

# Pyrogenic Responses to Staphylococcal Enterotoxins A and B in Cats<sup>1</sup>

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Pyrogenic responses, ranging up to 4.8 F, were induced in cats by oral administration of highly purified staphylococcal enterotoxin B in doses from 10 to 100  $\mu\text{g}/\text{kg}$ . Fever was a more sensitive indicator of intoxication than was emesis. Highly purified preparations of enterotoxin A, whether administered intravenously (0.01 to 1.0  $\mu\text{g}/\text{kg}$ ), orally (10 to 25  $\mu\text{g}/\text{kg}$ ), or into the cerebral ventricles (0.005 to 0.020  $\mu\text{g}$  in 0.20 ml), were also pyrogenic in cats. Tolerance to the pyrogenic activity was produced by repeated intravenous injection of a given dose of enterotoxin A but not by repeated intracerebroventricular injection. Enterotoxin A was more potent than enterotoxin B after intravenous injection in causing both fever and emesis. Cross-tolerance could not be demonstrated between enterotoxin A and enterotoxin B or *Salmonella typhosa* endotoxin. This lack of cross-tolerance plus the inability of large oral doses (100 to 4,700  $\mu\text{g}/\text{kg}$ ) of endotoxin to cause fever or emesis indicate that the reported responses were attributable to the specific toxins administered and not to contamination by other pyrogens.

Ingestion of preformed staphylococcal enterotoxins has long been recognized as a causative factor in food poisoning (9). The role of enterotoxin, which has been introduced or released within the intestine, in producing enteritis and enterocolitis has been studied more recently (18). Four types of enterotoxin have been distinguished (1, 5, 15). Enterotoxin A is the type most commonly associated with staphylococcal food poisoning, whereas enterotoxin B is more likely to be associated with enteritis (3, 4). Enterotoxin B was the first type obtained in a highly purified form (2) and has been the most studied. In view of the pyrogenic activity of purified enterotoxin B, which has been demonstrated after intravenous or intracerebroventricular administration to cats (7) and after intravenous injection into rabbits (12, 16, 20) and monkeys (8), it is likely that enterotoxin absorption is at least partially responsible for the sudden fevers that herald the development of *Staphylococcus*-induced enterocolitis (19). On the other hand, it is, perhaps, surprising that fever is not a commonly reported symptom of *Staphylococcus*-induced food poisoning. A survey of various textbooks of medicine and microbiology supports the impression that a

subnormal temperature is more likely to occur than is fever. Absence of high fever is even considered a useful diagnostic aid in distinguishing staphylococcal food poisoning from certain other types of food poisoning (14). However, J. J. Bronfenbrenner (22) cites an outbreak, presumably due to staphylococci, in which approximately one-half of the people stricken with food poisoning at a banquet listed fever as one of their symptoms.

There are at least four possible explanations for this apparent lack of association of fever with staphylococcal food poisoning. (i) Oral administration exposes enterotoxin to conditions not encountered after intravenous administration that reduce pyrogenic activity to a greater extent than emetic activity. (ii) Enterotoxin A does not share the pyrogenic activity exhibited by enterotoxin B, at least in doses effective in producing emesis. (iii) Enterotoxins are not pyrogenic in humans. (iv) Fever, although present, is overlooked during the short illness due to the greater distress caused by other symptoms such as vomiting and diarrhea. The experiments reported in this paper were designed to study the first two possibilities.

## MATERIALS AND METHODS

Purified material estimated to be at least 95% enterotoxin A (6) or enterotoxin B (20) was supplied by M. S. Bergdoll (Food Research Institute, University of Wisconsin, Madison). Lipopolysaccharide

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prepared by the Boivin method from *Salmonella typhosa* (Difco) was used for endotoxin tests.

Cats weighing 2 to 4 kg were treated with feline distemper and pneumonitis vaccines; they were caged separately from the experimental colony for at least 2 weeks before use. Unless otherwise specified, toxins were administered to animals which, to our knowledge, had had no previous exposure to any of the three toxins (designated "novice" cats). No tests for the presence of antibodies against the toxins were performed, however. It has been called to our attention that perhaps as many as 10% of cats bought on the open market have antibodies against enterotoxin B.

Procedures for automatically recording retroperitoneal temperature in unrestrained cats, for tabulating temperature changes, and for making injections into chronic jugular venous catheters or into a lateral cerebral ventricle were the same as those described previously (7, 21), with the following modifications. The average of temperature readings at 7, 8, and 9 AM was used as the base line from which changes were measured. Thermocouples were enclosed in Teflon sleeves which, in later experiments, were arranged so that the thermocouples could easily be replaced without additional surgery. Environmental temperature was maintained at  $75 (23.89\text{ C}) \pm 2\text{ F}$ . Control injections of 0.9% NaCl solution were given 1 or 2 days prior to toxin injections, except during induction of tolerance. Ventricular injections were made in a volume of 0.20 ml without a saline flush through a modified Collision-type cannula with a dead space of 6 to 8  $\mu$ liters (17). Stock enterotoxin solutions (10  $\mu$ g/ml) were diluted to the proper concentrations immediately before making ventricular injections. This was necessary because the pyrogenic activity of weaker solutions (0.1  $\mu$ g/ml) diminished considerably within a few days. Glassware was sterilized in dry heat at 175 C or higher for at least 2 hr. Tests of solutions for sterility were carried out whenever appropriate.

With the exception of some tests with endotoxin, orally administered toxins were ingested in reconstituted condensed milk. If an animal completely drank a volume of 30 ml/kg, it was given the toxin in one-half or less of that volume on the following day. When this first portion was finished, the remaining milk was given in two or three additional portions, each swirled around the bowl to pick up any toxin that might remain. In no case was more than 6 ml of milk unconsumed.

Responses were plotted on graph paper with time (1 inch = 2 hr) on the abscissa and temperature change (1 inch = 1 F) on the ordinate. The area, in square inches, beneath the curves was measured with a planimeter and doubled to give a "fever index" (change in temperature, F, times hours). Each unit of fever index was, therefore, equivalent to a 1 F change lasting for 1 hr. A pyrogenic response was assumed to have ended when the temperature had returned and remained within one-half a degree of the original base line.

## RESULTS

*Enterotoxin B administered orally.* Preliminary studies indicated that doses as low as 10  $\mu$ g/kg might be pyrogenic. As it became available, each novice cat was administered one of four doses, ranging from 10 to 100  $\mu$ g/kg, which had been predetermined by randomizing the order of the four doses within each of five successive cycles. A single solution of toxin (100  $\mu$ g/ml) was employed throughout the experiment. Animals were watched continuously until emesis occurred or for at least 5 hr after toxin administration. Mean responses to the three lower doses of enterotoxin B and to milk alone in the same animals are shown in Fig. 1. Responses usually began between 1.5 and 2.5 hr after ingestion. The maximal increase observed was 4.8 F. Because of the wide variability of the responses to 100  $\mu$ g/kg, a mean response would not be representative of that dose and hence is not shown. Table 1 gives more information about these pyrogenic and emetic responses. Control responses in the same animals (dose = 0  $\mu$ g/kg) were based on durations equal to those of the responses to the toxin. The latent period for emesis, in the five animals which vomited, ranged from 130 to 204 min (average, 156 min). All five eventually had fevers of at least 2.5 F. At the time of the initial vomiting episode, their fevers ranged from 0.3 to 3.5 F (average, 1.4 F). Seven of the animals which did not vomit also had fevers of at least 2.5 F.

*Enterotoxin A administered intravenously.* Novice cats, in order of their availability, were randomly assigned to receive various doses of enterotoxin A, enterotoxin B, or 1.0  $\mu$ g of endotoxin per kg. Enterotoxin A produced biphasic responses, which began less than 1 hr after administration and lasted up to 60 hr. Figure 2 shows mean responses to the three lower doses of

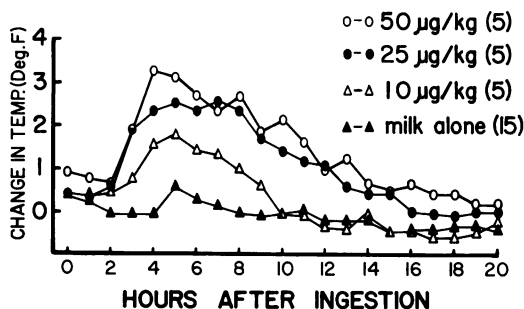


FIG. 1. Mean pyrogenic responses of previously untested cats to various doses of orally administered enterotoxin B. The mean response of the same animals to milk alone is also shown. Numbers in parentheses indicate the number of animals in each group.

TABLE 1. *Pyrogenic and emetic responses to oral enterotoxins and endotoxin<sup>a</sup>*

Type of toxin	Dose ( $\mu\text{g}/\text{kg}$ )	No. of cats	Fever index $\Delta$ Temp (F)·hr	Maximal rise (F)	Duration (hr)	Emesis (%)
Enterotoxin B . . . .	0	19	-0.5 (-3.7-2.7)	0.8 (0.5-1.1)		0
	10	5	12.0 (-2.1-26.1)	1.9 (0.7-3.1)	7.9 (5.9-9.9)	0
	25	5	20.4 (12.1-28.7)	3.1 (2.8-3.4)	13.2 (10.4-16.0)	40
	50	5	29.5 (15.0-44.0)	3.6 (2.4-4.8)	16.4 (11.4-21.4)	20
	100	4	13.5 (2.6-24.4)	2.7 (0.7-3.4)	10.4 (6.0-14.8)	50
Enterotoxin A . . . .	10	3	15.4 (-2.2-33.0)	2.6 (-0.7-6.9)	12.0 (3.0-21.0)	33
	25	4	25.1 (14.3-35.9)	3.7 (3.2-4.2)	13.5 (11.3-15.7)	75
Endotoxin . . . . .	4,000-4,700	5	-3.2 (-13.4-7.0)	0.8 (0.2-1.4)		0

<sup>a</sup> Results are expressed as mean values with 95% confidence limits shown in parentheses.

enterotoxin A and the mean response of the same animals to saline solution. Again, as with oral administration, the wide variability of the responses to the highest dose (1.0  $\mu\text{g}/\text{kg}$ ) precludes plotting the mean as a representative response. Additional information for both enterotoxins is listed in Table 2. Mean fever indexes after enterotoxins A and B are plotted against dose on a log scale in Fig. 3. If it is assumed that responses to 0.1 and 0.5  $\mu\text{g}$  of enterotoxin A and to 0.5 and 1.0  $\mu\text{g}$  of enterotoxin B per kg are on the linear portions of their respective sigmoid-shaped log-dose response curves, potency ratios can be calculated (Table 2). Enterotoxin A appeared to be approximately four times as potent as enterotoxin B, whether fever indexes, maximal rises, or the durations of the responses were used for the calculations. The incidence and latencies of the emetic responses also indicated a greater potency for enterotoxin A than for enterotoxin B.

Repeated daily injections of a given dose of enterotoxin A produced diminishing pyrogenic responses. This diminution was most apparent between the first and second injections in the second phase of the response. Such "tolerance" seemed somewhat less complete than that produced by enterotoxin B and also appeared to lapse more rapidly when administration was stopped.

*Lack of cross-tolerance between enterotoxin A and enterotoxin B or endotoxin.* Animals from the above experiments which had been randomly assigned 1.0  $\mu\text{g}/\text{kg}$  of the three toxins were made tolerant by repeated daily injections. The

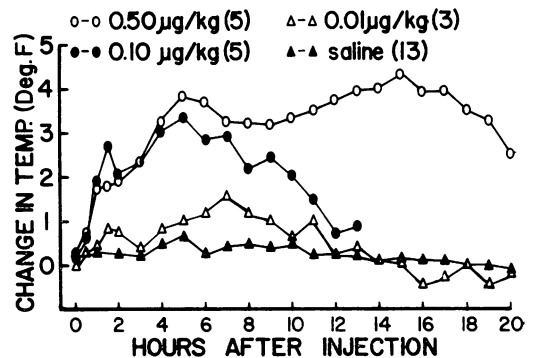


FIG. 2. Mean pyrogenic responses of previously untested cats to enterotoxin A injected intravenously. The mean response of the same animals to saline injection is also shown. Numbers in parentheses indicate the number of animals in each group.

results of some subsequent cross-tolerance tests can be seen in Fig. 4. Comparison of the initial and final responses to enterotoxin A before testing with enterotoxin B or endotoxin indicates that considerable tolerance to enterotoxin A had been produced. An average of 10 injections of enterotoxin A were given. That the final responses to enterotoxin A were very similar to those produced in novice animals by 0.1  $\mu\text{g}/\text{kg}$  indicates, perhaps, as much as a 90% reduction in the sensitivity of the tolerant animals to enterotoxin A. Subsequent responses to enterotoxin B or endotoxin gave responses very similar to those of novice cats receiving the same doses. As the assay of relative

potency progressed, it became apparent that 1.0  $\mu\text{g}$  of enterotoxin A per kg was not on the linear portion of the log-dose response curve, and was a poor dose for testing enterotoxin A in animals

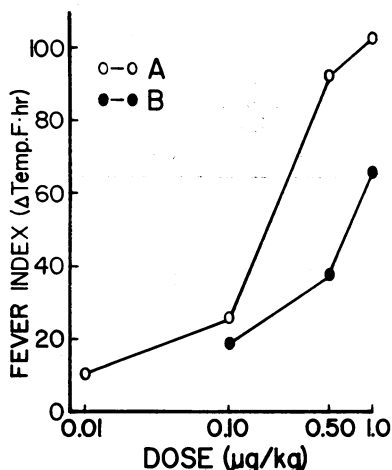


FIG. 3. Pyrogenic dose-response curves for enterotoxins A and B in cats. All points represent the mean value obtained from five animals, except for 0.01  $\mu\text{g}$  of enterotoxin A per kg (three animals).

tolerant to enterotoxin B or endotoxin. Animals tolerant to enterotoxin B or endotoxin were subsequently tested with 0.5  $\mu\text{g}$  of enterotoxin A per kg. Although not statistically significant, the quantitative febrile responses following enterotoxin A (whether 1.0 or 0.5  $\mu\text{g}/\text{kg}$ ) were consistently on the low side of values obtained in the controls. However, the lack of tolerance to enterotoxin B or endotoxin with considerable tolerance to the supramaximal dose of 1.0  $\mu\text{g}$  of enterotoxin A per kg strongly indicates that no appreciable cross-tolerance develops. Emetic responses to enterotoxin A after enterotoxin B or endotoxin did not indicate any tolerance development.

*Enterotoxin A administered intraventricularly.* Novice cats responded to intraventricularly injected enterotoxin A with monophasic fevers similar to those produced by enterotoxin B. Mean responses are shown in Fig. 5 and additional data are given in Table 3. None of the animals vomited in response to the toxin. Unlike enterotoxin B, repeated injections of 0.02  $\mu\text{g}$  of enterotoxin A in three cats did not produce a consistent, sequential diminution of responses indicative of tolerance development. Considerable tolerance

TABLE 2. Pyrogenic and emetic responses to intravenous enterotoxins<sup>a</sup>

Type of enterotoxin	Dose ( $\mu\text{g}/\text{kg}$ )	No. of cats	Fever index $\Delta\text{Temp}$ (F)·hr	Maximal rise (F)	Duration (hr)	Emesis	
						%	Latency <sup>b</sup>
A	0	18		1.2 (0.8-1.6)		0	<i>min</i>
	0.01	3	10.4 (5.4-15.4)	1.8 (-0.1-3.6)	12.1 (10.1-14.1)	0	
	0.1	5	26.1 (23.0-29.2)	3.5 (3.2-3.7)	12.2 (10.0-14.4)	40	92 (50-135)
	0.5	5	94.4 (49.5-139.3)	4.9 (4.0-5.9)	37.0 (17.4-56.6)	100	29 (12-40)
	1.0	5	102.5 (32.5-172.4)	4.6 (3.6-5.6)	34.1 (21.6-46.6)	100	24 (12-50)
B	0	15		1.2 (0.8-1.5)		0	
	0.1	5	18.1 (10.1-26.2)	2.6 (2.1-3.0)	12.9 (8.1-17.7)	0	
	0.5	5	37.6 (24.6-50.6)	3.6 (2.9-4.3)	18.1 (15.3-20.9)	20	37
	1.0	5	65.1 (38.1-92.0)	4.6 (3.7-5.4)	25.0 (15.9-34.1)	100	69 (43-142)
B/A <sup>c</sup>			0.26 (0.18-0.31)	0.28 (0.11-0.56)	0.26 (0.11-0.51)		

<sup>a</sup> Results are expressed as mean values with 95% confidence limits shown in parentheses.

<sup>b</sup> Mean values, with the ranges in parentheses.

<sup>c</sup> These values represent the potency ratio with 95% confidence limits shown in parentheses.

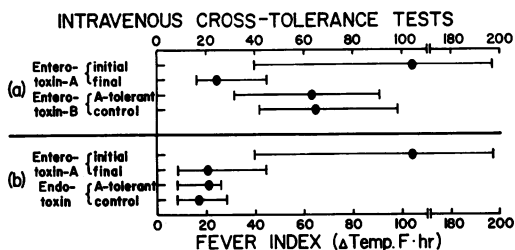


FIG. 4. Responses to intravenously injected enterotoxin B (a) or endotoxin (b) of cats which were tolerant to enterotoxin A. The range and mean (●) of fever indexes in groups of five animals are shown. A dose of 1.0  $\mu\text{g}/\text{kg}$  was used for all tests. Initial and final tests with enterotoxin A and the subsequent cross-tolerance tests with enterotoxin B or endotoxin were performed in the same animals. The control enterotoxin B and endotoxin responses were obtained in separate groups of previously untested animals.

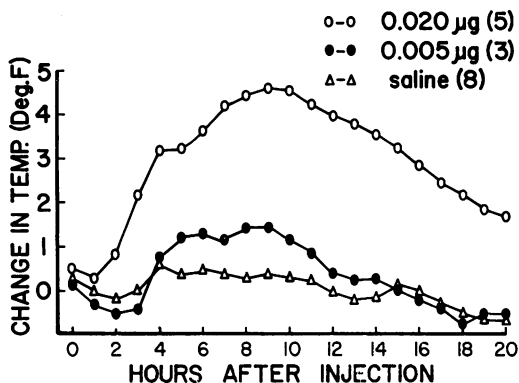


FIG. 5. Mean pyrogenic responses of cats to enterotoxin A injected into a lateral ventricle. The mean response of the same animals to saline injection alone is also shown. Numbers in parentheses indicate the number of animals in each group.

to enterotoxin B was subsequently produced in the same animals by repeated administration of 0.02  $\mu\text{g}$  and higher doses. No attempts were made to induce tolerance to enterotoxin A by giving higher doses. No cross-tolerance was observed between the enterotoxins in crossover studies in these animals.

*Enterotoxin A administered orally.* Results of a limited number of tests with ingested enterotoxin A are listed in Table 1. Responses were similar to those to enterotoxin B, although enterotoxin A appeared to be slightly more potent. The four cats which vomited eventually had fevers of at least 3.4 F above normal.

*Endotoxin administered orally.* Results of experiments with large doses of endotoxin are

TABLE 3. Pyrogenic responses to intracerebroventricular enterotoxin A<sup>a</sup>

Dose ( $\mu\text{g}/\text{kg}$ )	No. of cats	Fever index $\Delta$ Temp (F)·hr <sup>2</sup>	Maximal rise (F)	Duration (hr)
0	8		1.0 (0.6-1.5)	
0.005	3	9.3 (-7.0-25.6)	1.5 (0.6-2.5)	12.7 (7.0-18.4)
0.02	5	65.5 (34.8-96.1)	4.7 (3.7-5.8)	25.8 (17.8-33.8)

<sup>a</sup> Results are expressed as mean values with 95% confidence limits shown in parentheses.

also summarized in Table 1. Since no obvious fever developed, the fever indexes were based on a period of 20 hr. None of the cats had had endotoxin before, but all had had previous tests with orally or intraventricularly administered enterotoxins. Two of the cats received the toxin in suspension in milk. The other three received the toxin in gelatin capsules to be certain that the total dose was ingested. Six other oral initial endotoxin tests of doses from 100 to 2,000  $\mu\text{g}/\text{kg}$ , likewise, produced no fever or emesis. In two of these cases, novice animals were treated with 1,000 or 2,000  $\mu\text{g}$  of endotoxin per kg.

DISCUSSION

The results of the above experiments and of previous investigations demonstrated that both enterotoxin A and enterotoxin B were pyrogenic when administered to cats by any of three routes, oral, intravenous, or intraventricular. Responses to the two types of enterotoxin differed only in minor respects, mainly tolerance development and potency. Tolerance to enterotoxin A injected intravenously seemed less complete than to B, whereas tolerance to enterotoxin A injected intraventricularly did not develop at all, in contrast to enterotoxin B.

A valid design for comparative bioassay was used only for intravenous administration; and the calculations indicated that the preparation of enterotoxin A used in these experiments was about four times as potent as the preparation of enterotoxin B. Although it appears certain that enterotoxin A was more potent than enterotoxin B, this specific estimate of relative potency must be viewed with caution because it is not certain that the doses chosen for the analysis were on the linear portion of the log-dose response curves, and a large departure from homogeneity of variance existed (11).

One possible explanation for the greater variability in the pyrogenic responses produced by

the higher doses of enterotoxin administered peripherally might be that shock and consequent diminution of fever had developed in some of the animals due either to fluid losses associated with vomiting or diarrhea, or both, or to some direct action of the large doses of enterotoxin. No studies of the ability of enterotoxins to produce shock in cats have been reported. However, much larger doses of enterotoxin B than those studied in this investigation are apparently required to produce shock in monkeys (13), which are generally more sensitive to the effects of enterotoxins than are cats. In addition, if tolerance developed to shock-inducing factors, the pyrogenic responses might actually be enhanced early in a series of injections. Instead, the responses progressively decreased with repeated administration regardless of the magnitude of the initial response.

Cross-tolerance could not be demonstrated between enterotoxin A and enterotoxin B or endotoxin. A similar lack of cross-tolerance to emetic activity in monkeys between enterotoxins A and B has been frequently reported (10). Such lack of cross-tolerance supports the contention that the pyrogenic responses were attributable to the toxins administered and not to contamination by other pyrogens. The absence of fever or emesis after large doses of orally administered endotoxin, even in novice animals, also indicates that contamination by endotoxin was not responsible for the effects observed after enterotoxin administration.

Oral administration demonstrated not only that pyrogenic responses could be produced by ingested enterotoxin but also that fever was a more sensitive indicator of intoxication than was emesis. It thus seems apparent that neither oral toxin ingestion nor the type of enterotoxin involved can account for the apparent lack of fever in association with enterotoxin-induced food poisoning.

There remains the possibility of species differences impairing the pyrogenicity of enterotoxin in the human. Rhesus monkeys do develop fever after intravenous injection of enterotoxin B (8). If humans are relatively more sensitive to the emetic activity than to the pyrogenic activity of enterotoxins, vomiting may prevent the absorption of amounts adequate to induce pyrogenic responses. Careful measurements of temperature in patients with staphylococcal food poisoning or, perhaps, better tests with the purified enterotoxins in volunteers, in which dosage could be controlled and temperature could be determined throughout the period of intoxication, should clear up this point.

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