

Structure-Epileptogenicity Relationship of Quinolones with Special Reference to Their Interaction with γ -Aminobutyric Acid Receptor Sites

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The relationship between the chemical structure and epileptogenic activity of quinolones was investigated. When the quinolones were administered intravenously to mice concomitantly with oral biphenylacetic acid, a major metabolite of the nonsteroidal antiinflammatory drug fenbufen, enoxacin, norfloxacin, ciprofloxacin, and pipemidic acid, which have an unsubstituted piperazine moiety at the 7 position of their parent nuclei, provoked clonic convulsions and subsequent death at doses of 6.25 mg/kg or more in a dose-dependent manner. AM-1091 and T-3262, which have an unsubstituted aminopyrrolidine moiety at their 7 positions, were less epileptogenic than the compounds listed above were. In contrast, ofloxacin, AT-4140, and nalidixic acid, which have piperazine substituted with methyl group(s) or no piperazine moiety at their 7 positions, never induced convulsions, even at doses of 100 mg/kg. Lomefloxacin, which has a 3-methyl piperazine, however, provoked convulsions at doses of 6.25 mg/kg or more. In the presence of biphenylacetic acid, all the test quinolones except nalidixic acid competitively inhibited [3 H]muscimol binding to receptor sites for γ -aminobutyric acid (GABA) *in vitro*. Nalidixic acid did not inhibit the binding at all, even at the highest concentration tested, i.e., 10^{-4} M. The 50% inhibition doses for [3 H]muscimol binding varied within 4 orders of magnitude or more, between 10^{-8} to more than 10^{-4} M for various compounds, and there was a close correlation between the epileptogenic activities of quinolones and their inhibitory potencies for [3 H]muscimol binding to GABA receptor sites. These results indicate that the epileptogenic activity of quinolones possibly relates to the GABA-like structures of substituents at their 7 positions, which act as antagonists of GABA receptors.

Recently, the clinical significance of new quinolones such as ofloxacin (19), ciprofloxacin (25), norfloxacin (11), and enoxacin (13) has been established because of their excellent tissue penetrability and high level of activity against gram-positive and gram-negative pathogens, including those that are resistant to commonly available antibiotics. On the other hand, through accumulated clinical experience, attention has been paid to the side effects of these drugs, especially those on the central nervous system, even though the incidence of these side effects has been quite low (3, 4, 17, 23). The most common reactions include headache, dizziness, and restlessness (5, 8, 16). Seizures and hallucinations, which are rare in patients who receive quinolones, have been observed more frequently in patients who receive both quinolones and nonsteroidal antiinflammatory drugs such as fenbufen (1, 3, 22; K. Morikawa, O. Nagata, S. Kubo, H. Yato, and K. Yamamoto, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 255, 1987). The convulsant actions of quinolones could be reproduced in animals as well when the quinolones were administered concomitantly with biphenylacetic acid (BPA), a major metabolite of fenbufen (26). Although the mechanism by which quinolones exhibit amplified epileptogenic activity in combination with nonsteroidal antiinflammatory drugs is still obscure, inhibition of γ -aminobutyric acid (GABA) binding to its receptor sites, resulting in central nervous system excitation, might be responsible for such adverse phenomena of quinolones (21, 24). Chemically, the new quinolones are characterized in two ways. They have a fluorine atom(s) in the molecules and either a piperazine or an aminopyrrolidine moiety at the 7 position of the quinoline or naphthylidene ring (Fig. 1), where

the compounds seem to share a common structure with GABA receptor agonists. Thus, we attempted to clarify the relationship between the structure and the epileptogenic activity of quinolones, with special reference to the interaction with GABA receptor sites.

MATERIALS AND METHODS

Compounds and reagents. Ofloxacin, ciprofloxacin, norfloxacin, enoxacin, lomefloxacin, AT-4140, pipemidic acid, AM-1091 (PD 127,391), T-3262, nalidixic acid, and des-piperazinyl-norfloxacin were synthesized at our institute (Fig. 1). These quinolones were dissolved separately in 0.1 N NaOH, except for ciprofloxacin, which was provided as an HCl salt form and dissolved in saline. [*methylene- 3 H(N)*]muscimol ([3 H]muscimol) was purchased from Dupont, NEN Research Products (Boston, Mass.). All other reagents were commercial products of analytical grade.

Animals. Outbred male ddY mice (age, 6 to 8 weeks; weight, 25 to 30 g) and outbred female Sprague-Dawley rats (age, 7 to 8 weeks; weight, 150 to 250 g) were obtained from the Shizuoka Cooperative for Experimental Animals (Hamamatsu, Japan) and were quarantined for at least 7 days before use. They received tap water and commercial food *ad libitum* and were kept in a room controlled at 23°C and 55% humidity.

In vivo studies. The ddY mice were fasted for at least 15 h prior to use. They were administered BPA (Aldrich Chemical Co., Inc., Milwaukee, Wis.) orally at a dose of 400 mg/kg. Thirty minutes later, they were injected intravenously with each quinolone solution at doses of 6.25, 12.5, 25, 50, or 100 mg/kg in a fixed volume of 0.1 ml/10 g of body weight. The administrations were carried out at a fixed speed of 1 ml/min. A group of four mice was allocated to each test

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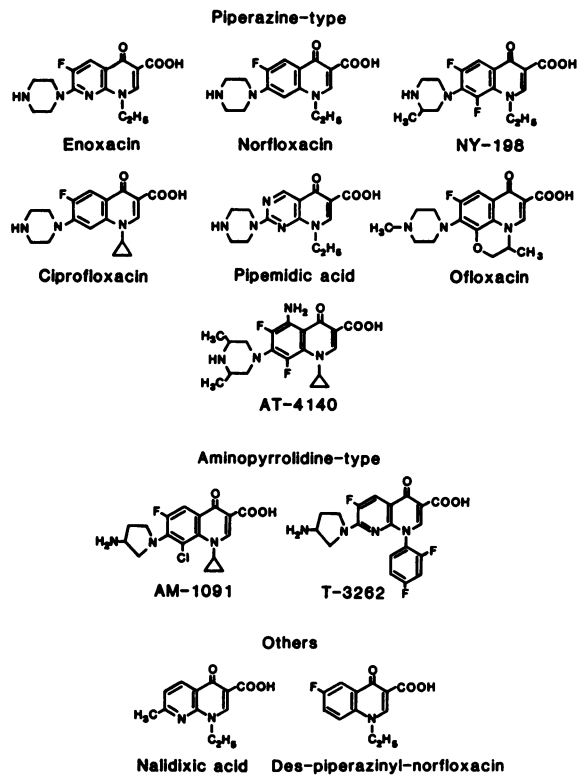


FIG. 1. Chemical structures of quinolones.

dose. Control mice received either 400 mg of BPA per kg or 100 mg of a quinolone per kg. Thereafter, the pharmacological effects of the drugs on mice were observed for up to 6 h after injection, and the onset of clonic convulsion and the subsequent death of each mouse was recorded. In another experiment, groups of six mice were given muscimol (Sigma Chemical Co., St. Louis, Mo.) or diazepam or baclofen (Daiichi Pharmaceutical) simultaneously with BPA and were then injected with norfloxacin.

Preparation of synaptic plasma membranes. Synaptic plasma membranes were prepared from the brains of Sprague-Dawley rats by the method of Zukin et al. (27), with minor modifications. The whole brains were homogenized in 10 volumes of ice-cold 0.32 M sucrose. The homogenate was centrifuged at $1,000 \times g$ for 10 min, and the supernatant was further centrifuged at $20,000 \times g$ for 20 min. The resultant crude membrane pellet was suspended in 50 volumes of 50 mM Tris hydrochloride buffer (pH 7.1) by dispersion with Biotron (BT-10-20-350D; Kinematica, Switzerland) and was centrifuged at $48,000 \times g$ for 20 min. The pellet was suspended in 0.05% Triton X-100, incubated for 30 min at 37°C (6), and washed three times in the buffer. The final suspension (2.5 mg of protein per ml) was stored at -80°C without loss of binding capacity for 60 days.

[^3H]muscimol-binding assay. The standard binding assay preparation (1 ml), which contained 100 μl of the membrane suspension, 200 μl of [^3H]muscimol (10 nM; specific activity, 20 Ci/mmol), 100 μl of the buffer or test quinolone, and 100 μl of the buffer or BPA (10^{-4} M), was incubated at 4°C for 30 min. The preparations were then quickly diluted by adding 10 ml of ice-cold buffer and were filtered through glass fiber filters (GF/B; Whatman Inc., Clifton, N.J.). The filters were washed twice with 5 ml of the buffer, placed in vials containing 10 ml of ACSII aqueous counting scintillant

TABLE 1. Epileptogenic activities of quinolones in combination with BPA in mice^a

Compound	Dose (mg/kg)	Incidence ^b (time of onset [min]) ^c of:	
		Clonic convulsion	Death
Enoxacin	6.25	4 (1.5 \pm 0.3)	4 (8.3 \pm 0.5)
	12.5	4 (<1.0)	4 (4.8 \pm 0.5)
	25	4 (<1.0)	4 (1.3 \pm 0.3)
Norfloxacin	6.25	4 (7.5 \pm 0.5)	4 (15.8 \pm 0.3)
	12.5	4 (4.8 \pm 0.5)	4 (10.8 \pm 1.4)
	25	4 (3.0 \pm 0)	4 (9.5 \pm 0.6)
Lomefloxacin	6.25	4 (12.8 \pm 2.7)	4 (30.5 \pm 3.3)
	12.5	4 (2.3 \pm 0.8)	4 (7.3 \pm 0.8)
	25	4 (<1.0)	4 (2.1 \pm 1.3)
Ciprofloxacin	6.25	4 (21.5 \pm 2.5)	1 (192)
	12.5	4 (6.8 \pm 1.4)	4 (23.5 \pm 3.0)
	25	4 (4.5 \pm 0.3)	4 (12.5 \pm 0.9)
Pipemidic acid	6.25	1 (37)	0
	12.5	2 (27, 33)	0
	25	4 (13.5 \pm 3.0)	4 (32.0 \pm 2.4)
Ofloxacin	25	0	0
	50	0	0
	100	0	0
AT-4140	25	0	0
	50	0	0
	100	0	0
AM-1091	25	2 (29, 31)	0
	50	3 (22.0 \pm 5.9)	2 (42, 44)
	100	4 (5.5 \pm 0.5)	4 (19.3 \pm 4.8)
T-3262	25	0	0
	50	0	0
	100	1 (70)	1 (84)
Nalidixic acid	25	0	0
	50	0	0
	100	0	0
Des-piperazinyl-norfloxacin	25	0	0
	50	0	0
	100	0	0

^a Fasted mice were injected intravenously with each quinolone 30 min after the oral administration of BPA (400 mg/kg).

^b Values indicate the number of mice with pharmacological effects. Four mice were tested in each experiment.

^c The mean \pm standard error of the time of onset for mice that developed pharmacological effects.

(Amersham Co., Arlington Heights, Ill.), and counted in a liquid scintillation counter (LSC-903; Aloka Co., Ltd., Tokyo, Japan). Specific binding was defined as the difference between the levels of binding observed in the presence and the absence of a large excess (1 mM) of unlabeled GABA (Tokyo Kasei Co., Tokyo, Japan). Results were expressed as the ratio of the specific binding in the presence of quinolone to that in its absence (percentage of control).

RESULTS

Epileptogenic activities of quinolones in mice. The epileptogenic activities of quinolones were compared in mice by intravenous injection (Table 1). Neither the tested quinolo-

TABLE 2. Inhibitory effects of muscimol, diazepam, and baclofen on the epileptogenic activity of norfloxacin induced by combination with BPA in mice^a

Expt no. and compound (route ^b)	Dose (mg/kg)	Incidence ^c (time of onset [min] ^d) of:	
		Clonic convulsion	Death
Expt 1			
Muscimol (i.p.)	2	5 (45.6 ± 22.7)	5 (109 ± 27.1)
	5	4 (143 ± 33.6)	4 (217 ± 47.2)
Control ^e		6 (9.5 ± 0.6)	6 (54.7 ± 12.2)
Expt 2			
Diazepam (p.o.)	10	5 (33.4 ± 1.2)	4 (96.0 ± 13.4)
	20	5 (58.0 ± 5.2)	5 (106 ± 11.2)
Baclofen (i.p.)	10	6 (7.3 ± 0.6)	6 (64.8 ± 12.1)
	20	6 (7.3 ± 1.4)	6 (42.8 ± 7.6)
Control ^e		6 (8.5 ± 0.4)	6 (29.3 ± 2.8)

^a Fasted mice were injected intravenously with norfloxacin (6.25 mg/kg) 30 min after the oral administration of BPA (400 mg/kg). Each test compound was injected by the indicated route simultaneously with BPA.

^b i.p., Intraperitoneal; p.o., oral.

^c Values indicate the number of mice with pharmacological effects. Six mice were tested in each experiment.

^d The mean ± standard error of the time of onset for mice that developed pharmacological effects.

^e Control mice received both norfloxacin and BPA.

nes (100 mg/kg each) nor BPA (400 mg/kg) exhibited any epileptogenic potency when administered alone (data not shown). When administered concomitantly with an oral BPA, however, quinolones with an unsubstituted piperazine moiety at the 7 position of their parent nuclei induced clonic convulsions and subsequent death at doses of 6.25 mg/kg or more in a dose-dependent manner. These compounds were enoxacin, norfloxacin, ciprofloxacin, and pipemidic acid. Among these compounds, ciprofloxacin and pipemidic acid were less epileptogenic than enoxacin and norfloxacin, as indicated by the lower incidence of pharmacological effects. AM-1091 and T-3262, which have unsubstituted aminopyrrolidine moieties at their 7 positions, also provoked convulsions at ≥25 and 100 mg/kg, respectively, in combination with BPA; and these were much less epileptogenic than enoxacin and norfloxacin. In contrast, ofloxacin and AT-4140, which have piperazine moieties substituted with methyl group(s), provoked neither convulsion nor death even at 100 mg/kg. Lomefloxacin, which has a 3-methyl piperazine at the 7 position, was, however, actually epileptogenic, as were enoxacin and norfloxacin. Nalidixic acid and des-piperazinyl-norfloxacin, which do not have a piperazine moiety at their 7 positions, induced no significant manifestations other than a transient decrease in locomotor activities. Although data are not shown, free piperazine also had no epileptogenic potency at a dose of 30 mg/kg, corresponding to approximately 100 mg of quinolones per kg on a molecular basis.

The simultaneous administration of muscimol intraperitoneally and BPA orally or diazepam orally and BPA decreased the incidence and delayed the onset of convulsions induced by norfloxacin, while baclofen, a GABA_B receptor agonist (7, 9), had no influence on the epileptogenic activity of norfloxacin (Table 2).

Effect of quinolones on [³H]muscimol binding to GABA receptor sites. [³H]muscimol binding to the preparation of rat

TABLE 3. Effect of quinolones on [³H]muscimol binding to rat synaptic plasma membranes in the presence or absence of BPA at 10⁻⁴ M in vitro

Compound	IC ₅₀ (M) ^a	
	Without BPA	With BPA
Enoxacin	>1.0 × 10 ⁻⁴	3.4 × 10 ⁻⁸
Norfloxacin	2.1 × 10 ⁻⁵	3.5 × 10 ⁻⁸
Lomefloxacin	>1.0 × 10 ⁻⁴	4.7 × 10 ⁻⁷
Ciprofloxacin	>1.0 × 10 ⁻⁴	2.1 × 10 ⁻⁶
Pipemidic acid	>1.0 × 10 ⁻⁴	3.2 × 10 ⁻⁶
Ofloxacin	>1.0 × 10 ⁻⁴	4.7 × 10 ⁻⁵
AT-4140	>1.0 × 10 ⁻⁴	9.4 × 10 ⁻⁵
AM-1091	>1.0 × 10 ⁻⁴	1.3 × 10 ⁻⁵
T-3262	>1.0 × 10 ⁻⁴	>1.0 × 10 ⁻⁴
Nalidixic acid ^b	>1.0 × 10 ⁻⁴	>1.0 × 10 ⁻⁴
Des-piperazinyl-norfloxacin ^b	>1.0 × 10 ⁻⁴	>1.0 × 10 ⁻⁴

^a IC₅₀s express the mean of two separate experiments that were performed in duplicate. Because of the low solubility of the compounds, concentrations of >10⁻⁴ M could not be tested.

^b No competitive inhibition with [³H]muscimol at 10⁻⁴ M was observed either with or without BPA.

brain synaptic membranes was displaced by cold GABA in a dose-dependent manner and showed both saturability and reversibility. The membrane preparation had a binding affinity of 5.4 × 10⁻⁸ M for [³H]muscimol, and the receptor density was 2.9 pmol/mg of protein.

The effect of quinolones on [³H]muscimol binding to GABA receptor sites in the presence or absence of BPA (10⁻⁴ M) in vitro is presented in Table 3. The concentration required to inhibit 50% of specific binding (IC₅₀) for each compound was derived from the dose-response curve. It was found that each quinolone inhibited [³H]muscimol binding competitively. In the absence of BPA, the IC₅₀s of all compounds, except that of norfloxacin, were more than 10⁻⁴ M, the maximal concentration tested because of the low solubility of the compounds. The IC₅₀ of norfloxacin was 2.1 × 10⁻⁵ M. In the presence of BPA, on the other hand, the IC₅₀s differed considerably among the quinolones tested, to between 3.4 × 10⁻⁸ M and more than 1 × 10⁻⁴ M. The inhibitory potencies were high for enoxacin, norfloxacin, and lomefloxacin; moderate for ciprofloxacin, pipemidic acid, AM-1091, ofloxacin, and AT-4140; and low for T-3262. Nalidixic acid and des-piperazinyl-norfloxacin did not inhibit the [³H]muscimol binding at all, even at 10⁻⁴ M. These results indicated that there is a close correlation between the inhibitory potency of quinolones on [³H]muscimol binding to GABA receptor sites and their epileptogenic activities in mice in combination with BPA.

DISCUSSION

The relationship between the chemical structure of quinolones and their epileptogenic activities in mice was investigated with special reference to the interaction with GABA receptor sites. The quinolones were administered intravenously to mice, thereby avoiding the difference in oral absorbability among the compounds and permitting the rapid onset of pharmacological effects without a large difference among individuals. Although differences might still exist among the quinolones in their penetrabilities into the mouse brain through the blood-brain barrier, the maximal concentrations of quinolones, including ofloxacin and ciprofloxacin, in the brains of mice after intravenous administration of 100 mg/kg were approximately 10⁻⁵ M (unpublished data).

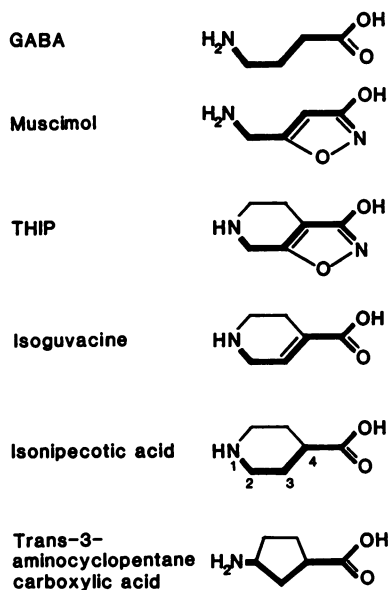


FIG. 2. Chemical structure of GABA receptor agonists. THIP, 4,5,6,7-Tetrahydroisoxazolo[5,4-c]pyridin-3-ol.

The epileptogenic activities of quinolones generally correlated well with their inhibitory activities on [³H]muscimol binding to GABA receptor sites. Both activities were enhanced in the presence of BPA, a metabolite of fenbufen, although the reasons for these augmentations are obscure. The pharmacokinetic parameters, as well as the protein binding of lomefloxacin, ofloxacin, and ciprofloxacin in serum, were not influenced by the combination of the quinolones with fenbufen (26; unpublished data). The epileptogenic activity of norfloxacin was suppressed by muscimol and diazepam, which are agonists for the GABA_A-benzodiazepine receptor complex (14, 18), while it was not influenced by baclofen, a GABA_B receptor agonist (7, 9), suggesting that the inhibition of GABA binding to the GABA_A-benzodiazepine receptor complex in the brain may be involved in the induction of epileptogenic activities of quinolones, as has been indicated previously (21, 24). Nevertheless, ofloxacin provoked neither convulsion nor death in mice, even at 100 mg/kg, while it had a moderate inhibitory activity on [³H]muscimol binding. This discrepancy might be attributed to the presence of a lower level of ofloxacin in the mouse brain than that which is required to inhibit GABA binding to the receptor sites.

Muscimol, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol, isoguvacine, isonipecotic acid, and *trans*-3-aminocyclopentane carboxylic acid (ACPCA) are established as GABA_A receptor agonists (12, 15, 20). These compounds possess a common element that fits onto the GABA structure (Fig. 2); this element provides zwitterions in molecules. The corresponding N⁺ to O⁻ distances estimated by Dreiding stereomodels were almost identical among these agonists. The distance in muscimol was reported to be in the range of 0.52 to 0.55 nm (2), and this conformation plays an important role in its activity as a GABA_A receptor agonist (2). Among the GABA_A receptor agonists, isonipecotic acid seems to share a common structure with the piperazine moiety in quinolones (Fig. 1 and 2). Introduction of a hydroxy or an amino group in the *cis* configuration at the 3 position of isonipecotic acid results in a marked increase in the IC₅₀s for the inhibition of GABA binding owing to steric

hindrance (15, 20). The quinolones that possess piperazine substituted with a methyl group(s), such as ofloxacin and AT-4140, exhibited lower inhibitory activities on [³H]muscimol binding than did those with unsubstituted piperazines at the 7 position, also probably owing to the steric hindrance corresponding to the introduction of a methyl group(s). Lomefloxacin, which has a 3-methyl piperazine at the 7 position, however, exhibited the same level of inhibitory activity as those of enoxacin and norfloxacin, which have unsubstituted piperazine moieties at their 7 positions (Table 1). This might be attributable to the flexibility of the piperazine ring, which might provide an optimal conformation for the GABA_A-benzodiazepine receptor complex. AM-1091, which showed moderate inhibition for [³H]muscimol binding, shares the common structure with ACPCA at the 7 position of the quinoline ring (Fig. 1 and 2), and the IC₅₀ of ACPCA for inhibition of GABA binding has been reported to be approximately 20 times higher than that of GABA per se (12, 15). Although T-3262 possesses an aminopyrrolidine moiety at the 7 position of the naphthylidene ring, as does AM-1091, it showed a lower level of inhibitory potency than that of AM-1091. Hori et al. (10) have indicated that a bulky difluorophenyl group at the 1 position of the ring might inhibit its interaction with GABA receptor sites.

Thus, the epileptogenic activities of quinolones possibly relate to the GABA-like structures of the substituents at the 7 positions of parent nuclei, which act as the antagonists of GABA receptors. This is consistent with the lack of inhibitory activity on [³H]muscimol binding of nalidixic acid and des-piperazinyl-norfloxacin, which do not have a piperazine or aminopyrrolidine moiety at their 7 positions.

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