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Inhibition of Rat Acute Inflammatory Paw Oedema by Dihemiphthalate of Glycyrrhetinic Acid Derivatives: Comparison with Glycyrrhetinic Acid

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Abstract—The anti-inflammatory profile of dihemiphthalate compounds of glycyrrhetinic acid derivatives in acute rat paw oedema induced by various vasoactive agents was compared with the parent compound. Three dihemiphthalate compounds (the di-sodium salt of 18β-olean-12-ene-3β,30-diol di-*O*-hemiphthalate, 18β-olean-9(11),12-dione-3β,30-diol di-*O*-hemiphthalate and olean-11,13(18)-diene-3β,30-diol di-*O*-hemiphthalate), significantly inhibited development of carrageenan-induced rat paw oedema during the first 3 h (ED50 70, 90, and 108 mg kg^{-1} respectively, p.o.), while glycyrrhetinic acid (ED50, 200 mg kg^{-1}) showed a significant inhibition of paw oedema 3 h after carrageenan treatment. The dihemiphthalate compounds also suppressed mouse paw oedema induced by histamine, bradykinin, and PAF acether at doses of less than 100 mg kg^{-1}. However, these compounds failed to inhibit 5-HT-induced mouse paw oedema. Glycyrrhetinic acid had little effect on mouse paw inflammation induced by the above irritants. The three compounds at 10^{-7}–10^{-4} M, inhibited histamine-induced contraction of guinea-pig isolated ileum. However, concentration-response curves to 5-HT and bradykinin were not affected by the same compounds. These results suggest that the dihemiphthalate compounds modulate vascular permeability caused by endogenous vasoactive agents as one of the anti-inflammatory mechanisms. This action is quite different from that of glycyrrhetinic acid.

Glycyrrhetinic acid (Ia) (Fig. 1), the aglycone of glycyrrhizin isolated from liquorice root (*Glycyrrhiza* spp.), has been found to have wide pharmacological effects such as anti-inflammatory activity (Finney & Somers 1958; Capasso et al 1983), anti-tumorigenic activity (Nishino et al 1986), and inhibition of both hepatic and renal 11β-hydroxysteroid dehydrogenase (Monder et al 1989), as well as inhibition of intercellular gap junction communication (Davidson et al 1986) and growth of mouse melanoma (Abe et al 1987). Glycyrrhetinic acid derivatives have been prepared to enhance the therapeutic property and suppress adverse effects (pseudo-aldosteronism) of the parent compound (Shibata et al 1987). Clinically, carbenoxolone sodium (Ib) (Fig. 1) has already been used for the treatment of gastric ulcer (Doll et al 1962). Glycyrrhetinic acid 3β-*O*-hemiphthalate sodium (Ic) has been shown to reduce pain at venous cannulation with transdermal 10% lignocaine base gel (Kano et al 1992). Furthermore, three kinds of anti-inflammatory dihemiphthalate compounds (Fig. 1; disodium salt of 18β-olean-12-ene-3β,30-diol di-*O*-hemiphthalate (IIc), 18β-olean-9(11),12-diene-3β,30-diol di-*O*-hemiphthalate (IIIa), and olean-11,13(18)-diene-3β,30-diol di-*O*-hemiphthalate (IVa)) have been reported to inhibit lipoxygenase and cyclo-oxygenase activities in a cell-free system prepared from cloned mastocytoma cells (Inoue et al 1986), type IV allergic reaction (Inoue et al 1987), prostaglandin E_2 (PGE_2) synthesis in mouse peritoneal fluid (Inoue et al 1990) and mouse skin inflammation induced by arachidonic acid (Inoue et al 1988) and 12-*O*-tetradecanoylphorbol-13-acetate (Inoue et al 1989). The anti-inflammatory action of dihemiphthalate compounds has been demonstrated as one of the mechanisms by which leukotrienes and PGE_2 synthesis is inhibited at the site of acute inflammation (Inoue et al 1988, 1990). Shamsa et al (1991) recently reported that inhibition by the dihemiphthalate on activity of cAMP-dependent protein kinase derived from Ehrlich ascites tumour cells may be implicated physiologically in its anti-inflammatory action. In addition, these compounds have been found to prevent experimental gastric ulcer by strengthening gastric mucosal defense mechanisms, which were independent of the protective effect of prostaglandins (Yano et al 1989).

In this study, we have compared the anti-inflammatory

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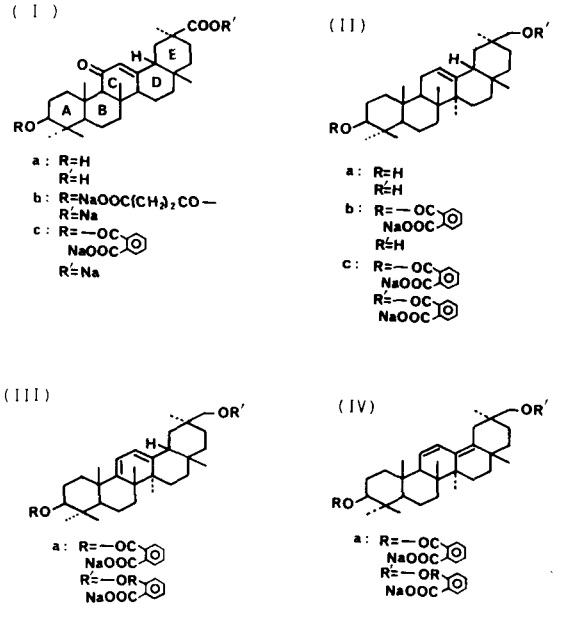

FIG. 1. The structures of glycyrrhetinic acid derivatives.

Table 1. Inhibition of glycyrrhetinic acid derivatives on carrageenan-induced rat paw oedema.

Compound	Dose (mg kg^{-1})	Paw oedema (mL) Control	Paw oedema (mL) Treated	Inhibition (%)
Ia	100	0·80±0·03	0·77±0·04	4
	200	0·80±0·03	0·68±0·04*	15
Ib	100	0·75±0·06	0·56±0·05**	25
Ic	100	0·73±0·06	0·61±0·07	16
	200	0·73±0·06	0·56±0·03*	23
IIa	200	0·61±0·06	0·59±0·03	3
IIb	200	0·61±0·06	0·57±0·01	7
IIc	25	0·67±0·02	0·48±0·05**	28
IIIa	25	0·72±0·04	0·52±0·05*	29
IVa	25	0·79±0·01	0·60±0·04**	24
Indomethacin	5	0·86±0·04	0·34±0·04***	60
Cyproheptadine	10	0·52±0·05	0·64±0·01	0

Test compounds were orally administered 30 min before injection of 1% carrageenin suspension. Each value represents the mean±s.e.m. of six animals 3 h after irritant treatment. * $P<0·05$, ** $P<0·01$, *** $P<0·001$.

profile of the dihemiphthalate compounds with glycyrrhetinic acid.

Materials and Methods

Materials

Glycyrrhetinic acid and its derivatives were prepared according to the method of Shibata et al (1987) who also reported the physicochemical data for these compounds. Indomethacin, pyrilamine, cyproheptadine, dexamethasone, 5-HT, bradykinin, PAF acether, λ carrageenan, and histamine were purchased from Sigma Chemical Co., USA and aspirin was from Nakarai Chemical Co., Japan.

Carrageenan-induced rat paw oedema

The induction of carrageenan-induced paw oedema was based on the method of Di Rosa et al (1971). Each hindpaw of male Wistar rats (Japan SLC Inc., Japan, 170–210 g) was injected with 0·1 mL 1% suspension of carrageenan in 0·9% NaCl (saline). Paw oedema was measured during 6 h after the irritant treatment by water plethysmometry (MK-500, Muromachi, Japan).

Vasoactive agent-induced mouse paw swelling

The hind paws of mice ddY, 6 weeks old (Japan SLC Inc., Japan), were injected with 5 μL of the following vasoactive agents: 0·3 μg 5-HT (Tsurufuji et al 1979), 10 μg bradykinin in saline (Oyanagui 1981), and 0·1 μg PAF acether combined with 0·1 μg PGE_2 in <5% ethanol/saline. Histamine-induced paw oedema was induced by injecting 5 μL 1 μg histamine combined with 0·1 μg PGE_2 in saline into the hindpaws of mice. The paw swelling was measured 15 min after each irritant treatment by a digital linear gauge (DG-911, Ono Sokki, Japan).

Drug treatment

Test compounds were dissolved or suspended in 1% polyoxyethylene sorbitan mono-oleate (Tokyo Kassel Chemical Industry, Japan) in saline and then were orally administered 30 min before each irritant treatment. Control groups received the vehicle only.

Contractile response of guinea-pig isolated ileum to irritant agents

Male Hartley guinea-pigs, 300–350 g (Japan SLC Inc., Japan), were killed by cervical dislocation and exsanguination. An approximate 20-mm length of ileum was removed and mounted in a 10-mL organ bath containing Tyrode solution (bubbled with 95% O_2–5% CO_2) of the following composition (mM): NaCl 136·9, KCl 2·7, $CaCl_2$ 1·4, $MgCl_2$ 1·0, NaH_2PO_4 0·4, $NaHCO_3$ 11·9, glucose 5·6. The tissue was equilibrated for 30–60 min under 0·4 g resting tension before test compounds were administered. After equilibration in Tyrode solution at 32°C, contractions were isometrically measured by a force displacement transducer (ME commercial, Japan) and displaced on a recorder (Hitachi, Japan). Concentration-response curves were generated by adding contractile agonists cumulatively to the organ bath. After washing the ileum and restoration of the base-line tension, test compounds were incubated in the bath for 3 min at 10^{-7}–10^{-4} M. Subsequent concentration-response curves in the presence of test compounds were obtained by adding agonists similarly. Test compounds and agonists were dissolved in Tyrode solution. The mean contractile response to each concentration of agonist, in the control and in the presence of the various concentrations of test compounds, was expressed as a percentage of the control maximum response.

Statistics

Statistical significance of differences between control and test groups was determined using the unpaired Student's *t*-test or the Cochran-Cox test.

Results

Effects of glycyrrhetinic acid and its derivatives on carrageenan-induced rat paw oedema

The effects of test compounds (Fig. 1) on carrageenan-induced paw oedema at 3 h after the irritant treatment are summarized in Table 1. The inhibitory effects of dihemiphthalate compounds, IIc, IIIa, and IVa, on carrageenan-induced paw oedema are shown in Fig. 2. The ED50 values

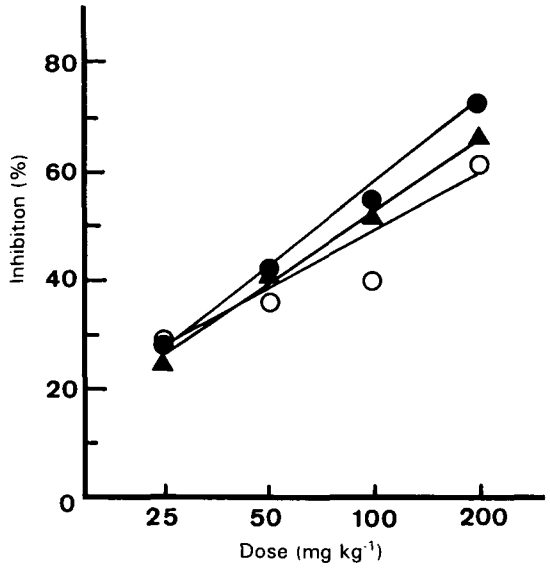

FIG. 2. The dose-dependent inhibition of the dihemiphthalate compounds on carrageenan-induced rat paw oedema. Various doses of the compounds were orally administered 30 min before carrageenan treatment. ● Compound IIc; ▲ compound IIIa; ○ compound IVa. Each point represents mean percent of inhibition compared with the control for seven animals.

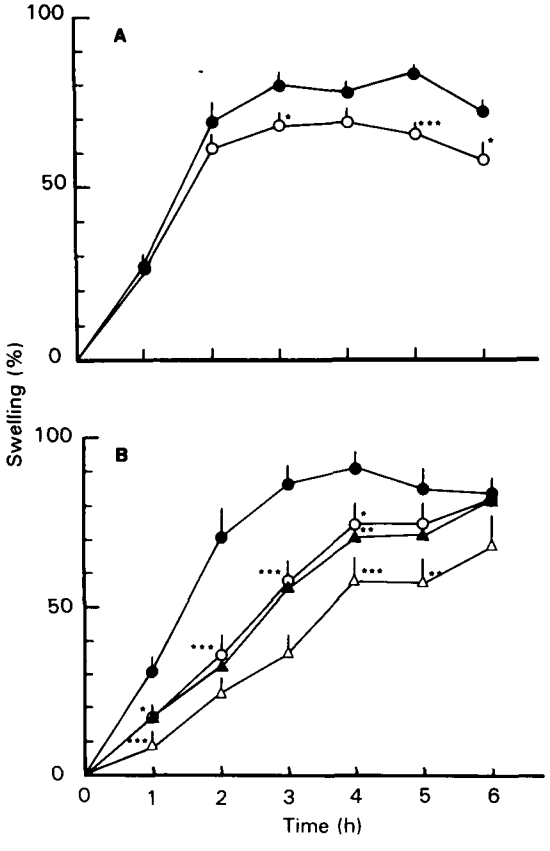

FIG. 3. Inhibitory effect of glycyrrhetinic acid and compound IIIa on carrageenan-induced rat paw oedema. Compounds were orally administered 30 min before carrageenan treatment. A. Glycyrrhetinic acid, ● saline; ○ 200 mg kg^{-1}. B. Compound IIIa, ● saline; ○ 50 mg kg^{-1}; ▲ 100 mg kg^{-1}; △ 200 mg kg^{-1}. Each point represents the mean ± s.e.m. of six animals. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

were 70 mg kg^{-1} for IIc, 90 mg kg^{-1} for IIIa, and 108 mg kg^{-1} for IVa; glycyrrhitinic acid significantly inhibited oedema ($P<0.05$) with an ED50 value greater than 200 mg kg^{-1}. Compound IIIa was strongly effective in inhibiting paw oedema during the first 3 h, but its inhibitory potency decreased by 6 h after the irritant treatment (Fig. 3). Inhibitory effects of other dihemiphthalate compounds (IIc and IVa) and cyproheptadine were also confirmed to act similarly to compound IIIa (data not shown), while glycyrrhetinic acid (Ia) had little effect during the first 2 h. Indomethacin failed to suppress an initial stage of oedema formation, although the inhibitory effect was observed 3 h after the irritant treatment. Furthermore, the dihemiphthalate compounds showed significant inhibition ($P<0.05$) of paw oedema at 6 h when administered twice, 0.5 h before and 4 h after the irritant treatment, while the paw oedema was not suppressed by two administrations of cyproheptadine (data not shown).

Effects of glycyrrhetinic acid derivatives on vasoactive agent-induced mouse paw swelling (Table 2)

Each paw oedema dramatically increased within 20 min after irritant injection. The increase in paw thickness caused by histamine, 5-HT, bradykinin, and PAF acether was 56.0 ± 3.7 ($\times 10^{-2}$ mm, s.e.m., n = 16), 53.3 ± 2.6 (n = 15), 48.6 ± 1.6 (n = 15), and 57.3 ± 0.9 (n = 15), respectively. Glycyrrhetinic acid (Ia), carbenoxolone sodium (Ib), and compound Ic showed no inhibition on the irritant-induced paw oedema at 200 mg kg^{-1}, although these compounds were able to suppress carrageenan-induced paw oedema. However, dihemiphthalate compound IIc, IIIa, and IVa significantly inhibited swelling induced by the other irritant, except for 5-HT at doses of less than 100 mg kg^{-1}. Furthermore, the dose-dependence of the inhibitory effect of compound IIc on histamine and PAF acether-induced oedema was found to have an ED50 value of 52.7 and 87.3 mg kg^{-1}, respectively. Compound IVa also showed an ED50 value of 69.7 mg kg^{-1} for bradykinin-induced paw oedema. Cyproheptadine was able significantly to inhibit every irritant-induced oedema ($P<0.01$ or $P<0.001$), while aspirin had little effect. Pyrilamine suppressed histamine oedema only ($P<0.001$).

Effect of dihemiphthalate compounds on responses of guinea-pig isolated ileum to contractile agonists

The effects of dihemiphthalate compounds (IIc, IIIa and IVa) on the responses of guinea-pig ileum to histamine, 5-HT, and bradykinin were examined. Maximal responses were 71.8 ± 6.9% (n = 10) for 5-HT and 103.0 ± 5.2% (n = 18) for bradykinin to the histamine-induced maximal contractile response. The inhibitory response to histamine (10^{-7}–10^{-4} M) by dihemiphthalate compounds (Fig. 4) was rapidly reversed by washing and exhibited competitive antagonism for the H_1 receptor, but was not evident in a dose-dependent manner. Glycyrrhetinic acid had no effect on the histamine response curve (data not shown). Increasing concentrations of dihemiphthalate compounds did not cause any shift to the right of 5-HT and bradykinin concentration-response curves (Fig. 4).

Discussion

Effects of glycyrrhetinic acid derivatives examined on the paw swelling induced by vasoactive agents showed that three

Table 2. Inhibition of glycyrrhetinic acid derivatives on mouse paw oedema induced by vasoactive agents.

Compound	Dose (mg kg^{-1})	Inhibition (%) Histamine	5-HT	Bradykinin	PAF-acether
Ia	200	0	11	8	0
Ib	200	13	7	0	20
Ic	200	20	0	16	22
IIc	25	38*	—	0	18
	50	52**	22	45***	31
	100	67***	28	53**	56**
IIIa	25	27	—	19	20
	50	19	17	33	46**
	100	47**	19	49**	48***
IVa	25	28	—	12	23
	50	28	0	30	29*
	100	61***	6	64***	45***
Aspirin	200	0	8	13	0
Cyproheptadine	20	83**	78***	43**	43**
Pyrilamine	20	47**	—	10	0

Test compounds were orally administered 30 min before injection of each irritant. Swelling was measured 15 min after irritant treatment. Statistical significance from the control at * $P<0.05$, ** $P<0.01$ and *** $P<0.001$ (n = 7).

kinds of dihemiphthalate compounds (IIc, IIIa, and IVa) inhibited all oedema formation except that induced by 5-HT. This finding supports the hypothesis that these compounds produced a moderately potent inhibition, compared with glycyrrhetinic acid, of the initial stage of carrageenan-induced paw oedema by preventing vascular permeability induced by chemical mediators such as histamine, bradykinin, and PAF. Glycyrrhetinic acid had little effect on paw swelling induced by vasoactive agents. The inhibitory effect of dihemiphthalate compounds on histamine-, bradykinin-, and PAF-oedema was less potent than that of cyproheptadine producing inhibition of about 40–80% of the paw swelling. Thus, biological amines such as histamine and 5-HT may play an important role in the development of bradykinin- and PAF-induced paw swelling. Compound IIc, a dihemiphthalate compound, showed inhibition of histamine-induced oedema in a dose-dependent manner. Furthermore, high concentrations of these compounds caused significant shifts to the right of the histamine log concentration-curves. This suggests that dihemiphthalate compounds at relatively high concentrations may partly act as blocking agents to prevent the direct action of histamine on H_1 receptors on tissues, including microvessels, although their structures are not similar to the novel receptor antagonist. However, these compounds failed to show the rightward shift of the response curves of the ileum to bradykinin but significantly inhibited bradykinin-induced oedema. Bradykinin possesses many pro-inflammatory properties including the ability of inducing hyperalgesia, vasodilatation, and increasing vascular permeability (Regoli & Barabé 1980). In addition, bradykinin can evoke release of mediators such as histamine from mast cells (Devillier et al 1985) as well as activation of B_2 receptors on endothelial cells of microvessels (Marceau et al 1981, 1983) and on ileal smooth muscle (Kachur et al 1987). The bradykinin-induced oedema is partly suppressed when pretreated with both diphenhydramine and methysergide, as well as with the B_2-receptor antagonist (Wang et al 1989). These observations indicate that the dihemiphthalate compounds indirectly inhibited bradykinin-induced paw oedema. PAF acether is also a potential mediator of inflammation which increases vascular permeability (Björk & Smedegard 1983) and induces oedema formation (Silva et al 1986). PAF-acether-induced oedema

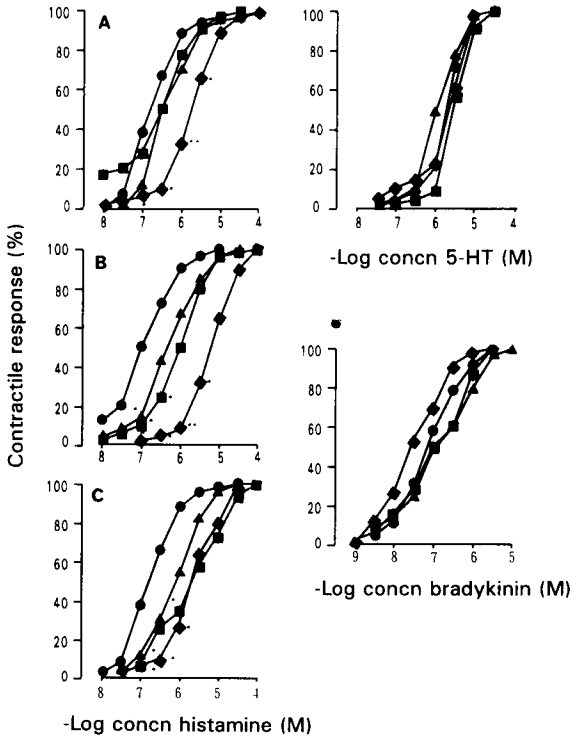

FIG. 4. Effects of the dihemiphthalate compounds on responses to histamine, 5-HT and bradykinin in guinea-pig ileum. Control curve (●). Histamine; A compound IIc, B compound IIIa, C compound IVa (▲ 10^{-7} M; ■ 10^{-5} M; ◆ 10^{-4} M). 5-HT and bradykinin; ▲ compound IIc (10^{-4} M), ■ compound IIIa (10^{-5} M), ◆ compound IVa (10^{-4} M). Each point represents the mean ± s.e.m. of 3–4 experiments. * $P<0.05$, ** $P<0.01$.

was known to be sensitive to dual inhibition of leukotrienes and prostaglandins and cyproheptadine, as well as to a PAF antagonist (Calhoun et al 1987). The dihemiphthalate compounds significantly inhibited the paw oedema development but failed to prevent PAF acether-induced rabbit platelet aggregation (data not shown). We previously demonstrated that the dihemiphthalate compounds are dual inhibitors of 5-lipoxygenase and cyclo-oxygenase in-vitro (Inoue et al 1986) and in-vivo (Inoue et al 1988). Thus, it is possible that inhibitory effects of the compounds on paw oedema are, at least, nonspecific and do not directly act via the bradykinin and PAF receptors. Further study is required to explain why these compounds prevented the oedema formation induced by bradykinin and PAF acether and did not inhibit the 5 HT-induced paw oedema.

In this study, the dihemiphthalate compounds of glycyrrhetinic acid derivatives were capable of suppressing paw oedema induced by carrageenan and vasoactive agents such as histamine, bradykinin, and PAF acether, which suggests that the compounds modulate vascular permeability in the process of the acute inflammatory response. This is quite different from the action of glycyrrhetinic acid.

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References

Abe, H., Ohya, N., Yamamoto, K. F., Shibuya, T., Arichi, S., Odashima, S. (1987) Effects of glycyrrhizin and glycyrrhetinic acid on growth and melanogenesis in cultured B16 melanoma cells. Eur. J. Cancer Clin. Oncol. 23: 1549–1555

Björk, J., Smedegard, G. (1983) Acute microvascular effects of PAF-acether, as studied by intravital microscopy. Eur. J. Pharmacol. 96: 87–94

Calhoun, W., Chang, J., Carlson, R. P. (1987) Effect of selected antiinflammatory agents and other drugs on zymosan, arachidonic acid, PAF and carrageenan induced paw edema in the mouse. Agents Actions 21: 306–309

Capasso, F., Mascolo, N., Autore, G., Duraccio, M. R. (1983) Glycyrrhetinic acid, leucocytes and prostaglandins. J. Pharm. Pharmacol. 35: 332–335

Davidson, J. S., Baumgarten, I. M., Harley, E. H. (1986) Reversible inhibition of intercellar junctional communication by glycyrrhetinic acid. Biochem. Biophys. Res. Commun. 134: 29–36

Devillier, P., Renoux, M., Giroud, J. P., Regoli, D. (1985) Peptides and histamine release from rat peritoneal mast cells. Eur. J. Pharmacol. 117: 89–96

Di Rosa, M., Giroud, J. P., Willoughby, D. A. (1971) Studies of the mediators of the acute inflammatory response induced in rats in different sites by carrageenan and turpentine. J. Pathol. 104: 15–29

Doll, R., Hill, I. D., Hutton, C., Underwood, D. J. (1962) Clinical trial of a triterpenoid liquorice compound in gastric and duodenal ulcer. Lancet ii: 793–796

Finney, R. S. H., Somers, G. F. (1958) The anti-inflammatory activity of glycyrrhetinic acid and derivatives. J. Pharm. Pharmacol. 10: 613–620

Inoue, H., Saito, H., Koshihara, Y., Murota, S. (1986) Inhibitory effect of glycyrrhetinic acid derivatives on lipoxygenase and prostaglandin synthetase. Chem. Pharm. Bull. (Tokyo) 34: 897–901

Inoue, H., Mori, T., Shibata, S., Saito, H. (1987) Pharmacological activities of glycyrrhetinic acid derivatives: analgesic and anti-type IV allergic effects. Chem. Pharm. Bull. (Tokyo) 35: 3888–3893

Inoue, H., Mori, T., Shibata, S., Koshihara, Y. (1988) Inhibitory effect of glycyrrhetinic acid derivatives on arachidonic acid-induced mouse ear oedema. J. Pharm. Pharmacol. 40: 272–277

Inoue, H., Mori, T., Shibata, S., Koshihara, Y. (1989) Modulation by glycyrrhetinic acid derivatives of TPA-induced mouse ear oedema. Br. J. Pharmacol. 96: 204–210

Inoue, H., Kurosu, S., Takeuchi, T., Mori, T., Shibata, S. (1990) Glycyrrhetinic acid derivatives: anti-nociceptive activity of deoxoglycyrrhetol dihemiphthalate and the related compounds. J. Pharm. Pharmacol. 42: 199–200

Kachur, J. F., Allbee, W., Danho, W., Gaginella, T. S. (1987) Bradykinin receptors: functional similarities in guinea pig gut muscle and mucosa. Regul. Pept. 17: 63–70

Kano, T., Hashiguchi, A., Nakamura, M., Morioka, T., Mishima, M., Nakano, M. (1992) A comparative study of transdermal 10% lidocaine gel with and without glycyrrhetinic acid monohemiphthalate disodium for pain reduction at venous cannulation. Anesth. Analg. 74: 535–538

Marceau, F., Knap, M., Regoli, D. (1981) Pharmacological characterization of the vascular permeability enhancing effects of kinins in the rabbit skin. Can. J. Physiol. Pharmacol. 59: 921–926

Marceau, F., Lussier, A., Regoli, D., Giroud, J. P. (1983) Pharmacology of kinins: their relevance to tissue injury and inflammation. Gen. Pharmacol. 14: 209–229

Monder, C., Stewart, P. M., Lakshmi, V., Valentino, R., Burt, D., Edwards, C. R. W. (1989) Licorice inhibits corticosteroid 11β-dehydrogenase of rat kidney and liver: in vivo and in vitro studies. Endocrinology 125: 1046–1053

Nishino, H., Yoshioka, K., Iwashima, A., Takizawa, H., Konishi, S., Okamoto, H., Okabe, H., Shibata, S., Fujiki, H., Sugimura, T. (1986) Glycyrrhetinic acid inhibits tumor-promoting activity of teleocidin and 12-*O*-tetradecanoylphorbol-13-acetate in two-stage mouse skin carcinogenesis. Jpn. J. Cancer Res. 77: 33–38

Oyanagui, Y. (1981) Steroid-like anti-inflammatory effect of superoxide dismutase in serotonin-, histamine- and kinin-induced edemata of mice: existance of vascular permeability regulating protein (s). Biochem. Pharmacol. 30: 1791–1798

Regoli, D., Barabé, J. (1980) Pharmacology of bradykinin and related kinins. Pharmacol. Rev. 32: 1–16

Shamsa, F., Nagata, N., Oh-Ishi, M., Ohtuski, K. (1991) The in vitro effects of glycyrrhizin and the derivatives of glycyrrhetinic acid on the activity of cAMP-dependent protein kinase and phosphorylation of cellular polypeptide by the kinase from Ehrlich ascites tumor cells. Tohoku J. Exp. Med. 165: 305–318

Shibata, S., Takahashi, K., Yano, S., Harada, M., Saito, H., Tamura, Y., Kumagai, A., Hirabayashi, K., Yamamoto, M., Nagata, N. (1987) Chemical modification of glycyrrhetinic acid in relation to the biological activities. Chem. Pharm. Bull. (Tokyo) 35: 1910–1918

Silva, P. M. R., Cordeiro, R. S. B., Martins, M. A., Henriques, M. G. M. O., Vargaftig, B. B. (1986) Platelet involvement in rat paw edema induced by 2-methoxy-PAF. Inflammation 10: 393–401

Tsurufuji, S., Sugio, K., Takemasa, F. (1979) The role of glucocorticoid receptor and gene expression in the anti-inflammatory action of dexamethasone. Nature 280: 408–410

Wang, J. P., Hsu, M. F., Ouyang, C., Teng, C. M. (1989) Edematous response caused by [Thi^{5,8}, D-Phe^{7}] bradykinin, a B_2 receptor antagonist, is due to mast cell degranulation. Eur. J. Pharmacol. 161: 143–149

Yano, S., Harada, M., Watanabe, K., Nakamura, K., Hatakeyama, Y., Shibata, S., Takahashi, K., Mori, T., Hirabayashi, K., Takeda, M., Nagata, N. (1989) Antiulcer activities of glycyrrhetinic acid derivatives in experimental gastric lesion models. Chem. Pharm. Bull. (Tokyo) 37: 2500–2504