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PEPTIDE-INDUCED EMESIS IN DOGS

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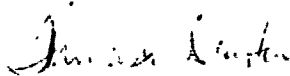ELECTE
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NOTICES

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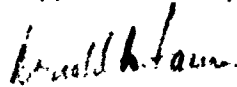
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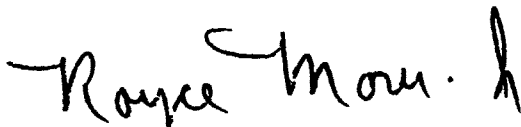
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Systemic administration of several but not all neuropeptides induces emesis in dogs. The threshold dose for leucine-enkephalin was 0.05 mg/kg, for angiotensin II was 0.20 mg/kg, and for neurotensin was 0.05 mg/kg. These values compare to a threshold of 0.005 mg/kg for apomorphine. Emesis was also observed after systemic administration of gastrin, vasoactive intestinal polypeptide (VIP), substance P, vasopressin, oxytocin, bombesin, methionine enkephalin, and thyrotropin-releasing hormone (TRH). Other peptides, including somatostatin,

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20. ABSTRACT (Continued)

cholecystokinin, secretin, bradykinin, carosine, and leutinizing hormone-re-
leasing hormone (LHRH), were not emetic.

Receptors for leucine-enkephalin and angiotensin II show receptor
desensitization, such that a second systemic administration 5 min after the
first is ineffective. Application of the other peptide or apomorphine is
effective at 5 min, however. These results indicate that there are distinct
receptors for angiotensin II and leucine-enkephalin, presumably located on
neurons of the chemosensory trigger zone in the area postrema.

The effects of chlorpromazine, domperidone, nalozone, and saralasin were
tested on emetic sensitivity to apomorphine, leucine-enkephalin, and
angiotensin II. Domperidone blocked the emetic response to apomorphine but
not to either peptide. Naloxone selectively blocked the leucine-enkephalin
response, while saralasin blocked responses to both angiotensin II and
leucine-enkephalin, but not apomorphine. Chlorpromazine prevented the emetic
response to all agents. These results suggest that domperidone has selective
actions at dopamine receptors, and naloxone at leucine-enkephalin receptors.
The saralasin results are unexpected, since it should block only at
angiotensin II receptors. The general blockage by chlorpromazine, a dopamine
receptor antagonist, may reflect a site of action on the brain side of the
blood-brain barrier.

In dogs with ablation of the area postrema, the emetic response to apomorphine
and peptides was prevented. This suggests that specific receptors for the
emetic peptides exist on area postrema neurons, which are outside of the
blood-brain barrier. The existence of excitatory responses of area postrema
neurons to local application of these substances has been confirmed in paral-
lel electrophysiological studies.

Since emesis due to drugs, endocrine disturbances, radiation, and motion is
abolished by area postrema ablation, these emetic peptides are possible candi-
dates for being the humoral mediator of at least some forms of emesis.

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PEPTIDE-INDUCED EMESIS IN DOGS

INTRODUCTION

Emesis is a complex reflex mediated by a brain-stem neuronal circuitry.
The reflex is triggered by drugs, motion, radiation, psychological factors,
intracranial pressure, gastric irritation or hormonal factors, as in preg-
nancy (cf. Wang, (24)). The reflex response consists of inhibition of
gastric tone, a negative intrathoracic pressure produced by inspiratory
intercostal muscles and the diaphragm, with positive pressure produced by
contraction of abdominal muscles (19). This reflex requires coordinated
activity of somatic and visceral musculature.

Much of our knowledge of the neural pathways involved in emesis comes
from the work of Wang and his colleagues (summarized by Wang (24)). The
motor reflex can be elicited by focal electrical stimulation in the dorso-
lateral border of the lateral reticular formation (3). The site of initial
action of drugs which are emetic, like apomorphine, was found to be the area
postrema. The emetic response to apomorphine is abolished after area
postrema ablation (2). The postrema, or whatever portion of it that had
this action, was named the "chemosensory trigger zone" (CTZ) for vomiting (4).
Since the area postrema is outside of the blood-brain barrier (27), the
neurons in the area postrema may respond to substances within the systemic
circulation, then project to the other side of the blood-brain barrier and
activate the brain stem-mediated reflex pathway. In contrast, emesis
resulting from local gastric irritation is not sensitive to area postrema
ablation, and is presumed to result from direct excitation of the motor
emetic center by vagal afferent fibers. Emesis due to radiation (25) and
motion (7) is abolished by area postrema ablation through mechanisms not
well understood.

An understanding of the nature of emesis to humoral agents, the neuronal
pathways, and pharmacological sensitivities of various forms of emesis is of
considerable importance. Nausea and vomiting are among the most common,
debilitating, and degrading side effects of chemo- and radiation therapy in
humans (cf. Frytak and Moertel(10)). Motion sickness is unpleasant and has
been experienced by almost everyone. Space sickness incapacitates about
half of the astronauts for half of their time in space (23).

These experiments were designed to determine whether a variety of
common neuroactive peptides were emetic and whether emetic actions were
dependent upon the area postrema, and to test some pharmacologic sensiti-
vities of emetic agents. These studies were done in parallel with an
investigation of the effects of peptides applied directly onto area postrema
neurons, and together indicate that several peptides are emetic because of
activation of specific receptors on area postrema neurons. Our results also
provide information on the sites of action of some common antiemetic drugs.

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METHODS

Conditioned random source dogs (8 to 12 kg) were obtained from commercial sources and maintained on dog chow. Upon arrival and at weekly intervals dogs were weighed and the foreleg shaved. Peptides and emetic agents were injected IV in saline at doses calculated by body weight. Except in desensitization experiments this was done not more frequently than every other day.

Agents tested include apomorphine hydrochloride, neurotensin, leucine-enkephalin, methionine-enkephalin, angiotensin II, gastrin, vasoactive intestinal polypeptide (VIP), thyrotropin-releasing hormone (TRH), substance P, vasopressin, oxytocin, secretin, bradykinin, triacetate, L-carnosine, bombesin, cholecystokinin 26-33 octapeptide amide sulfate, and somatostatin. Vasopressin was obtained from Calbiochem, and all the rest from Sigma.

Most agents tested for antiemetic activity were injected IM 30 min prior to challenge with peptides. These include chlorpromazine (Sigma, 1.5 mg/kg), domperidone (Janssen Pharmaceutica, 1.0 mg/kg), and naloxone hydrochloride (Endo Laboratories, 0.2 mg/dog). Saralasin acetate (Norwich-Eaton Pharmaceuticals, 0.25 mg/kg IV) was administered IV 30 sec before challenge.

Ablation of the area postrema was performed under Nembutal anesthesia (30 mg/kg). The area postrema was exposed as previously described (6) through a small opening over the floor of the fourth ventricle. After opening the dura, the ablation was made using a flat plate tip of an electrocautery, applied for only a few seconds. Ablations were bilateral, performed in two stages on each side. Animals were closed, treated with antibiotics, and returned to their cages. While both animals showed some transient ataxia (due to cerebellar irritation) they recovered to appear completely normal. Testing was resumed after one week. The dogs survived with repeated testing for 3 months. At the end of that period they were anesthetized with Nembutal, the abdominal aorta was clamped, and they were perfused through the left ventricle with cold saline followed by 10% formaldehyde. After removal of the brain stem and embediment in paraffin, sections were cut at 7 μm and stained with Weil's stain, cresyl violet-luxol fast blue, or neutral red for evaluation of spatial distribution of lesions.

RESULTS

Systemic administration of many peptides induced emesis. Figure 1 shows that behavioral emesis was a function of dose for apomorphine, a classical emetic agent, neurotensin, angiotensin II, and leucine-enkephalin. The threshold for emesis for a given peptide was similar in different animals, as was the nature of the emetic response. With all four substances emesis usually occurred within 30 sec of IV administration, occasionally followed by a second emetic episode a few moments later. At the doses given, emesis was the principal effect of injection, although angiotensin II and neurotensin both caused an unsteady gait, neurotensin stimulated defecation, and angiotensin II stimulated drinking and panting. Leucine-enkephalin did not cause obvious effects other than emesis.
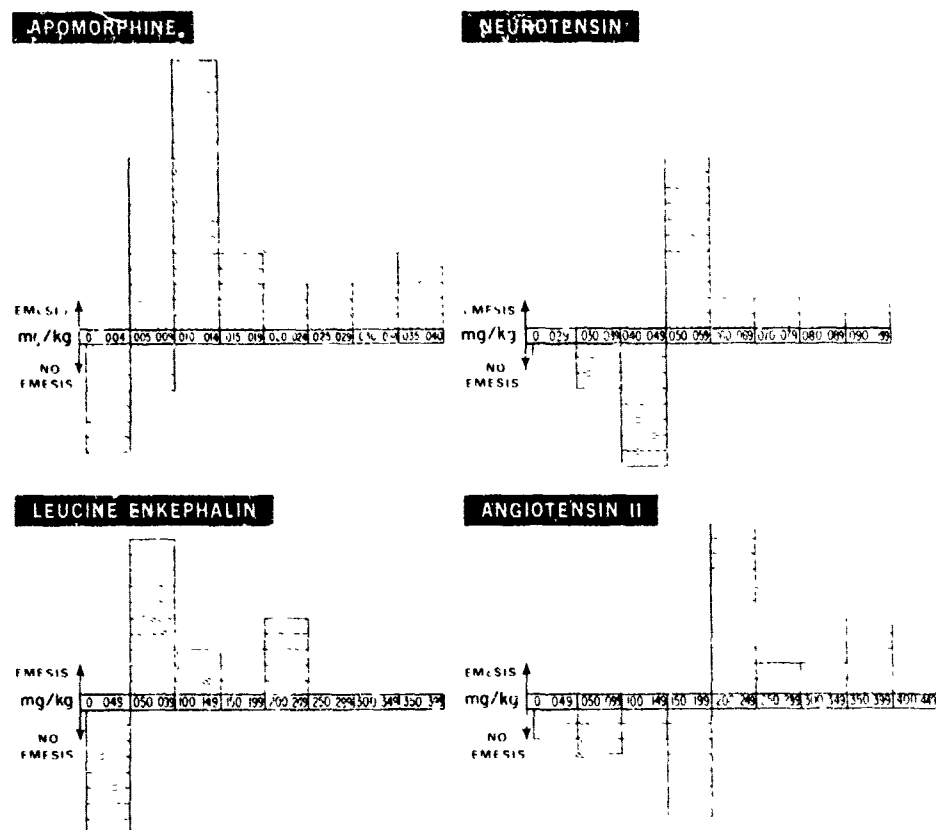
Figure 1. Dose response curves for emesis to apomorphine, neurotensin,
leucine-enkephalin, and angiotensin II administered to
conscious dogs by IV injection. The center lines show the
applied doses, and the results for each trial are shown as
a bin above the line if emesis occurred within 15 min, and
below the line if emesis did not occur. In actuality emesis
always resulted in less than 5 min.

Table 1 shows the results of less extensive tests of other peptides.
Many peptides, but not all, produced emesis at similar concentrations. For
some, such as substance P, VIP, and gastrin, there were pronounced effects
in addition to emesis, such as defecation and micturition, often accompanied
by obvious stimulation of peristalsis.

Table 2 shows results of studies designed to test the effects of
multiple application of emetic agents. Failure of emesis on multiple tests
could result either from receptor desensitization, in which case it should
be specific for one substance, or fatigue of the motor emetic center, in
which case it should be independent of the stimulating substance. For both
angiotensin II and leucine-enkephalin, a second dose applied 5 min after the
first did not produce emesis, although application of either the other
peptide or apomorphine was effective. Apomorphine did not show receptor
desensitization at 5 min. At 30 min a second application of either angio-
tensin II or leucine-enkephalin was effective in producing emesis.

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TABLE 1. EMETIC AND NONEMETIC PEPTIDES

Substance	Nonemetic dose (mg/kg IV)	Number of trials	Emetic dose (mg/kg IV)	Number of trials
Gastrin	(0.03-0.04)	3	(0.05-0.20)	6
VIP	(0.02-0.04)	3	(0.05-0.20)	5
Substance P	(0.01-0.02)	4	(0.03-0.20)	6
Vasopressin	(0.02-0.05)	12	(0.04-0.07)	22
Oxytocin	(0.02-0.06)	3	(0.05-0.20)	5
Bombesin	(0.05-0.06)	3	(0.07-0.08)	6
TRH	(0.02-0.05)	14	(0.05-0.20)	5
Methionine enkephalin	(0.05-0.06)	4	(0.06-0.07)	5
Somatostatin	(0.03-0.20)	7		
CCK	(0.05-0.06)	4		
Secretin	(0.05-0.20)	6		
Bradykinin triacetate	(0.05-0.20)	5		
L-Carnosine	(0.04-0.20)	9		
LHRH	(0.04-0.20)	8		

TABLE 2. EFFECTS OF MULTIPLE INJECTIONS OF EMETIC SUBSTANCES

| Substance | Control | 5 minutes | | | 30 minutes | |
		Angio	Leu-Enkep	Apo	Angio	Leu-Enkep
Angiotensin II (0.25 mg/kg)	11/11	0/4	4/4	4/4	4/4	
Leucine-enkephalin (0.075 mg/kg)	10/10	4/4	0/4	4/4		4/4
Apomorphine hydrochloride (0.015 mg/kg)	5/5			4/4		

The ratios show the number of dogs showing emesis or injection over the total number of tests. At 5 and 30 min, the initial test was made with the substance listed at the left at zero time, followed by the indicated substances at 5 or 30 min. angio = angiotensin II, leu-enkep = leucine-enkephalin, apo = apormorphine, all at the same concentration listed at the left.

Table 3 shows results of attempts to pharmacologically distinguish responses to apomorphine, angiotensin II, and leucine-enkephalin. These substances are of interest since presumably specific antagonists exist for each. Chlorpromazine and domperidone are antagonists for dopamine receptors but differ in that domperidone is known not to cross the blood-brain barrier (14). Consequently both would be expected to block the response to apomorphine, a dopamine agonist, at the level of the area postrema. This result was observed. Naloxone is thought to be specific for opioid receptors. Naloxone blocked the response to leucine-enkephalin, but did not change the response to apomorphine or angiotensin II. This is consistent with the view that leucine-enkephalin acts as a specific receptor within the area postrema, and that naloxone blocks this receptor without interfering in the pathway from apomorphine or angiotensin II receptors. Saralasin, a structural analogue of angiotension II, blocked responses to angiotensin II and, surprisingly, to leucine-enkephalin, but not apomorphine. Chlorpromazine was effective against all three drugs.

TABLE 3. EFFECTS OF VARIOUS ANTAGONISTS ON APOMORPHINE AND PEPTIDE EMESIS

Substance	Angiotensin II (0.25 mg/kg)	Leucine-Enkephalin (0.15 mg/kg)	Apomorphine (0.015 mg/kg)
Domperidone 1.0 mg/kg (IM)	16/16	16/16	0/15
Chlorpromazine 1.5 mg/kg (IM)	0/16	1/16	0/12
Naloxone hydrochloride 0.2 mg/dog (IM)	12/12	0/12	12/12
Saralasin acetate 0.25 mg/kg (IV)	0/12	0/12	12/12

All antagonists except saralasin were given 30 min prior to test. Saralasin was given 30 sec prior to test. Numbers reflect the number of emetic responses over the number of animals tested.

To confirm that peptide-induced emesis was mediated through the area postrema, ablations of this structure were made in two dogs. Table 4 shows the effectiveness of apomorphine and peptides in producing emesis in these dogs before and after ablation of the area postrema. Figure 2 shows transverse sections through the level of the area postrema in a control animal and two dogs with bilateral ablations. In the first animal, the ablation was shallow and virtually restricted to the area postrema. Examination of Neisl-stained sections gave no indication of injury to adjacent nuclear groups. The ablation in the second animal was deeper. The area postrema was completely removed. On the right side extensive damage occurred to the hypoglossal nucleus and dorsal motor nucleus of the vagus, and the medial side of the rostral division of the gracile nucleus. The dorsal half of the solitary fasciculus sustained injury together with the medial and lateral solitary nuclei, particularly the former. A smaller amount of damage on the left involved the dorsal motor nucleus of the vagus and the dorsal part of the hypoglossal nucleus, but not the solitary nuclei. The uvula also was injured in this case. With a single exception neither dog vomited on any test after ablation, indicating that peptide-induced emesis is mediated through the area postrema.

TABLE 4. EFFECTS OF BILATERAL AREA POSTREMA ABLATION
ON PEPTIDE-INDUCED EMESIS

Substance	Dog #1		Dog #2	
	Pre	Post	Pre	Post
Apomorphine (0.005-0.015 mg/kg) (to 0.018 mg/kg post)	4/4	0/4	3/3	0/3
Neurotensin (0.05-0.09 mg/kg) (to 0.10 mg/kg post)	3/3	1/4	3/3	0/3
Leu-enkephalin (0.05-0.15 mg/kg) (to 0.2 mg/kg post)	4/4	0/7	4/4	0/6
Angiotensin II (0.2-0.3 mg/kg) (to 0.35 mg/kg post)	3/3	0/5	3/3	0/5

The numbers show the number of emetic responses over the number of tests before and after bilateral area postrema ablation. Some substances were tested at higher doses after ablation, as indicated in the left column.
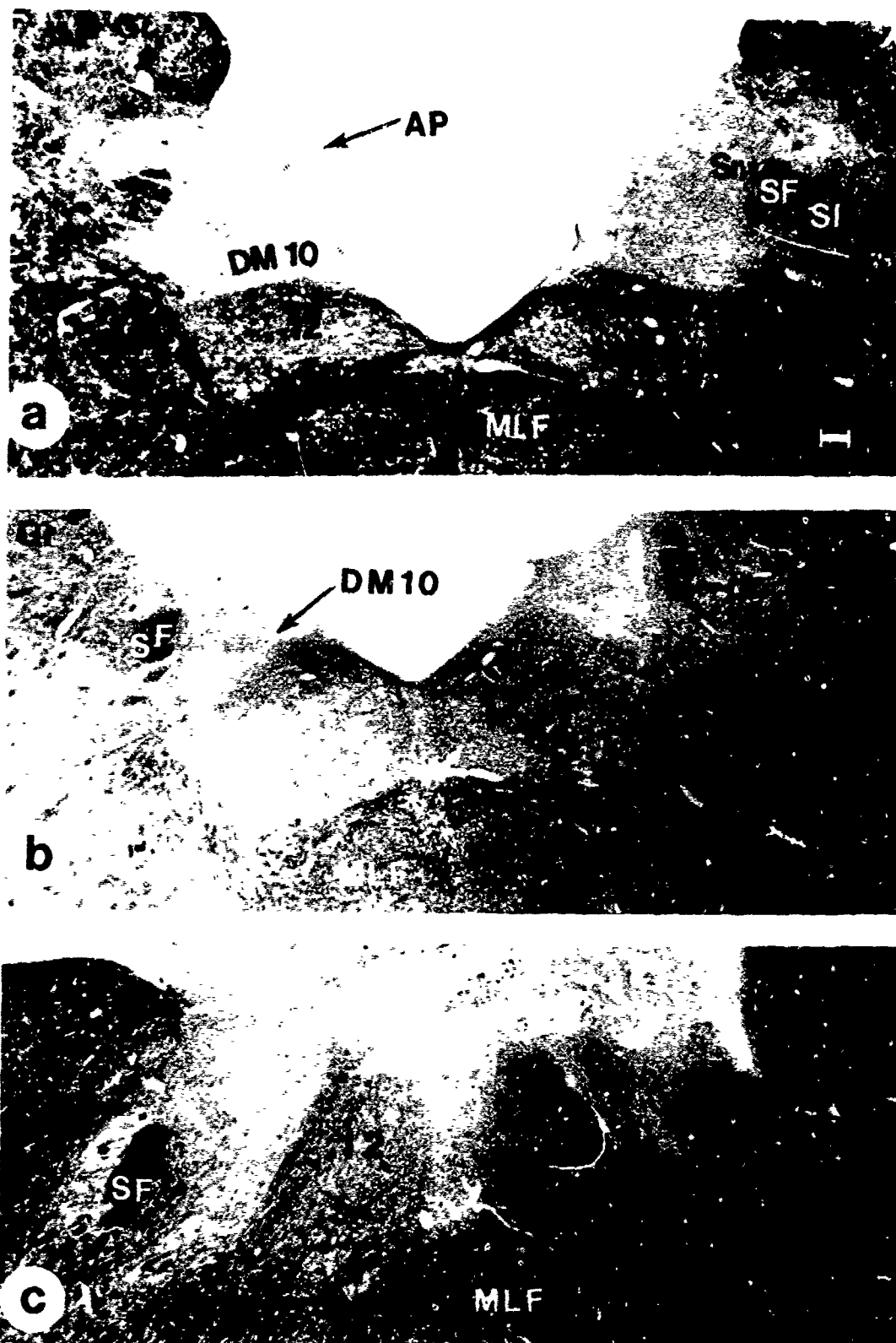
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Figure 2. Photomicrographs of transverse sections at the level of the obex show
the area postrema (AP) in control (a) and bilaterally ablated (b, c)
dogs. Structures in proximity to the AP are labelled in the control
as follows: DM 10, dorsal motor nucleus of the vagus; Gr, rostral
division of the gracile nucleus; MLF, medial longitudinal fasciculus;
SF, solitary fasciculus; Sl, lateral solitary nucleus; Sm, medial
solitary nucleus; 12, hypoglossal nucleus. Marker indicates 100-μm
Weil stain.

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DISCUSSION

The principal conclusions of this study are that 1) many small peptides are emetic at relatively low concentrations, 2) peptide-induced emesis is dependent upon the integrity of the area postrema, and 3) the desensitization properties and pharmacological sensitivities of the responses support the view that specific receptors exist in the area postrema for each emetic peptide. These conclusions are totally consistent with the proposed role of the area postrema as the "chemosensory trigger zone" (CTZ) for emesis (cf. Borison(5); Wang (24)).

The identification of the CTZ and its role in emesis was first made by Borison and Wang (4) on the basis of their observations that apomorphine-induced emesis was abolished after area postrema ablation, while emesis due to local gastric irritation was not. They proposed that the CTZ initiated all humoral emesis, which was possible since this structure is outside of the blood-brain barrier (27). The present studies, when considered together with our concurrent investigation of the effects of peptides applied onto area postrema neurons by ionophoresis (6), provide rigorous support for this hypothesis. Not only have our electrophysiological studies shown that area postrema neurons are excited by apomorphine and dopamine, but also we have found excitatory responses to every emetic peptide which we have tested (neurotensin, angiotensin II, leucine-enkephalin, gastrin, VIP, TRH, substance P, and vasopressin), but elicited no excitatory response to two peptides which in the present studies were not found to be emetic (somatostatin and CCK).

The desensitization experiments and studies with naloxone and domperidone argue that the receptors mediating apomorphine and peptide-induced emesis are distinct, and furthermore, that different peptides have distinct receptors. These results are also in agreement with the electrophysiological studies of chemosensitivity of area postrema neurons, where it was found that any given neuron might respond to one but not another peptide, while the next neuron might have the opposite response (6). Desensitization is thought to be a characteristic of the receptor protein (20), and thus it is not surprising that the apomorphine receptor does not show as marked desensitization as do the angiotensin II and leucine-enkephalin receptors. The fortuitous desensitization of leucine-enkephalin and angiotensin II receptors does, however, allow an important test of receptor independence. The lack of cross-desensitization between angiotensin II and leucine-enkephalin responses is proof that their emetic responses are mediated through distinct receptors.

The antagonist studies are more complex to interpret since one must make assumptions concerning both the specificity and sites of drug action. Domperidone is a dopamine receptor antagonist (26) which does not cross the blood-brain barrier (14). The observation that domperidone blocked apomorphine-induced emesis without altering responses to the peptides is consistent with its action at only "peripheral" dopamine receptors. Chlorpromazine, also a dopamine antagonist, is known to be effective in treatment of a variety of forms of emesis (18). The effectiveness of chlorpromazine against peptide as well as apomorphine emesis indicates that it has actions at some site in addition to "peripheral" dopamine receptors.

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Most likely this second site is also a dopamine receptor but on the brain side of the blood-brain barrier. This is important and new information, and implicates dopamine at least at one site between the area postrema and the motoneurons. Fuxe and Owman (11) have described catecholamine fluorescing neurons in the canine area postrema, and the terminals of these neurons on the motor emetic center may be dopaminergic. It is likely that the phenothiazine, butyrophenone, and trimethylbenzamide derivatives used as antiemetic agents, all of which have been assumed to act only at the level of the area postrema (cf. Seigel and Longo (22); Janssen et al. (13); Cockel (8)) also act principally at some central site. Of dopamine antagonists, probably only domperidone and metachlorpromaide are principally or exclusively peripheral in sites of action (cf. Gylys (12)).

It has been known for some time that emesis due to morphine (2) and enkephalin (1) is abolished on area postrema ablation, and that naloxone blocks emesis due to these agents without effects on that to apomorphine (9, 16). Our results confirm these conclusions and provide the additional evidence that the opiate receptors are distinct also from receptors to other peptides.

The action of saralasin in blocking the angiotensin II response was not unexpected, although the blockade of the leucine-enkephalin response was a surprise. Saralasin (Sar-Arg-Val-Try-Val-His-Pro-Ala) is a structural analogue of angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe). Leucine-enkephalin (Tyr-Gly-Gly-Phe-Leu) is a quite different structure. While the blockade of leucine-enkephalin emesis by saralasin remains unexplained, the desensitization experiments provide clear evidence that the angiotensin II and leucine-enkephalin receptors are distinct.

The central role of the area postrema in emesis is most dramatically illustrated in the human study of Lindstrom and Brizzee (17) who treated five patients having intractible vomiting with an area postrema ablation. All showed subsequent relief from nausea and vomiting, as well as hiccups in some cases. The patients also became resistant to apomorphine emesis.

The functional significance of peptide-induced emesis is not clear. These studies were begun in an effort to find a humoral agent mediating radiation-induced emesis. Emesis from both radiation (25) and motion sickness (7) are abolished after area postrema ablation, implying they are mediated via some humoral substance. It is likely that the nausea and vomiting of chemotherapy are also mediated through the area postrema, at least for some agents (10, 15). For each of these stimuli release of emetic peptides from some site could be the mechanism triggering the emesis, and thus measurement of circulating levels of emetic peptides under these conditions merits study. An association between circulating vasopressin and emesis has been noted, although it is not clear which event is primary (21). Our results do provide evidence that several neuroactive peptides are emetic at systemic concentrations which are not grossly unphysiologic. Activation of area postrema receptors by these agents may be of physiologic importance in some forms of emesis.

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