Emetic Effect of Purified Staphylococcal Enterotoxin in Cats.*† (27745)

WESLEY G. CLARK,‡ GERARD F. VANDERHOOFT AND HERBERT L. BORISON§
Department of Pharmacology, University of Utah College of Medicine, Salt Lake City

Staphylococcal enterotoxin is a major cause of food poisoning, yet the mechanism of emetic action of this substance remains uncertain. Bayliss(1) studied intensively the emetic effect of crude enterotoxin-containing filtrates in cats prepared acutely with a variety of lesions. He concluded that enterotoxin evokes emesis through a peripheral action which is mediated mainly by the vagus nerves. Despite the fact that decerebration prevented the emetic response to enterotoxin, Bayliss minimized a central action of the substance. Direct application of the crude enterotoxin to the medulla oblongata failed to evoke emesis. Recent studies by Sugiyama, Chow and Dragstedt(2), with partially purified enterotoxin in chronic monkeys, have implicated an action of the toxin on the emetic chemoreceptor trigger zone (CTZ) of the medulla oblongata(3). However, these workers found also that subdiaphragmatic vagotomy afforded protection. This suggests the possibility that centrally-coursing vagal afferents might have been interrupted inadvertently during ablation of the trigger zone. The present investigation was undertaken to test the emetic effect of purified enterotoxin(4)‖ administered by intravenous and intracerebroventricular routes of injection in cats with chronic neurological lesions.

Methods. Cats were employed as experimental animals. The lateral cerebral ventricle was cannulated according to the method of Feldberg and Sherwood(5). Proper placement of the ventricular cannula was confirmed by elicitation of vomiting in response to intraventricular injection of 250 μg/kg of apomorphine HCl in 0.25 ml of 0.9% NaCl solution(6). Intravenous injections were made either directly into the cephalic vein or through a permanently indwelling jugular catheter. In no case was a cat anesthetized for purposes of injection.

Vagotomy was performed by the transthoracic route. Spinal cord transection was made between levels T1 and T3. Ablation of the CTZ was made by gentle thermal cauterization. Effectiveness of the CTZ lesion was indicated by emetic refractoriness to 150 μg/kg of intravenous lanatoside C(7) or to 250 μg of apomorphine injected intraventricularly(6). *Cerveau isolé* preparations were made by retracting the occipital lobes and transecting the midbrain with a blunt retractor. Sterile precautions were employed wherever necessary. Enterotoxin was administered only after the animals showed good postoperative recovery with freedom from infection. Emetic tests were performed no sooner than 4 days and as late as 4 weeks after operation. Animals were observed for emesis up to 5 hours after injection of enterotoxin.

Results. Enterotoxin did not evoke emesis in any instance when injected intraventricularly in 22 cats, even after doses which were emetic when given intravenously.

Results obtained with initial intravenous injection of enterotoxin are summarized in Table I. The dose of 1.0 μg/kg of enterotoxin was uniformly effective in eliciting emesis in normal cats. Increasing the dose to 5.0 μg/kg or higher decreased the latency of the response. Tolerance to the emetic action of enterotoxin developed rapidly as a result of the first injection. Thus, although a total of 21 emetic responses was obtained with 21 initial injections of 1.0 μg/kg of enterotoxin, only 2 emetic responses were obtained after 35 subsequent injections of this same dose in these animals.

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‡ Predoctoral trainee under U.S.P.H.S. Pharmacology Training Grant. Present address: Dept. of Pharmacology, Univ. of Texas, Southwestern Medical School, Dallas.

§ Present address: Dept. of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, N. H.

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TABLE I. Emetic Responses to Initial Intravenous Injection of Staphylococcal Enterotoxin.

Experimental condition	Dose μg/kg	Responses/ tests	Latency (min) Average	Range
Normal	.1	0/4	—	—
	1.0	21/21	43	15–130
	>5.0	5/5	23	14–35
CTZ ablation	1.0	5/6	52	10–186
	2.0–10.0	5/5	58	19–110
Vagotomy	2.0– 5.0	3/7	42	17–82
" & cord section	5.0	0/3	—	—
Cerveau isolé	2.5–9.0	0/4	—	—

Ablation of the CTZ did not alter the emetic response to intravenous enterotoxin in cats. On the other hand, transthoracic vagotomy was effective in raising the threshold for emesis. Only 3 of 7 vagotomized cats vomited to large doses of enterotoxin. Those vagotomized cats which did not vomit usually exhibited various prodromal signs such as salivation, forward licking and defecation. Of 3 cats tested after recovery from high thoracic cord section as well as vagotomy, none vomited to 5.0 μg/kg of enterotoxin. That all were capable of vomiting was shown by their emetic responses to intravenous lanatoside C.

Midbrain transection prevented the emetic response to large doses of intravenous enterotoxin. The ability of these animals to vomit was demonstrated by intravenous injection of veratrum (8).

Discussion. Two observations made in this study bear upon the question of a central action of enterotoxin. Both findings militate against a central mechanism. First, CTZ ablation did not influence the emetic response to intravenous injection of enterotoxin and, second, intraventricular injection of the toxin failed to elicit vomiting. Sugiyama, Chow and Dragstedt(2) found that CTZ ablation in the monkey protected against the emetic effect of enterotoxin, and they suggested that the species difference may account for the discrepancy between results of CTZ ablation in cats and monkeys. However, failure of intraventricular injection to elicit emesis further weakens the postulate of a central action at the CTZ. Since midbrain transection invariably prevented enterotoxin-induced emesis, in our study as in Bayliss'(1), it is possible that specific emetic receptors might be located in the forebrain. The fact that vomiting did not occur after intraventricular enterotoxin may indicate that (a) enterotoxin does not diffuse from the ventricular and subarachnoid spaces to the receptor site, (b) a metabolite of enterotoxin, but not enterotoxin itself, produces emesis centrally, (c) enterotoxin evokes emesis through peripheral receptors and that essential afferent pathways through the brain anterior to the midbrain are interrupted by the transection, or (d) facilitation by forebrain structures is essential for enterotoxin-induced emesis.

Transthoracic vagotomy raised the threshold for emesis to enterotoxin. This was in agreement with the results of Bayliss(1) in cats and of Sugiyama and co-workers(2) in monkeys. None of the 3 cats vomited when tested with enterotoxin after both transthoracic vagotomy and high spinal cord section. The situation in enterotoxin-induced emesis appears to be similar to that for emesis induced by both x-radiation(9) and nitrogen mustard(10). Supradiaphragmatic vagotomy plus spinal cord section at T4 abolished emesis to these stimuli while neither procedure alone abolished the emetic response uniformly. In addition, mid-collicular decerebration or frontal lobectomy raised the threshold for emesis after administration of nitrogen mustard or x-radiation. Thus, it is possible that, in the cat at least, the emetic response to enterotoxin, like that to x-radiation and nitrogen mustard, is mediated through visceral afferents in both vagi and spinal cord and that this response is facilitated by supracollicular activity, or utilizes long recurrent pathways through the forebrain.

Summary. Intraventricular administration of enterotoxin did not produce vomiting. Chemoreceptor trigger zone ablation in cats did not affect the emetic response to intravenous enterotoxin. Transthoracic vagotomy raised the threshold for enterotoxin-induced emesis. Midbrain transection abolished the emetic response. The possibility was considered that the emetic stimulus provided by enterotoxin traverses afferent pathways that are concerned in vomiting responses to x-radiation and nitrogen mustard.

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Metabolism of the Transplanted Dog Kidney. (27746)

PAUL NATHAN,* ERNEST C. FOULKES,* LAWRENCE J. WILCHINS, AND BENJAMIN F. MILLER

May Institute for Medical Research, Cincinnati Jewish Hospital, and Department of Physiology, Surgery and Medicine, University of Cincinnati College of Medicine, Cincinnati, O.†

Organs and tissues transplanted from one dog to another are usually rejected by the recipients in 5 to 10 days. In the present work, a search was made for a correlation between biochemical changes and the course of tissue rejection in homologous transplants of dog kidneys to provide some insight into the mechanism of homotransplant destruction. The kidney was selected for study because well-established methods are available for determination of renal function and metabolism. Our results show that several sensitive measures of cellular function and metabolism in tissue from transplanted kidneys remain relatively unaffected by the rejection process. Even during accelerated rejection of a kidney in a specifically immunized animal, the metabolism of tissue measured *in vitro* remains within the range observed for normal tissue. Because damage to the parenchyma by a cytotoxin would very likely manifest itself in changed metabolic activity, another cause for tissue rejection is postulated. It is suggested that interference with cell nutrition might constitute the primary mechanism responsible for rejection of homologous kidney transplants.

Methods. Adult mongrel dogs from different sources were employed in these experiments. Vascular anastomoses were performed between the renal vessels of freshly removed donor kidneys and the iliac artery and vein of the recipient (first-set transplant). The kidney was placed in the abdominal cavity and its ureter exteriorized through a stab wound. These transplants were removed for metabolic studies one day after the operation.

Specific sensitization was produced in a series of animals by allowing the homologous transplants to remain in place until urine flow ceased. This usually occurred within a week after transplantation. If routine inspection showed an abscess, these kidneys were removed; otherwise, they were left undisturbed. Within 4 weeks of rejection of the primary transplant, the second kidney from the donor was transferred to the specifically immunized recipient (second-set transplant). These second-set transplants were then removed for the metabolic studies 20 to 24 hours after the operation, when the rejection appeared to be well advanced as evidenced by gross hemorrhage in the kidney tissue and a reduced flow of urine.

Primary sensitization was also achieved in 5 dogs by cross perfusion for one hour between donor and recipient(1). One week later the second-set kidney was introduced into the recipient.

Control autotransplants were prepared by

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