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BRIEF COMMUNICATION

Effects of Isofloxythepin Enantiomers on Prolactin Secretion and Postdecapitation Convulsions in Rats

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MATSUO, N., K. YAMADA, S. MATSUMOTO, M. DOMAE, K. SHIRAKAWA AND T. FURUKAWA. *Effects of isofloxythepin enantiomers on prolactin secretion and postdecapitation convulsions in rats.* PHARMACOL BIOCHEM BEHAV **30**(4) 1081–1083, 1988.—Racemic isofloxythepin and its enantiomers (0.05–1.0 mg/kg) andministered subcutaneously increased serum prolactin levels in a dose-dependent manner in rats. The potencies of the drugs were equal for this variable. They (0.05–1.0 mg/kg, SC) also decreased dose-dependently the incidence and duration of postdecapitation convulsions, the convulsions being abolished at 1.0 mg/kg in all groups. Although (−)-enantiomer had slightly stronger effects than those of raceme and (+)-enantiomer, there were no great differences in their inhibitory effects on postdecapitation convulsions. The results indicate that isofloxythepin enantiomers in addition to raceme increase serum prolactin levels and inhibit postdecapitation convulsions and that they seem to have similar potency in blocking of dopamine receptors and α_1-adrenoceptors.

Prolactin Postdecapitation convulsions Neuroleptic Isofloxythepin and its enantiomers Dopamine receptors α_1-Adrenoceptors

ISOFLOXYTHEPIN, 3-fluoro-8-isopropyl-10-[4-(2-hydroxyethyl) piperazino]-10,11-dihydrodibenzo [b,f] thiepin, is a newly synthesized neuroleptic drug [10]. Isofloxythepin has been reported to increase the concentrations of homovanillic acid in the striatum and block [^{3}H]-spiperone binding to striatal dopamine D-2 receptors [4,14]. Other dibenzothiepin derivatives such as zotepine [3, 11, 18] and oxyprothepin [15] have also been reported to exert an antidopaminergic action in the brain. Recently, we demonstrated that isofloxythepin increased serum prolactin levels and inhibited postdecapitation convulsions in rats [18]. On the other hand, the molecule of isofloxythepin is chiral because it contains an asymmetric center in position 10 of the skeleton. By resolution of the racemic isofloxythepin, its (+)- and (−)-enantiomer in the form of methanesulfonate were prepared, and the stereoselectivity of antidopaminergic effect of isofloxythepin was reported. (−)-Isofloxythepin was more effective in cataleptic activity and antagonistic activity against apomorphine-induced chewing than those of raceme and (+)-isofloxythepin. Thus, (−)-enantiomer was found to have higher neuroleptic effects than the (+)-enantiomer [6].

The present study was therefore undertaken to compare racemic isofloxythepin and its enantiomers for dopamine D-2 and α_1-adrenoceptor blocking properties, the former assessed by enhancement of prolactin release and the latter by inhibition of the postdecapitation convulsions.

METHOD

Male Wistar rats (350–450 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 (lights on at 7:00 a.m.). Commercial food (CE-2, Clea, Ltd., Japan) and tap water were freely available except during the time of the experiments.

Racemic isofloxythepin and its enantiomer methanesulfonate (kindly supplied by Research Institute for Pharmacy

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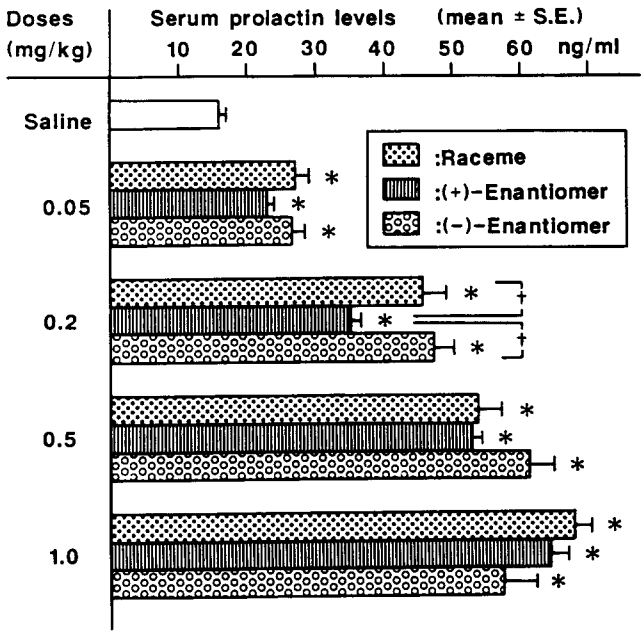

FIG. 1. Dose-related increases of serum prolactin levels produced by racemic isofloxythepin and its enantiomers in rats. All drugs were given subcutaneously 1 hr prior to killing the animals. Each value represents the mean±S.E. of prolactin levels (ng/ml) from 9–10 rats. *$p<0.01$; significant difference from saline-injected group. †$p<0.05$; significant difference from (+)-enantiomer-injected group.

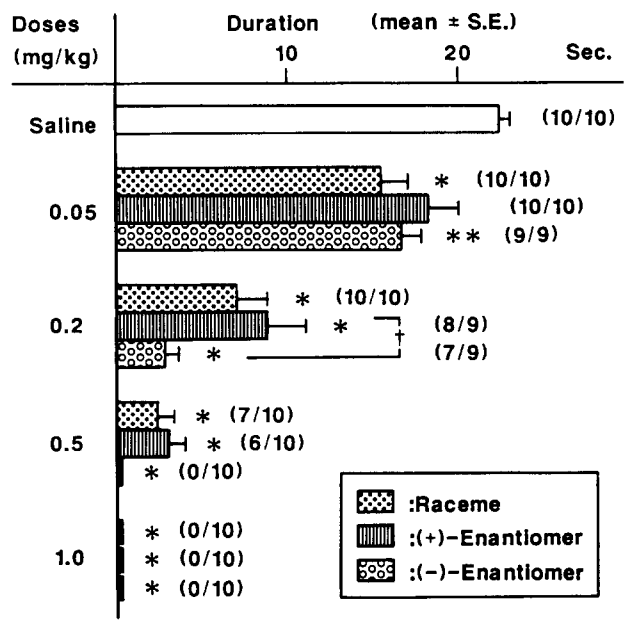

FIG. 2. Dose-related inhibition of postdecapitation convulsions induced by racemic isofloxythepin and its enantiomers in rats. Rats were treated with raceme and its enantiomers (0.05–1.0 mg/kg. SC) 1 hr prior to killing. Numbers in parentheses are ratios of the numbers of rats showing convulsions. Each value represents the mean±S.E. of duration of the convulsions from 9–10 rats. *$p<0.05$, **$p<0.01$; significant difference from saline-injected group. †$p<0.05$; significant difference between (+)-enantiomer- and (−)-enantiomer-injected groups.

and Biochemistry, CSSR) were freshly dissolved in saline and administered subcutaneously (SC) 1 hr prior to sacrifice. Animals receiving injection of saline served as controls. Rats were decapitated with a guillotine and the latency and duration of postdecapitation convulsions were thereafter measured. For determination of serum prolactin levels, blood was taken from the trunk of decapitated rats and centrifuged at 3000×g for 30 min. Prolactin levels were measured by radioimmunoassay based on protocols and reagents kindly supplied from the National Hormone and Pituitary Agency (rat prolactin PR-3 standard and anti-rat prolactin serum-9) [18].

Duration of postdecapitation convulsions and prolactin levels were expressed as the mean value. Statistical analysis was done using a one-way analysis of variance followed by the Dunnett's *t*-test [17].

RESULTS

As shown in Fig. 1, serum prolactin level in the saline-injected group was 15.8±1.1 ng/ml (n=9–10). Prolactin levels were elevated in a dose-dependent manner after subcutaneous injections of isofloxythepin and its both enantiomers (0.05–1.0 mg/kg). The rises of prolactin levels induced by these drugs were substantially equal, except for the levels at a dose of 0.2 mg/kg of (+)-enantiomer. (+)-Enantiomer (0.2 mg/kg)-induced increases in prolactin levels were lower than those by raceme and (−)-enantiomer.

Following acute decapitation at the midcervical levels, decapitation convulsions appeared in all saline-treated rats. It was generally composed of clonic convulsions of the hind limbs, which occurred with a latency of about 3 sec and lasted for 21–26 sec in each control rat. The postdecapitation convulsions were dose-dependently inhibited in both duration and incidence by raceme and its enantiomers (0.05–1.0 mg/kg, SC). After treatment with (−)-enantiomer at a dose of 0.2 mg/kg, the duration of the convulsions was significantly shorter than that by (+)-enantiomer. The postdecapitation convulsions completely disappeared after treatment with (−)-enantiomer at a dose of 0.5 mg/kg or (+)-enantiomer and raceme at a dose of 1.0 mg/kg.

DISCUSSION

It has been well documented that prolactin secretion is tonically inhibited by dopamine released from the tuberoinfundibular dopaminergic neuron. The secretion is thereby stimulated by dopamine receptor antagonists which block dopamine D-2 receptors at the pituitary [1, 5, 7, 8]. Isofloxythepin has been reported to block [^{3}H]-spiperone binding to striatal dopamine D-2 receptors [4] and increase serum prolactin levels [14,18]. In the present experiment, racemic isofloxythepin and its enantiomers increased prolactin levels in a dose-dependent manner, but their potencies in prolactin secretion were substantially equal. Considered together, it is suggested that blocking effects on dopamine D-2 receptors at the pituitary of these agents may be almost equal.

Rapid transection of rats in the cervical spinal cord is followed by a generalized clonic convulsion. This postdecapitation convulsion typically occurs within a few seconds after decapitation and lasts for about 20 seconds. The convulsion is suppressed by catecholamine depleting agents such as reserpine [2]. It has also been shown that

there are close correlations between reduction of spinal norepinephrine levels and inhibition of postdecapitation convulsions after intraventricular or intraspinal injections of 6-hydroxydopamine which selectively decreases the norepinephrine contents in the spinal cord [12,13]. On the basis of such facts, postdecapitation convulsions have been proposed to be a release phenomenon from tonic inhibition mediated by the bulbospinal norepinephrine neurons [12]. Recently, we have observed that racemic isofloxythepin inhibited postdecapitation convulsions without decreasing spinal norepinephrine contents [18]. Furthermore, chlorpromazine, which is effective in blocking α_1-adrenoceptors, and prazosin, a preferential α_1-adrenoceptor antagonist, also inhibited decapitation convulsions [9, 16, 19]. The α_1-binding activity of isofloxythepin in the rat brain cortex was demonstrated to be similar to that of chlorpromazine, though weaker than that of prazosin [19]. It is thus suggested that the inhibition of decapitation convulsions by isofloxythepin may be attributed to the blockade of postsynaptic α_1-adrenoceptors in the spinal cord [19]. In the present study, racemic isofloxythepin and its enantiomers inhibited postdecapitation convulsions in a dose-dependent manner. Although the inhibitory effect of (−)-enantiomer was slightly stronger than those of raceme and (+)-enantiomer, there were no great differences among their inhibitory effects. These results may suggest that raceme and its enantiomers have similar blocking effects on α_1-adrenoceptors which are involved in inhibiting postdecapitation convulsions.

The results suggest that both isofloxythepin enantiomers as well as raceme have similar activities in blocking of dopamine D-2 receptors at the pituitary gland and α_1-adrenoceptors in the spinal cord.

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