Abstract—A newly synthesized compound, \([3-(1H-tetrazol-5-yl)-phenyl] amino\)oxoacetic acid n-butyl ester (MTB) has been demonstrated to be an orally active antiallergic agent. This compound inhibited the 48-hr passive cutaneous anaphylaxis (48-hr PCA) induced by IgE in rats. In guinea pigs, MTB also inhibited the 8-day passive cutaneous anaphylaxis (8-day PCA) and the 8-day passive systemic anaphylaxis induced by IgE. The compound partially inhibited the IgG-mediated 3-hr PCA in rats and guinea pigs, but failed to have any effect on the rabbit IgG-mediated 3-hr PCA in these animals. In the rat, MTB was not an antagonist of histamine or serotonin. The antiallergic effect of MTB was not mediated via any adrenergic mechanisms. MTB significantly inhibited histamine release from rat peritoneal cells induced by rat IgE in vitro.

The pharmacological effects of disodium cromoglycate (DSCG), an agent for the treatment of bronchial asthma, depend on the inhibition of the liberation of mediators of allergic reactions initiated by a reaginic antibody-antigen interaction (1-3). DSCG, however, is not absorbed orally to any significant extent, and its effectiveness was brought about by an aerosol preparation. Considerable interest has been stimulated in the development of agents for prophylaxis in allergic asthma which are effective by an oral route (4-6). This report describes the immunopharmacology of a newly synthesized compound, \([3-(1H-tetrazol-5-yl)-phenyl] amino\)oxoacetic acid n-butyl ester (MTB), which has been found to inhibit IgE-mediated PCA and PSA in animals when it is administered orally. The chemical structure of MTB is shown in Fig. 1.

MATERIALS AND METHODS

Animals: Male Wistar rats (150-250 g), male Hartley guinea pigs (300-400 g), and male albino rabbits (3.0-4.0 kg) were obtained from the Japan Laboratory Animals Corporation. Adrenalectomy or splenectomy in rats was performed by the usual procedure. Adrenalectomized rats were provided with saline instead of tap water for 5 days before they were used in experiments.

Chemicals: The following chemicals were used: egg albumin (EA, Sigma), Freund's complete adjuvant (FCA, Difco), killed...
Bordetella pertussis (Chiba Serum Institute), disodium cromoglycate (DSCG, Intal, Fisons), compound 48/80 (Sigma), Evans Blue, serotonin, and histamine (Wako). MTB was synthesized in the Wakamoto Pharmaceutical Laboratories.

IgE-mediated 48-hr PCA reaction in rats: Rat anti-dinitrophenylated ascaris extract antiserum (anti-DNP-Asc) was prepared by the method of Okumura and Tada (7). The serum thus obtained sensitized the rat skin for a PCA reaction for at least 1 week. The rat 48-hr PCA titer of the antiserum was 1:64–256 and inactivated by heating at 56°C for 4-hr. Male rats were sensitized intradermally with 0.1 ml of an appropriate dilution of rat IgE anti-DNP-Asc. Forty eight hours later, the animals were challenged with an i.v. injection of 0.5 ml saline containing 1 mg of DNP-Asc and 2.5 mg of Evans Blue and sacrificed after 30 min. The skin was everted and the wheal sizes were measured. The mean wheal size for each group was calculated, and the percent inhibition was calculated by the following equation: \((\text{Sc} - \text{St}/\text{Sc}) \times 100\), where Sc is the wheal size of the control group, and St is the wheal size of the drug-treated group. The significance of the difference in the control and drug-treated groups was determined by the use of the Student's test. The dose bringing about 50% inhibition (ID50) was calculated graphically from the dose-inhibition relationship and expressed as the inhibition percent of the wheal size against the dose on a logarithmic scale. A minimum of four animals was used for each data point. Drugs were administered by various routes before the antigen challenge. MTB was incorporated as a fine suspension in saline with 2 drops of Tween 80 or dissolved in 1% sodium bicarbonate solution, and DSCG was dissolved in saline. In the case of an oral administration, MTB suspended in 0.5% CMC was used.

Rat IgG-mediated and rabbit IgG-mediated 3-hr PCA reaction in rats: Rat hyperimmune anti-EA antiserum (anti-EA) was prepared by the method of Casey et al. (6). The antiserum with the rat 3-hr PCA titer of 1:64 did not induce 48-hr PCA. Rabbit anti-EA antiserum was prepared by the method of Koda et al. (8). The rat 3-hr PCA titer was 1:6. The rats were sensitized intradermally with 0.1 ml of each antiserum, appropriately diluted. After three hours, the animals were challenged intravenously with a solution of 1 mg of EA and evaluated in the manner described for 48-hr PCA.

Guinea pig IgG-mediated 8-day, guinea pig IgG-mediated 3-hr, and rabbit IgG-mediated 3-hr PCA reactions in guinea pigs: Guinea pig anti-DNP-Asc antiserum was prepared according to the immunization procedure of Levine et al. (9) using DNP-Asc as the antigen. The guinea pig 8-day PCA titer of the antiserum was 1:4,000, and the titer of the serum heated at 56°C for 4-hr was markedly reduced to 1:250.

Guinea pig hyperimmune anti-EA serum was prepared according to the immunization procedure of Levine et al. (9) using EA as the antigen. The guinea pig 3-hr PCA titer of antiserum was 1:4,000, and the 8-day PCA titer could not be detected. Male guinea pigs were sensitized intradermally with 0.1 ml of an appropriately diluted guinea pig IgE anti-DNP-Asc, guinea pig IgG anti-EA, and rabbit IgG anti-EA. After three hours or eight days, the animals were challenged intravenously with a solution of 0.5 mg of antigen and were evaluated in a manner similar to that described for the rats.

IgE-mediated 8-day passive systemic anaphylaxis (8-day PSA) in guinea pigs: Guinea pigs were passively sensitized with 0.5 ml of the IgE anti-DNP-Asc anti-serum described above. Eight days later, the animals were challenged with an i.v. injection of a lethal dose (2.5 mg/head) of DNP-Asc. The lethal dose was the lowest dose producing
nearly 100% mortality and was determined by treating the guinea pigs with various amounts of antigen. The various symptoms of the anaphylactic reaction including restlessness, coughing, cyanosis, gasping, ataxia, loss of righting, convulsions, and spastic breathing; and the times of death were recorded.

Guinea pig IgG-mediated and rabbit IgG-mediated 3-hr PSAs: Guinea pigs were passively sensitized with 0.25 ml of the guinea pig IgG anti-EA and 0.5 ml of the rabbit IgG anti-serum. Three hours later, the animals were challenged with an i.v. injection of a lethal dose (1.0 or 0.25 mg/head) of EA. The lethal dose was determined in the same way as that for 8-day PSA.

IgE-mediated histamine release from isolated rat mast cells: This was performed by the method of Azuma et al. (10). The cell suspension was incubated with 2 ml of anti-DNP-Asc for 30 min at 37°C and then washed twice with the buffer solution. The sensitized mast cells (2×10⁵/2.2 ml) were pre-warmed to 37°C for 5 min. To this solution was added 20 μg/0.6 ml of DNP-Asc with or without 0.2 ml of the test solutions containing 0.1 to 1,000 μM of MTB or DSCG. The mixture was incubated for 15 min, cooled to 4°C, and then centrifuged at 500 g for 10 min at 4°C. The supernatant was assayed for histamine release, and the precipitate was assayed for residual cellular histamine according to the method of Shore et al. (11). The histamine release from the antigen challenged sensitized cells was corrected for the spontaneous release. The net release thus obtained was expressed as the percent of the total histamine released.

Compound 48/80-induced histamine release: The nonsensitized cell suspension (2.2×10⁶/2.2 ml) was incubated for 15 min with 0.5 μg/0.6 ml of compound 48/80. Either the MTB or DSCG test solution (0.2 ml) mentioned above was added simultaneously with compound 48/80. The histamine release was determined in the same manner as the determination of IgE-mediated histamine release.

RESULTS

Inhibitory effect of MTB on the PCA reaction in rats: In the IgE-mediated 48-hr PCA reactions, the same 50% inhibition dose (ID₅₀) of 0.5 mg/kg was obtained with MTB and DSCG when the agents were injected simultaneously with the antigen challenge into the animals. MTB given 5 min before the antigen challenge was about seven times more potent than DSCG. In contrast, the ID₅₀s of MTB administered p.o. at 5, 15, and 30 min before the antigen challenge were 9.6, 7.1, and 32.0 mg/kg, respectively (Table 1). However, when MTB was given 10 min before the antigen challenge directly into the duodenum of anesthetized and laparotomized rats, the ID₅₀ obtained was 0.9 mg/kg; and when MTB was administered 10 min before the antigen challenge into the stomach of a pylorus ligated rat, the ID₅₀ was 1.5 mg/kg (a mean value of 4 was obtained experimentally, data not show). Enhanced effects of drugs by direct administration into the gastrointestinal tract were also reported by Augstein et al. (12). MTB and DSCG given simultaneously (20 mg/kg, i.v.) along with the antigen challenge significantly inhibited the rat IgG-mediated 3-hr PCA (Table 1).

Time course of inhibitory effect: In order to make a comparison of the duration of the inhibitory effects of MTB with that of DSCG on the rat IgE-mediated 48-hr PCA reaction, 5 mg/kg of drugs were injected simultaneously with the antigen and at various time intervals preceding the antigen challenge. The maximum activity (100% inhibition) of MTB (5 mg/kg, i.v.) in vivo was observed when the antigen was given within 15 min following administration of the drug, whereas that of DSCG was observed only within 5 min (Fig. 2). When the antigen was given 30 min
Table 1. Effects of MTB and DSCG on various PCA reactions in rats

| PCA test                  | Route | Time | Measurement | MTB       | DSCG      |
|--------------------------|-------|------|-------------|-----------|-----------|
| Rat IgE, rat PCA (48-hr PCA) | i.v.   | 0    | ID50        | 0.5 mg/kg | 0.5 mg/kg |
|                          | i.v.   | 5    | ID50        | 2.6 mg/kg | 19.2 mg/kg|
|                          | p.o.   | 5    | ID50        | 9.6 mg/kg | N.D.      |
|                          | p.o.   | 15   | ID50        | 7.1 mg/kg | N.D.      |
|                          | p.o.   | 30   | ID50        | 32.0 mg/kg| N.D.      |
| Rat IgG, rat PCA (3-hr PCA) | i.v.   | 0    | % inhibition | 62% at 20 mg/kg | 57% at 20 mg/kg |
|                          | p.o.   | 15   | % inhibition | 52% at 50 mg/kg | N.D.      |
| Rabbit IgG, rat PCA (3-hr PCA) | i.v.   | 0    | % inhibition | 3% at 20 mg/kg | 8% at 20 mg/kg |
|                          | p.o.   | 15   | % inhibition | 10% at 50 mg/kg | N.D.      |

a) Drugs were given simultaneously with the antigen challenge or at time intervals before the antigen challenge.  
b) N.D.=not done

Fig. 2. Time course of the inhibitory action of MTB on the rat 48-hr PCA. MTB or DSCG were given i.v. (a) and MTB was given p.o. (b) at various times before the antigen challenge. Each point represents the mean value of four animals.

after the drug administration, the mean inhibitory percent of MTB decreased to 28.5±1.9% and that of DSCG to less than 10% (Fig. 2). The inhibitory activity of MTB was also determined by oral administration in the amount of 50 or 100 mg/kg, and inhibition was significant even when the antigen was given 6-hr after the drug.

Inhibitory effects of MTB on the PCA reaction in guinea pigs: MTB (2.5, 5.0, and 10 mg/kg, i.v.) given simultaneously with the antigen challenge markedly inhibited the guinea pig IgE-mediated PCA reaction. The IgG-mediated 3-hr PCA was inhibited significantly with MTB, but not with DSCG. Apparently, the inhibitory effect of MTB was more potent than that of DSCG as shown in both the guinea pig IgE and IgG-mediated PCA reactions (Table 2).

Inhibitory effects of MTB on the PSA reaction in guinea pigs: In the guinea pig IgE-mediated 8-day PSA, the guinea pigs were sensitized with 0.5 ml of the guinea pig IgE anti-DNP-Asc. After eight days, the antigen challenge with DNP-Asc of 0.6, 1.2, or 2.5 mg/head increased the mortality rate within 6 min with increasing dose as shown in Table 3. Animals which did not die within these 6 min survived for a considerable period of time. Two and a half milligrams per head
Table 2. Effects of MTB and DSCG on various PCA reactions in guinea pigs

| Drugs<sup>a</sup> | Dose (mg/kg, i.v.) | Homologous PCA, mm<sup>2</sup> | Heterologous PCA, mm<sup>2</sup> |
|------------------|-------------------|-----------------|-----------------|
|                  |                   | 8-day 3-hr | 3-hr 3-hr |
| Saline           | ---               | 157.3±5.6<sup>b</sup> | 217.5±9.4 | 235.9±14.1 |
| MTB              | 2.5               | 97.9±13.2**   | N.D.<sup>c</sup> | N.D. |
|                  | 5.0               | 76.3±9.9**    | 169.5±9.0* | 206.2±12.4 |
|                  | 10.0              | 51.7±7.9**    | 120.3±11.2** | 202.2±9.6 |
| DSCG             | 10.0              | 115.0±7.4**   | 179.2±12.9 | 233.8±2.6  |
|                  | 20.0              | 107.0±11.8**  | 194.4±9.1  | 227.9±15.0 |

<sup>a</sup> MTB or DSCG was given simultaneously with the antigen challenge.  
<sup>b</sup> Mean±S.E. (n=4)  
<sup>c</sup> N.D. = not done  
*P<0.05, **P<0.01 as compared to the saline control.

Table 3. Mortality rate with antigen dose on the PSA reactions in guinea pigs

| PSA               | Antigen Dose (mg/head) | Total number of animals | Mortality<sup>3</sup> of animals |
|-------------------|------------------------|------------------------|---------------------------------|
| Homologous 8-day PSA | 0.6                    | 11                      | 2                               |
|                   | 1.2                    | 11                      | 7                               |
|                   | 2.5                    | 11                      | 11                              |
|                   | 5.0                    | 10                      | 10                              |
| Homologous 3-hr PSA | 0.25                   | 7                       | 1                               |
|                   | 0.50                   | 9                       | 5                               |
|                   | 1.00                   | 13                      | 13                              |
|                   | 2.00                   | 5                       | 5                               |
| Heterologous 3-hr PSA | 0.06                   | 10                      | 1                               |
|                   | 0.12                   | 10                      | 3                               |
|                   | 0.25                   | 10                      | 10                              |
|                   | 0.50                   | 10                      | 10                              |

<sup>3</sup> Mortality was determined by death within 30 min after administration of the antigen challenge.

DNP-Asc produced 100% mortality. Protection from anaphylactic shock by MTB was observed as shown in Table 4. All 23 control animals died from anaphylactic shock between 3 and 6 min following the antigen challenge of 2.5 mg of DNP-Asc. Five or ten milligrams per kilogram of MTB given i.v. 1 min before the antigen challenge provided a marked protection from anaphylactic shock and prevented death in 6 out of 14 or 13 out of 14 animals, respectively (Table 4). On the other hand, 20 mg/kg of DSCG slightly prevented death; and at a higher dose, 40 mg/kg, 50% of the animals survived. In the guinea pig IgG-mediated 3-hr PSA, the guinea pigs were sensitized with 0.25 ml of the IgG anti-EA (PCA titer, 1:4000). Three hours later, the animals were challenged with a lethal dose of EA (1.0 mg/head). The method for lethal dose determination is shown in Table 3. Twenty milligrams per kilogram of MTB administered i.v. 1 min before the antigen challenge very rarely prevented death, but it markedly lessened the symptoms and delayed the death time. DSCG did not have such effects. In the rabbit IgG-mediated 3-hr PSA, the guinea pigs were sensitized with 0.5 ml of the rabbit IgG anti-EA (PCA titer,
Table 4. Effects of MTB and DSCG on various PSA reactions in guinea pigs

| Drugs\(^a\) | Dose\(^b\) (mg/kg, i.v.) | Homologous PSA | Heterologous PSA |
|-------------|--------------------------|----------------|-----------------|
|             |                          | 8-day Mortality Died/Total | 3-hr Mortality Died/Total | 3-hr Mortality Died/Total |
| Control     | —                        | 23/23          | 18/18           | 11/11          |
| MTB         | 5                        | 8/14**         | N.D.            | N.D.\(^c\)     |
|             | 10                       | 1/14**         | 16/16           | N.D.           |
| DSCG        | 20                       | N.D.           | 11/13           | 11/11           |
|             | 40                       | 9/11**         | 8/8             | N.D.           |

\(^a\) Drugs were dissolved or suspended in saline with 2 drops of Tween 80. \(^b\) Drugs were given 1 min before the antigen challenge. \(^c\) P<0.01 \(\ast\) P<0.05 as compared to the control. N.D. = not done.

Table 5. Effect of MTB on IgE-mediated PCA in adrenalectomized rats

| Compound          | Dose\(^b\) (mg/kg, i.v.) | Dimension (mm\(^2\)) |
|-------------------|--------------------------|----------------------|
| Sham operated rat | Saline                   | 135.7±5.4\(^b\)      |
| Adrenalectomized rat | Saline     | 127.2±5.7          |
|                   | MTB 0.25                 | 79.7±6.2*            |
|                   | 0.50                     | 49.4±10.0*          |
|                   | 1.00                     | 0                    |
|                   | DSCG 0.25                | 67.2±1.6*            |
|                   | 0.50                     | 34.8±13.2*          |
|                   | 1.00                     | 0                    |

\(^b\) Compounds were administrated simultaneously with the antigen challenge. Mean±S.E. (n=4) \(\ast\) P<0.01 as compared to the adrenalectomized rat (saline).

1:4000). The lethal dose of EA was 0.25 mg/head (Table 3). MTB and DSCG (20 mg/kg, i.v.) showed no appreciable effects on the rabbit IgG-mediated 3-hr PSA (Table 4).

Modifications of the inhibitory action of MTB by adrenalectomy and adrenergic antagonist: An investigation was made on whether the PCA-inhibiting action was mediated via adrenal hormones and \(\beta\)-adrenergic mechanisms. Although PCA reactivity tended to be reduced somewhat by adrenalectomy, an inhibition ratio of the PCA reaction by MTB was observed (Table 5) as was also the case for normal rats (Fig. 2). No particular influence of adrenalectomy on the inhibition of the PCA reaction could be recognized. In contrast to the reversal of the inhibitory action of isoproterenol, a \(\beta\)-adrenergic agonist, the administration of propranolol, a \(\beta\)-adrenergic antagonist, did not affect the inhibition of the PCA reaction by MTB (Table 6).

Effects of MTB on dye-leakage onto the dorsal skin through the action of histamine and other compounds: Effects of MTB on increased vascular permeability caused by histamine, serotonin, compound 48/80, and Dextran T-70 were investigated. Neither MTB nor DSCG had any significant inhibitory effects on the increased vascular permeability (Table 7).

IgE-mediated histamine and compound
### Table 6. Effects of β-blockade on inhibition by MTB of rat IgE-mediated PCA

| Compound                        | Dose (i.v.) | Dimension (mm²) |
|---------------------------------|-------------|-----------------|
| Control                         | —           | 158.1±8.9b)     |
| MTB                             | 3 mg/kg     | 0               |
| Propranolol                     | 1 mg/kg     | 174.8±3.1       |
| Isoproterenol                   | 10 µg/kg    | 0               |
| Propranolol+Isoproterenol       | 1 mg/kg+10 µg/kg | 177.7±11.3      |
| MTB+Propranolol                 | 3 mg/kg+1 mg/kg | 0              |

a) Compounds were administrated simultaneously with the antigen challenge.
b) Mean±S.E. (n=4)

### Table 7. Effects of MTB and DSCG on dye-leakage onto the dorsal skin of rats resulting from histamine, serotonin, compound 48/80, and Dextran T-70

| Compound | Dose (g/kg, i.v.) | Histamine 10 µg | Serotonin 0.1 µg | Compound 48/80 5 µg | Dextran T-70 500 µg |
|----------|-------------------|-----------------|------------------|----------------------|---------------------|
| Saline   | 20                | 110±9b)         | 149±13           | 155±10               | 117±11              |
| MTB      | 20                | 106±12          | 120±12           | 166± 8               | 109± 9              |
| DSCG     | 20                | 98± 8           | 134± 7           | 147±10               | 115±10              |

a) MTB or DSCG with Evans blue was given i.v. immediately before the i.d. administration of histamine and other compounds.
b) Mean±S.E. (n=4)

48/80-induced histamine release: Peritoneal cells sensitized with rat anti-DNP-Asc were incubated with test drugs and an antigen challenge at the same time. In the preliminary experiments, a marked inhibition of histamine release by MTB was observed when added along with the antigen; the effects gradually decreased with a longer preincubation period with MTB before the antigen challenge. The histamine release was significantly inhibited by 1, 10, 100, or 1000 µM of MTB. Similarly, DSCG showed inhibition of histamine release at 10, 100, or 1000 µM, but not at 0.1 or 1.0 µM. The compound 48/80 which induced histamine release was significantly inhibited by both MTB and DSCG at 10, 100, and 1000 µM, but not at 0.1 and 1.0 µM (Fig. 3).

**DISCUSSION**

A number of orally effective antiallergic drugs such as WY-16,922 (4), AA-344 (5), SQ-13,847 (6), EPL 52,791 (12), and Y-12,141 (13) have been developed. MTB, a newly synthesized compound intended for use as an orally effective agent toward prophylaxis in asthma, was demonstrated to be more potent in vivo than DSCG, particularly for the IgE-mediated PCA and PSA reactions. When administered 5 min before the antigen challenge, inhibitory effects of MTB were about 7 times more potent than DSCG in the rat IgE-mediated 48-hr PCA. The oral administration of MTB was also effective in bringing about inhibitory effects and a peak effect occurred when it was given 15 min before the antigen administration. This rapid appearance of the inhibitory effects by MTB is considered due to absorption not only by the intestine but by the stomach as well. In fact, gastric absorption was demonstrated in pylorus ligated rats. A direct administration of MTB into the duodenum or stomach showed more inhibitory effects than conventional oral admin-
Fig. 3(a). Effects of MTB and DSCG on IgE-mediated histamine release from rat sensitized peritoneal cells. The total histamine was 18.4±1.2 μg/10⁶ mast cells. Histamine release induced by DNP-Asc and spontaneous histamine release occurring in the absence of antigen were 34.4±3.9% and 7.8±1.4%, respectively. Each point represents the mean ±S.E. from 4 experiments. *P<0.05, **P<0.01 vs. the immunological histamine release without drug addition.

Fig. 3(b). Effects of MTB and DSCG on the compound 48/80 induced histamine release from the rat peritoneal cells. The total histamine was 24.6±1.8 μg/10⁶ mast cells. Histamine release induced by compound 48/80 and spontaneous histamine release occurring in the absence of antigen were 36.1±3.7% and 7.1±1.6%, respectively. Each point represents the mean±S.E. from 4 experiments. *P<0.05, **P<0.01 vs. compound 48/80 induced histamine release without drug addition.

In the study on the relationship between structure and activity, a number of oxanilic acid esters and N-heteroaryl oxaminic acid esters was examined using IgE-mediated PCA; these were found to be orally active. The hydrolysis of an ester from the oxanilic ester moiety resulted in a loss of oral activity (14). We also examined the oral activity of several alkyl esters of oxanilic acid, and the butyl ester was found to have the maximum activity (unpublished data). These results may perhaps parallel the intestinal absorbability of the oxanilic ester. Also, MTB showed greater stability in serum than DSCG (Table 1, Fig. 2).

Marked inhibitory effects toward the IgE-mediated 8-day PCA in guinea pigs were also demonstrated with MTB, and inhibitory effects were found to a lesser extent with DSCG. This later observation is consistent with the result of Taylor (15) in which DSCG moderately inhibited the PCA reaction induced by IgE-like activity in guinea pigs. Moreover, significant inhibitory effects of MTB on both the rat and guinea pig IgG-mediated 3-hr PCA were demonstrated. Rabbit IgG-mediated PCA in rats and guinea pigs was not inhibited by MTB or DSCG given simultaneously with the antigen challenge.

MTB (5 or 10 mg/kg, i.v.) given 1 min before the antigen challenge markedly prevented death in the guinea pig IgE-mediated 8-day PSA. A higher dose of DSCG (40 mg/kg, i.v.) was required to prevent death in the 8-day PSA. MTB did not prevent death, but alleviated the symptoms in the guinea pig IgG-mediated PSA. In the rabbit IgG-mediated PSA, neither MTB nor DSCG provided any protection from anaphylactic shock in the guinea pigs. Failure to prevent heterologous PSA by MTB was analogous to the heterologous PCA reaction.

The action mechanism did not involve β-
adrenergic or hormonal stimulation since neither propranolol antagonized the inhibitory effects of the compound, nor was the action modified by adrenalectomy.

According to Orange and Austein (16), the inhibition of histamine release from rat peritoneal cells induced by an immunologic mechanism or compound 48/80 is useful for evaluating the effectiveness of antiallergic agents. In vitro, MTB and DSCG markedly inhibited histamine release from rat peritoneal cells by the IgE antibody-antigen reaction or compound 48/80. MTB failed to inhibit skin edema brought on by the intradermal injection of histamine, serotonin, compound 48/80 and Dextran T-70.

In summary, MTB is an orally effective compound capable of inhibiting homologous IgE and IgG-mediated anaphylaxis.

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