, Faculty of Medicine, Kagoshima University, Kagoshima 890, Japan

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YAMADA, K., N. MATSUO, T. MATSUDA, M. TANAKA, T. FURUKAWA, T. KOJA AND T. FUKUDA. *Effects of new neuroleptics, isofloxythepin and zotepine, on post-decapitation convulsions and prolactin secretion in rats.* PHARMACOL BIOCHEM BEHAV **24**(5) 1445–1449, 1986.—Oral administration of isofloxythepin (0.5–8.0 mg/kg) inhibited decapitation convulsions in a dose-dependent manner as shown by decreasing the incidence and shortening the convulsion's duration, the effects continuing until 24 hr after administration. Zotepine (8, 16 mg/kg, SC) also decreased the duration but not the incidence of the convulsion. However, the other neuroleptics such as haloperidol, spiperone, perphenazine, trifluoperazine, pimozide and sulpiride failed to affect decapitation convulsions. Reserpine (8 mg/kg, SC) inhibited decapitation convulsions, accompanied by decreasing levels of norepinephrine, dopamine and serotonin in the spinal cord. Isofloxythepin at doses of 4 and 8 mg/kg, PO which completely abolished decapitation convulsions, failed to change norepinephrine and dopamine levels but increased serotonin levels in the spinal cord. Isofloxythepin (0.5–8.0 mg/kg) increased serum prolactin levels in a dose-dependent manner and zotepine (16 mg/kg), haloperidol (1 mg/kg) and reserpine (8 mg/kg) also elevated the levels. The results imply that both isofloxythepin and zotepine, but not the other neuroleptics, inhibit convulsions without decreasing spinal levels of norepinephrine which appears to be the amine most directly involved in the occurrence of decapitation convulsions, although these neuroleptics enhance prolactin secretion by blocking dopamine receptors in the pituitary.

Neuroleptic Isofloxythepin Zotepine Haloperidol Reserpine Decapitation convulsion
Norepinephrine Dopamine Serotonin Prolactin

IT is known that decapitation of rats or mice in the cervical region is followed by a generalized clonic convulsion. The post-decapitation convulsion is suppressed by pretreatment with catecholamine depleting agents such as reserpine [3,5], α-methyltyrosine [5], 6-hydroxydopa [13] and 6-hydroxydopamine [4,17]. In previous studies, we have reported that inhibition of the post-decapitation convulsion closely correlated with a reduction of the norepinephrine content of the spinal cord in 6-hydroxydopamine-treated rats, suggesting that spinal norepinephrine neurons are important in the occurrence of decapitation convulsions [16,17]. On the other hand, haloperidol has been reported to not affect the decapitation convulsion and effects of other neuroleptics on the convulsion have not been reported in detail [19].

Zotepine, 2-chloro-11-(2-dimethylaminoethoxy dibenzo [b,f] thiepin) (Fig. 1), which is a new neuroleptic structurally different from known neuroleptics [6, 7, 15, 21], has been clinically used for treatment of psychosis [1, 18, 20]. Another derivative of dibenzothiepin, isofloxythepin, 3-fluoro-8-isopropyl-10-[4-(2-hydroxyethyl) piperazino]-10,11-dihydrodibenzo [b,f] thiepin (Fig. 1), has been selected from a series of related compounds and is expected to have the character of neuroleptic drug [8, 9, 12, 22, 23].

In the present investigation, we found that isofloxythepin and zotepine did inhibit decapitation convulsions in rats and

[1]Requests for reprints should be addressed to K. Yamada.

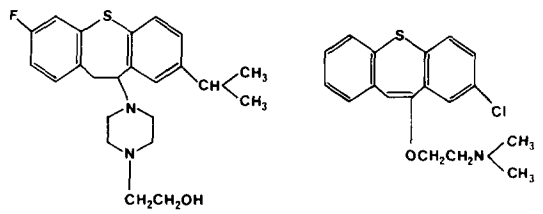

FIG. 1. Chemical structures of isofloxythepin and zotepine.

TABLE 1

DOSE-RELATED INHIBITION OF DECAPITATION CONVULSIONS BY ISOFLOXYTHEPIN IN RATS

Drugs (mg/kg)	Incidence	Duration (Mean (sec) ± S.E.)
Saline	10/10	21.3 ± 0.6
Isofloxythepin 0.5	10/10	17.9 ± 0.8*
Isofloxythepin 1.0	10/10	11.7 ± 0.8*
Isofloxythepin 2.0	8/10	3.1 ± 1.2*
Isofloxythepin 4.0	0/10*	0.0 ± 0.0*
Isofloxythepin 8.0	0/10*	0.0 ± 0.0*

Rats were treated with isofloxythepin (0.5–8.0 mg/kg, PO) 3 hr prior to sacrifice.

Statistics were done by the Fisher exact probability test or by a one-way analysis of variance followed by the Dunnett's *t*-test.

*$p<0.01$; Significantly different from saline-treated group.

TABLE 2

TIME COURSE OF THE INHIBITORY EFFECTS OF ISOFLOXYTHEPIN ON DECAPITATION CONVULSIONS IN RATS

Time after isofloxythepin (hr)	Incidence	Duration (Mean (sec) ± S.E.)
0	10/10	22.6 ± 2.5
1	5/10*	4.8 ± 2.0†
3	0/10†	0.0 ± 0.0†
6	5/10*	3.7 ± 2.2†
12	6/10*	4.3 ± 1.5†
24	10/10	10.9 ± 0.6*

Rats were treated with isofloxythepin (4 mg/kg, PO) 0, 1, 3, 6, 12 or 24 hr prior to sacrifice.

*$p<0.05$, †$p<0.01$; Significantly different from zero time control.

TABLE 3

EFFECTS OF VARIOUS ANTIPSYCHOTROPIC DRUGS ON DECAPITATION CONVULSIONS IN RATS

Drugs (mg/kg)	Incidence	Duration (Mean (sec) ± S.E.)
Saline	10/10	20.1 ± 1.4
Reserpine 5	6/10*	4.3 ± 1.5†
Reserpine 8	2/10†	0.8 ± 0.6†
Isofloxythepin 2	4/10†	1.4 ± 0.6†
Zotepine 8	10/10	5.7 ± 0.8†
Zotepine 16	8/10	3.7 ± 0.8†
Haloperidol 1	10/10	18.3 ± 1.0
Spiperone 2	10/10	21.8 ± 1.2
Perphenazine 0.2	10/10	22.4 ± 1.3
Trifluoperazine 4	10/10	21.3 ± 1.6
Pimozide 5	10/10	23.3 ± 1.4
Sulpiride 2	10/10	21.2 ± 0.9

Rats were injected subcutaneously with dopamine receptor blockers 1 hr or reserpine 24 hr prior to sacrifice.

*$p<0.05$, †$p<0.01$; Significantly different from saline-treated group.

possible neuronal mechanisms involved was thereby investigated.

METHOD

Animals

Male Wistar rats (220–250 g) obtained from Kyudo Animals Laboratory (Kumamoto, Japan) were maintained in air conditioned laboratories at a temperature of 22±1°C in a 12 hr light-dark cycle (7:00 a.m.–7:00 p.m.). Commercial food (CE-2, Clea, Ltd., Japan) and tap water were available ad lib except for during the time of the experiments.

Drugs and Administration

Isofloxythepin methanesulfonate (Research Institute for Pharmacy and Biochemistry, CSSR) was freshly dissolved in distilled water and administered orally (PO) 0, 1, 3, 6, 12 or 24 hr prior to sacrifice. Zotepine (Fujisawa Pharmaceutical) was dissolved in distilled water using crystalline tartaric acid, and pimozide (Fujisawa Pharmaceutical) and trifluoperazine (Yoshidomi Pharmaceutical) were administered as a suspension in 0.5% carboxymethyl cellulose. The other drugs used were reserpine (Apoplon Injection, Daiich Pharmaceutical), haloperidol (Serenace Injection, Dainippon Pharmaceutical), perphenazine (PZC injection, Yoshidomi Pharmaceutical), spiperone (Spiropitan Injection, Eisai Pharmaceutical) and sulpiride (Dogmatyl Injection, Fujisawa Pharmaceutical). These drugs were injected subcutaneously (SC) into experimental animals 1 hr prior to sacrifice except for reserpine which was injected 24 hr before decapitation. Doses are expressed in terms of their base except for isofloxythepin. Animals receiving injection of saline served as controls. Rats were decapitated and the latency and duration of decapitation convulsions were measured. The spinal cord (thoracic and lumbar region) was quickly removed for amine assay.

Determination of Spinal Amine Levels

Norepinephrine, dopamine and serotonin were deter-

TABLE 4

EFFECTS OF ISOFLOXYTHEPIN AND RESERPINE ON SPINAL AMINE LEVELS IN RATS

Drugs (mg/kg)	Norepinephrine	Dopamine	Serotonin
Saline	341.9 ± 20.1	53.7 ± 3.6	646.3 ± 34.8
Isofloxythepin 4	386.6 ± 15.5	61.6 ± 4.8	775.1 ± 33.2†
Isofloxythepin 8	393.6 ± 15.8	60.5 ± 5.5	853.5 ± 24.9†
Reserpine 8	261.5 ± 26.5*	—	30.0 ± 3.0†

Rats were treated with saline (1 ml/kg, PO) or isofloxythepin (4, 8 mg/kg, PO) 3 hr or reserpine (8 mg/kg, SC) 24 hr prior to sacrifice.

Each value represents the mean ± S.E. of the concentration of amine (ng/g wet tissue) as determined from 8 rats.

*$p<0.05$, †$p<0.01$; Significantly different from saline-treated control.

mined simultaneously by high performance liquid chromatography (HPLC). The spinal tissues were homogenized in 1 ml of 0.1 N perchloric acid containing 3,4-dihydroxybenzylamine (30 ng/ml). The homogenate was centrifuged at 25000×g for 20 min. The supernatant was filtered in membrane filter (FR-20, 0.2 μm, 13 mm; Fuji Photo Film Co., Ltd.) and a 10 μl aliquot of the filtered solution was injected into the HPLC system. The HPLC system was composed of a dual piston pump (PM-3A, Bioanalytical Systems Inc.), a reverse phase column (Biophase ODS, 250×4.6 mm o.d., 5 μm particle size) and an electrochemical detector (LC-4B amperometric detector, Bioanalytical Systems Inc.) set at a potential of 0.8 V. The mobile phase was a 0.15 M monochloroacetate buffer (pH 3.0) containing 2 mM EDTA Na_2, 0.01% sodium octyl sulfate and 10% methanol. The flow rate was adjusted to 1 ml/min.

Determination of Serum Prolactin Levels

Blood was taken from the trunk of decapitated rats and centrifuged at 2000×g for 30 min. Prolactin levels in serum were measured by radioimmunoassay based on protocols and reagents supplied from the National Hormone and Pituitary Agency (rat prolactin RP-3 standard and anti-rat prolactin serum-9).

Statistical Analysis

Amine and prolactin levels and duration of decapitation convulsions were expressed as the mean values. Statistical analysis was done using a one-way analysis of variance followed by the two-tailed Dunnett's *t*-test. The incidence of decapitation convulsions was statistically evaluated by means of 2×2 contingency table and the Fisher exact probability test [24].

RESULTS

Inhibitory Effects of Isofloxythepin on Decapitation Convulsions

Following acute decapitation at the midcervical level, decapitation convulsions appeared in all saline-treated rats. It was generally composed of clonic convulsions of the hind limbs, lasting 18–24 sec with a latency of about 2 sec, in each control rat. The decapitation convulsion was inhibited by the oral administration of isofloxythepin. The duration of the convulsion was shortened in a dose-dependent manner (0.5–8.0 mg/kg). Moreover, in all rats treated with isofloxythepin at doses of 4 and 8 mg/kg, decapitation convulsions were not observed at all (Table 1). A peak of inhibitory effects of isofloxythepin on the convulsion was observed 3 hr after administration of the drug and 24 hr after the drug, the duration was still shorter than that in zero time control group (Table 2).

Effects of Various Antipsychotropic Drugs on Decapitation Convulsions

As shown in Table 3, the incidence and duration of decapitation convulsions were also decreased by subcutaneous injection of reserpine (5, 8 mg/kg) or isofloxythepin (2 mg/kg). Zotepine at doses of 8 and 16 mg/kg significantly decreased the duration but not the incidence of the convulsion. Other neuroleptics such as haloperidol (1 mg/kg), spiperone (2 mg/kg), perphenazine (0.2 mg/kg), trifluoperazine (4 mg/kg), pimozide (5 mg/kg) and sulpiride (2 mg/kg) failed to affect decapitation convulsions.

Effects of Isofloxythepin and Reserpine on Spinal Amine Levels

Table 4 represents the levels of amines in the spinal cord of rats treated with saline, isofloxythepin (4, 8 mg/kg) or reserpine (8 mg/kg). Isofloxythepin did not change norepinephrine and dopamine levels but increased serotonin levels in a dose-dependent manner. In rats treated with reserpine, the levels of norepinephrine and serotonin were significantly decreased and dopamine content was not detected.

Effects of Isofloxythepin, Zotepine, Haloperidol and Reserpine on Serum Prolactin Levels

As demonstrated in Table 5, isofloxythepin (0.5–8.0 mg/kg) increased prolactin levels in a dose-dependent manner. In the time-course experiment, higher levels of prolactin were observed 1, 3 and 6 hr after treatment with isofloxythepin at a dose of 4 mg/kg (Table 6). Treatment with zotepine (16 mg/kg), haloperidol (1 mg/kg) or reserpine (5 mg/kg) also increased prolactin levels (Table 5).

DISCUSSION

It is well known that prolactin secretion from the pituitary was regulated by the tuberoinfundibular dopamine system and was increased by neuroleptics dopamine receptor

TABLE 5

EFFECTS OF ISOFLOXYTHEPIN, ZOTEPINE, HALOPERIDOL AND RESERPINE ON SERUM PROLACTIN LEVELS IN RATS

Drugs (mg/kg)	Prolactin (ng/ml)
Saline	19.2 ± 2.2
Isofloxythepin 0.5	20.4 ± 3.4
Isofloxythepin 1.0	25.0 ± 2.9
Isofloxythepin 2.0	37.0 ± 3.6†
Isofloxythepin 4.0	38.4 ± 2.8†
Isofloxythepin 8.0	43.9 ± 4.9†
Zotepine 16.0	66.6 ± 3.4†
Haloperidol 1.0	51.0 ± 3.2†
Reserpine 5.0	31.6 ± 1.7*

Rats were treated with saline (1 ml/kg, PO), isofloxythepin (0.5–8.0 mg/kg, PO), zotepine (16 mg/kg, SC) haloperidol (1.0 mg/kg, SC) or reserpine (5 mg/kg, SC).

Each value represents the mean ± S.E. of serum prolactin levels (ng/ml) as determined from 9–10 rats.

*$p<0.05$, †$p<0.01$; Significantly different from saline-treated control.

TABLE 6

TIME COURSE OF THE EFFECTS OF ISOFLOXYTHEPIN ON SERUM PROLACTIN LEVELS IN RATS

Time after isofloxythepin (hr)	Prolactin (ng/ml)
0	14.4 ± 1.9
1	51.2 ± 3.3*
3	38.4 ± 2.8*
6	32.6 ± 3.0*
12	24.8 ± 2.4
24	23.6 ± 3.1

Rats were treated with isofloxythepin (4 mg/kg, PO) 0, 1, 3, 6, 12 or 24 hr prior to sacrifice.

Each value represents the mean ± S.E. of serum prolactin levels (ng/ml) as determined from 8–9 rats.

*$p<0.01$; Significantly different from zero time control.

antagonists and catecholamine-depleting agents such as reserpine [10, 11, 14]. The increase of prolactin secretion appears to be dependent on the antidopaminergic action of the drugs, although the increment is considered to be one of the side effects of antipsychotropic drugs. Isofloxythepin has been reported to accelerate the striatal dopamine metabolism and antagonize the stereotyped behavior induced by apomorphine [8, 9, 22, 23]. In the present experiment, oral administration of isofloxythepin accelerated prolactin secretion in a dose-dependent manner and elevation of prolactin levels was observed 1–6 hr after administration. This is in agreement with previous report [22] showing the isofloxythepin-induced increases in prolactin levels measured by radioimmunoassay. Enhancement of prolactin secretion was also observed after subcutaneous injection of zotepine, haloperidol or reserpine. Uchida *et al.* [21] previously reported that zotepine increased secretion of prolactin, which was determined by bioassay using tissue-culture of the mammary gland of pregnant mice. Considered together, these results may suggest that both isofloxythepin and zotepine increase prolactin secretion by blocking dopamine receptors in the anterior pituitary.

Kamat and Sheth [5] have reported that the latency of decapitation convulsions is prolonged by pretreatment with reserpine in mice and the convulsion may be a release phenomenon from the tonic inhibition of spinal interneurons which is mediated by monoaminergic pathways. Richardson and Jacobowitz [13] have also observed a reduction in duration of the decapitation convulsion in norepinephrine-depleted rats which are pretreated with 6-hydroxydopa and proposed that the convulsion depends on norepinephrine rather than dopamine levels in the central nervous systems. Our previous report [16] showed that intraspinal injection of 6-hydroxydopamine, which decreased the norepinephrine content of the spinal cord without affecting the norepinephrine content of the various regions in the rat brain, caused a significant inhibition of decapitation convulsions as shown by prolongation of the latency and shortening of the convulsion's duration. From such previous reports, it is supposed that decapitation convulsion is induced by release from tonic inhibition mediated by the bulbospinal norepinephrine neurons. These previous proposals [2, 5, 13, 16] are also supported by the present results in which pretreatment with reserpine causes a significant inhibition of decapitation convulsions with the decreasing levels of norepinephrine, dopamine and serotonin in the spinal cord.

On the other hand, various neuroleptics such as haloperidol, spiperone, perphenazine, trifluoperazine, pimozide and sulpiride failed to change decapitation convulsions in the present experiment. However, oral administration of isofluoxythepin decreased the incidence and duration of decapitation convulsions for up to 24 hr after administration. In addition, decapitation convulsions completely disappeared after dosing of 4 and 8 mg/kg of isofloxythepin. These doses of isofloxythepin, however, failed to decrease norepinephrine and dopamine content in the spinal cord. Accordingly, the inhibitory effects of isofloxythepin on decapitation convulsions may not be mediated by the decreasing levels of catecholamine in the spinal cord.

Interestingly, serotonin content in the spinal cord was increased in a dose-dependent manner in the rats treated with isofloxythepin. This increment of serotonin content might be resulted from an inhibition of release or an increase of synthesis of serotonin in the spinal cord although the turnover rate of serotonin was not measured in this experiment. Suenaga *et al.* [16] have reported that intraspinal injection of 5,6-dihydroxytryptamine did not change the decapitation convulsion although the treatment markedly decreased the serotonin content of the spinal cord without affecting either the serotonin content of the brain or the norepinephrine content of the spinal cord, and suggested that the bulbospinal serotonin neurons are not involved in the occurrence of decapitation convulsions. Moreover, Thut and Myslinski [19] have observed that 5-hydroxytryptophan, a precursor of serotonin, did not alter decapitation convulsions in mice. Therefore, the inhibition of decapitation convulsions by isofloxythepin may not be related to the increase of serotonin content in the spinal cord.

Subcutaneous injection of another dibenzothiepin derivative, zotepine, also induced a significant inhibition of decapitation convulsions as shown by shortening of the convulsion's duration. It has been reported that there was no essential difference between the zotepine-treated and control animals in norepinephrine and dopamine concentration in

the brain although zotepine accelerated the turnover rate of dopamine [21]. Accordingly, inhibitory effects of zotepine on decapitation convulsions may not be mediated by the decreasing levels of bulbospinal catecholamine, either.

However, it is likely that isofloxythepin and zotepine induce their inhibitory effects on decapitation convulsions by blocking the action of norepinephrine on the postsynaptic sites. In fact, isofloxythepin inhibited the norepinephrine-induced contraction of the rat vas deferens (K. Oguro *et al.*, Showa Denko, Tokyo, Japan, personal communication). In addition, we recently found that subcutaneous injections of prazosin (0.5–4.0 mg/kg, SC), a selective α_1-receptor antagonist, inhibited decapitation convulsions in a dose-dependent manner in rats (K. Yamada *et al.*, unpublished observation). Accordingly, the blocking effect of isofloxythepin on postsynaptic α_1-receptors may be involved. Furthermore, it is possible that the convulsions are reduced by decreasing the release of norepinephrine from presynaptic sites but the effect of isofloxythepin on presynaptic sites has not been determined. Thus, detailed neuronal mechanisms which participate in the inhibitory effect of dibenzothiepin derivatives on decapitation convulsions remain to be elucidated.

These results indicate that isofloxythepin and zotepine, dibenzothiepin derivatives, inhibit decapitation convulsions without decreasing norepinephrine levels in the spinal cord.

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REFERENCES

1. Amamoto, H. and T. Gotoh. Clinical study of zotepine, a new neuroleptic drug. *Clin Rep* **14:** 1660–1682, 1980.
2. Eichbaum, F. W., O. Slemer and W. J. Yasaka. Post-decapitation convulsions and their inhibition by drugs. *Exp Neurol* **49:** 802–812, 1975.
3. Eichbaum, F. W. and W. J. Yasaka. Inhibition of post-decapitation convulsions by reserpine. *Experientia* **29:** 816–817, 1973.
4. Fukuda, T., Y. Araki and N. Suenaga. Inhibitory effects of 6-hydroxydopamine on the clonic convulsion induced by electroshock and decapitation. *Neuropharmacology* **14:** 579–583, 1975.
5. Kamat, U. G. and U. K. Sheth. The role of central monoamines in decapitation convulsions of mice. *Neuropharmacology* **10:** 571–579, 1971.
6. Lai, H., M. A. Carino and A. Horita. Chronic treatments with zotepine, thioridazine, and haloperidol affect apomorphine-elicited stereotypic behavior and striatal ^{3}H-spiroperidol binding sites in the rat. *Psychopharmacology (Berlin)* **75:** 388–390, 1981.
7. Lai, H., M. Carino, R. Sperry and A. Horita. Effects of microinjection of 2-chloro-11 (2-dimethylaminoethoxy)-dibenzo [b,f]-thiepine (zotepine), thioridazine and haloperidol into the striatum and nucleus accumbens on stereotypic behaviour and motor activity. *J Pharm Pharmacol* **33:** 252–254, 1981.
8. Metyšová, J. and J. Metyš. Inhibition of 4,α-dimethyl-m-tyramine (H 77/77)-induced hyperactivity in mice by single oral administration of isofloxythepin, haloperidol and clozapine. *Act Nerv Super* **23:** 240–241, 1981.
9. Metyšová, J., J. Metyš, M. Valchář and A. Dlabač. Kinetics of central actions of isofloxythepin, an oral neuroleptic drug with prolonged action in rodents. *Act Nerv Super* **22:** 164–165, 1980.
10. Moore, K. E. and K. T. Demarest. Tuberoinfundibular and tuberohypophyseal dopaminergic neurons. In: *Frontiers in Neuroendocrinology, vol 7*, edited by W. F. Ganong and L. Martini. New York: Raven Press, 1982, pp. 161–190.
11. Morgan, W. W., R. W. Steger, M. S. Smith, A. Bartke and C. A. Sweeney. Time course of induction of prolactin-secreting pituitary tumors with diethylstilbestrol in male rats: Response of tuberoinfundibular dopaminergic neurons. *Endocrinology* **116:** 17–24, 1985.
12. Protiva, M. and J. Metyšová. Novel information about the influence of fluorination on activity in a series of tricyclic neuroleptic agents. *Act Nerv Super* **20:** 270–272, 1978.
13. Richardson, J. S. and D. M. Jacobowitz. Depletion of brain norepinephrine by intraventricular injection of 6-hydroxydopa: A biochemical, histochemical and behavioral study in rats. *Brain Res* **58:** 117–133, 1973.
14. Sarkar, D. K., P. E. Gottschall and J. Meites. Decline of tuberoinfundibular dopaminergic function resulting from chronic hyperprolactinemia in rats. *Endocrinology* **115:** 1269–1274, 1984.
15. Satoh, H., Y. Satoh and J. Mori. Effect of zotepine and various drugs on apomorphine- and methamphetamine-induced rotational behaviour in rats with unilateral lesions of the substantia nigra. *Jpn J Pharmacol* **33:** 363–372, 1983.
16. Suenaga, N., R. Oishi and T. Fukuda. The role of locus coeruleus in decapitation convulsions of rats. *Brain Res* **177:** 83–93, 1979.
17. Suenaga, N., K. Yamada and T. Fukuda. Correlation between central catecholamine level and post-decapitation convulsion in rats treated with 6-hydroxydopamine. *Brain Res* **122:** 165–169, 1977.
18. Tanaka, M., I. Tanaka and S. Maeda. Effects of zotepine in schizophrenics. *Clin Rep* **14:** 1684–1704, 1980.
19. Thut, P. D. and N. R. Myslinski. The role of dopamine and serotonin in the prolongation of post-decapitation convulsions in mice. *Life Sci* **19:** 1569–1578, 1976.
20. Torii, H., H. Yoshimoto, M. Hiraguchi, F. Enoto, M. Yanashita, H. Enoto, S. Matsubara, N. Nakagawa and H. Tomioka. Clinical study of zotepine in schizophrenics. *Pharmacol Ther* **7:** 2651–2679, 1980.
21. Uchida, S., F. Honda, M. Otsuka, Y. Satoh, J. Mori, T. Ono and M. Hitomi. Pharmacological study of [2-chloro-11-(2-dimethylaminoethoxy) dibenzo [b,f] thiepine] (zotepine), a new neuroleptic drug. *Arzneimittelforsch* **29:** 1588–1594, 1979.
22. Valchář, M., J. Metyšová, J. Chlebounová and A. Dlabač. Induction of dopaminergic supersensitivity after a single dose of the neuroleptic isofloxythepin. *Psychopharmacology (Berlin)* **76:** 381–384, 1982.
23. Valchář, M., J. Metyšová and A. Dlabač. The effect of a new fluorinated tricyclic neuroleptic drug isofloxythepin on the rat striatal dopamine metabolism. *Act Nerv Super* **21:** 130–131, 1979.
24. Winer, B. J. *Statistical Principles in Experimental Design*, 2nd edition. Tokyo: McGraw-Hill, 1971.