NAUSEA AND EMETIC REFLEX IN THE MINIPIG: LEGEND AND REALITY

S. MILANO, C.S.O. Europe
WRC LYON

Roma, 2013
-Nausea and Vomiting are biological defence mechanisms. The major physiological function of emesis (vomiting) is to remove toxic or harmful substances from the body after ingestion.

However, emesis is multifactorial in origin and can be caused by a range of stimuli, including medical interventions, some of which apparently have little to do with ingesting poisonous substances. In addition to poison ingestion and gastroenteritis, emetic stimuli include motion, surgery, pregnancy, various drugs and radiation.

Disgusting sights, smells or memories can also cause nausea and vomiting, and this has a physiological basis leading to avoidance.
NAUSEA AND VOMITING : AN INTRODUCTION

The impact of nausea and vomiting on the development of novel chemical entities.

Side effects encountered in 16 phase 1 clinical studies conducted by Pfizer between 2003 and 2005. While the most commonly encountered side effect was headache, with approximately 250 instances, the next most encountered was nausea, which accounted for over 80 instances, nearly half of which were rated as either moderate or severe.
- The body has several hierarchical lines of defense against toxins:

- **First line of defense:** Avoidance of certain foods due to smell or taste cues

- **Second line of defense:** Detection of toxins in the gut followed by nausea (prevents further consumption) and vomiting (purges the body of already ingested toxin)

- **Third line of defense:** Detection of toxins in the circulation by a sensor in the central nervous system, also followed by vomiting.
These frogs have a powerful defensive mechanism, alkaloid toxins that they secrete through canals in their skin. If touched or bitten, they expel the toxic substance. Typically, the toxins have a particular odor and a bitter, peppery taste that can induce vomiting, thereby forcing a predator to spit out the frog.
TASTE AVERSION LEARNING IN SUCKLING AND WEANLING PIGS

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Supported by N.S.F. Grant BNS 77-16510 NIH Grant AM-17601

Fig. 1. Taste aversion tests in suckling pigs. Clear columns: intake of feed with novel flavor just before injection of 0.9% NaCl or apomorphine. Cross-hatched columns: intake 3 days later of same flavored feed.
The process of emesis can be classified into three phases: **Nausea**, **Retching** and **Vomiting**.

Nausea is described as an unpleasant sensation that immediately proceeds vomiting. A cold sweat, pallor, salivation, a noticeable disinterest in the surroundings, loss of gastric tone, duodenal contractions and the reflux of intestinal contents into the stomach often accompany nausea.

Prodromics signs of emesis
Vomiting is a complex suite of coordinated muscular actions, controlled by a group of nuclei in the brainstem. In essence, great pressure is put on the stomach by surrounding respiratory muscles and the esophagus is opened. The result is that the stomach's contents are expelled forcefully from the mouth.
VOMITING REFLEX

Inspiratory (INSPIRATION) and expiratory (EXPIRATION) stages of the vomiting reflex. The diagram illustrates the neural pathways involved in the vomiting response, including the role of the medulla oblongata, pons, and respiratory centers in the brainstem. The reflex is mediated by the vagus nerve, which stimulates contractions of the stomach and intestines, leading to the urge to vomit.
Respiratory network
Retching follows nausea, and comprises laboured **spasmodic respiratory movements** against a **closed glottis** with contractions of the abdominal muscles, chest wall and diaphragm without any expulsion of gastric contents. Retching can occur without vomiting but normally it generates the pressure gradient that leads to vomiting.
The final common pathway for efferent responses that produce emesis is the « Vomiting Centre », which controls the act of vomiting. Numerous neuronal pathways converge on the Vomiting Centre in the medulla (part of the hind brain) where the vomiting reflex is initiated. The Vomiting Centre is not a discrete anatomical site, but represents inter-related neuronal networks.
The Chemoreceptor Trigger Centre (CTZ) in the area postrema of the 4th ventricle of the brain acts as the entry point for emetic stimuli and substances. The CTZ is outside the blood-brain barrier and therefore responds to stimuli from either the cerebral spinal fluid (CSF) or the blood.
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**On the Structure of the Area postrema in some Domestic Animals**

The present paper concerns the structure of the A. P. of the horse, ox, pig and dog. Since these animals differ markedly from each other from the physiological point of view, e.g., great differences in the vomiting can be observed, it was believed that the potential structural differences could elucidate the function of the organ. As far as we know no one has described the structure of the A. P. of these species, except that of the dog described by Wislocki and Putnam (1924) and Cammermeyer (1949).

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**Fig. 3.11. Blood capillary with fenestrated endothelium and a wide perivascular space.** They are typical in circumventricular organs. L - lumen, blue arrow - endothelial pore, red arrow - basal lamina, P - perivascular space, F - fibrocyte. Insert: blood capillary with the wide perivascular space. Scale = 200 nm. (Rat, area postrema.)
## Reflux of the Intestinal Content

<table>
<thead>
<tr>
<th></th>
<th>Maximal Frequency [contractions/min]</th>
<th>Velocity [cm/sec]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>5.2</td>
<td>0.8-1.1</td>
</tr>
<tr>
<td>Rabbit</td>
<td>4.6</td>
<td>0.4-0.5</td>
</tr>
<tr>
<td>Pig</td>
<td>3.3</td>
<td>—</td>
</tr>
<tr>
<td>Sheep</td>
<td>5.4</td>
<td>—</td>
</tr>
<tr>
<td>Human</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Small intestine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>15.8–17.8</td>
<td>7-12</td>
</tr>
<tr>
<td>Jejunum</td>
<td>17–17.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Ileum</td>
<td>13.3–13.8</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td>Pig</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>17–18</td>
<td>8</td>
</tr>
<tr>
<td>Jejunum</td>
<td>15</td>
<td>5.6</td>
</tr>
<tr>
<td>Ileum</td>
<td>11</td>
<td>0.5</td>
</tr>
<tr>
<td>Sheep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>14.4–14.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>11</td>
<td>—</td>
</tr>
</tbody>
</table>
REFLUX OF THE INTESTINAL CONTENT

RCG originates in the proximal jejunum, propagates orally towards the stomach and moves up to the proximal antrum. The RCG forces the chyme of the proximal small intestine across the widely opened pylorus into the relaxed gastric body. Some minutes later retching and vomiting occurs. Rhythmic inspiratory movements against a closed glottis produce negative oscillations in intrathoracic pressure and concomitant contractions of the abdominal muscles and the diaphragm cause an increase in intra-abdominal pressure.
Figure 3. Phylogenetic tree showing the presence or absence of the ability to vomit in members of the 11 major mammalian orders, representing ~98% of mammalian species, based on key reports in the published literature (note that the number of species indicated is limited only by space and not by the number of reports that are available in the literature) (e.g. Marsupialia [49], Primate [50], Insectivora [51], Perissodactyla [52], Artiodactyla [50,52,53], Cetacea [54], Chiroptera [55], Carnivora [50,56], Lagomorpha [50], Rodentia [51,56]). Note that in a few cases (e.g. elephant) the presence of vomiting is based on a single clinical report. Functional motilin system, Functional ghrelin system. X = point at which it is proposed that the vomiting reflex was lost and X = point at which a functional motilin system was lost. Shaded box indicates order and species in which the vomiting reflex is absent. The arrow next to the rabbit silhouette indicates that coprophagia is a normal part of digestive behaviour of this animal.

The translational value of rodent gastrointestinal functions: a cautionary tale.
Sanger GJ, Helbrook JD, Andrews PL.
“(Mini)pigs are much less prone to emesis than dogs”

Apomorphine ✓
Xylazine ✓
Ipecac syrup ✓
Hydrogen peroxide ✓
Chemotherapy ✓
Radiation ✓
Motion ✓

Copper sulfate ?
“(Mini)pigs are much less prone to emesis than dogs”

**Table 1** Species differences in the emetic sensitivity to the dopamine receptor agonist apomorphine

<table>
<thead>
<tr>
<th>Species</th>
<th>Emetic sensitivity to apomorphine</th>
<th>Dose of apomorphine</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Very sensitive</td>
<td>10–66 µg·kg⁻¹, i.v.</td>
<td>i.v.: Klein et al. (1968); Shields et al. (1971); Islaas and MacArthur (1954); Islaas (1956); Proctor et al. (1978)</td>
</tr>
<tr>
<td>Monkey (Macca cynomologus/mulatta)</td>
<td>Insensitive</td>
<td>Doses up to 25 mg·kg⁻¹, i.v.</td>
<td>Brizzée et al. (1955)</td>
</tr>
<tr>
<td>Marmoset</td>
<td>Weakly sensitive</td>
<td>0.5 mg·kg⁻¹, s.c.</td>
<td>Costall et al. (1986)</td>
</tr>
<tr>
<td>Pig</td>
<td>Very sensitive</td>
<td>0.01–0.15 mg·kg⁻¹, s.c.</td>
<td>Parrott et al. (1991)</td>
</tr>
<tr>
<td>Dog</td>
<td>Very sensitive</td>
<td>2.5–20 µg·kg⁻¹, i.v.</td>
<td>Niemegeers (1971; 1982; Harding et al. (1987); Borison and Heberson (1959); Share et al. (1965)</td>
</tr>
<tr>
<td>Cat</td>
<td>Relatively insensitive</td>
<td>25 mg·kg⁻¹, s.c.</td>
<td>Laffan and Borison (1957); Borison (1959)</td>
</tr>
<tr>
<td>Ferret</td>
<td>Relatively sensitive</td>
<td>~0.025–0.25 mg·kg⁻¹, s.c.</td>
<td>Costall et al. (1989); Andrews et al. (1990)</td>
</tr>
<tr>
<td>House musk shrew (Suncus)</td>
<td>No response</td>
<td>Up to 100 mg·kg⁻¹, s.c.</td>
<td>Ueno et al. (1987)</td>
</tr>
<tr>
<td>Least shrew</td>
<td>Sensitive</td>
<td>~2 mg·kg⁻¹, s.c.</td>
<td>Darmani et al. (1999)</td>
</tr>
<tr>
<td>Rat</td>
<td>CTA</td>
<td>1 mg·kg⁻¹, i.p.</td>
<td>Wang et al. (1997)</td>
</tr>
<tr>
<td>Rat</td>
<td>Pica</td>
<td>10 mg·kg⁻¹, i.p.</td>
<td>Takeda et al. (1993)</td>
</tr>
</tbody>
</table>

Opportunities for the replacement of animals in the study of nausea and vomiting

AM Holmes1, JA Rudd1, TD Tattersall1, Q Aziz1 and PLR Andrews1
“(Mini)pigs are much less prone to emesis than dogs”

Vomitoxin, also known as deoxynivalenol (DON), is a type B trichothecene. This mycotoxin occurs predominantly in grains such as wheat, barley, oats, rye, and maize. The occurrence of deoxynivalenol is associated primarily with Fusarium graminearum (Gibberella zeae) and F. culmorum, both of which are important plant pathogens which cause fusarium head blight in wheat and gibberella or fusarium ear blight in maize.

Deoxynivalenol: Toxicity, mechanisms and animal health risks

James J. Pestka

7. Conclusions

Animals differ with regard to sensitivity to DONs effects with pigs being highly susceptible and poultry and ruminants being relatively resistant. Many of the immunologic and physiological effects seen in laboratory animals are also relevant to farm animals. The primary safety concern for acute high dose DON exposure is its capacity to cause acute gastroenteritis with vomiting effects that might be caused by dysregulation of immune and/or neuroendocrine function. Animal studies indicate that primary chronic effects involve impaired feed intake and growth as well as altered immune function. Both 3- and 15-acetyl
“(Mini)pigs are much less prone to emesis than dogs”

Staphylococcal food poisoning results from the ingestion of enterotoxins formed in foods by certain strains of *Staphylococcus aureus*. The primary symptoms of staphylococcal food poisoning in humans are nausea, vomiting, abdominal cramping, and diarrhea occurring within 1 to 4 h after ingestion of the contaminated food. Monkeys have been the primary animal models because peroral administration of staphylococcal enterotoxins elicits an emetic response from them. Other animals display emetic responses to staphylococcal enterotoxins but not when enterotoxins are administered perorally. 

*Cats and dogs vomit after intravenous administration.*
"(Mini)pigs are much less prone to emesis than dogs"

**TABLE 1.** Emetic and neurobehavioral effects of SEA after peroral administration to 4.1- to 9.1-kg weanling pigs

<table>
<thead>
<tr>
<th>Dose of SEA (µg)</th>
<th>Response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emesis</td>
<td>Neurobehavioral symptoms</td>
</tr>
<tr>
<td>75</td>
<td>4/4a</td>
<td>4/4</td>
</tr>
<tr>
<td>50</td>
<td>12/16</td>
<td>14/16</td>
</tr>
<tr>
<td>40</td>
<td>2/8</td>
<td>8/8</td>
</tr>
<tr>
<td>30</td>
<td>2/8</td>
<td>4/8</td>
</tr>
<tr>
<td>20</td>
<td>1/4</td>
<td>3/4</td>
</tr>
<tr>
<td>0</td>
<td>0/4</td>
<td>0/4</td>
</tr>
</tbody>
</table>
Motion sickness

In order to maintain control of the body balance, the brain must combine signals from:

- The vestibular receptors in the inner ear, which measure rotation and translation of the head in space
- The eyes
- Stretch receptors in the muscle tissue that inform the brain on the current position of the arms and legs relative to the body.

The vestibular system primary function is to detect rotational and translational movements of the head and generate a corresponding response signal. These signals contribute to perceptions of motion and orientation, the effective coordination of eye movements, posture and balance.
Motion sickness

How developers are trying to solve motion sickness in video games

By Alexa Ray Corriea on Oct 26, 2013 at 9:00a @AlexaRayC
VOMITING AND SPECIES

“(Mini)pigs are much less prone to emesis than dogs”

Motion sickness
VOMITING AND SPECIES
CISPLATIN-INDUCED VOMITING

![Graph showing the intensity of emesis over time after chemotherapy, with peaks for serotonin (peripheral) and substance P (central), and a delay of 16 hours.]
Figure 3: Mean number of emetic events per 1-hour epoch after Cisplatin administration (Mean ± sem, n=4).
CISPLATIN-INDUCED VOMITING

A
CONTROL

Mas.-----------------------------

Abd.-----------------------------

ECG
Heart rate: 102 beats/min

B
NAUSEA ACTIVITY

Heart rate: 138 beats/min

C
VOMITING

Heart rate: 154 beats/min

2 sec

The Piglet as a Suitable Animal Model for Studying the Delayed Phase of Cisplatin-Induced Emesis

STÉPHANE MILANO, PETER BLOWER, DIDIER ROMAIN and LAURENT GRÉLOT

The Journal of Pharmacology and Experimental Therapeutics
Copyright © 1995 by The American Society for Pharmacology and Experimental Therapeutics
JPET 274:961-961, 1995
CISPLATIN-INDUCED VOMITING

Ondansetron 3.5 mg/kg
CISPLATIN-INDUCED VOMITING

GR205171
Potent inhibition of both the acute and delayed emetic responses to cisplatin in piglets treated with GR205171, a novel highly selective tachykinin NK₁ receptor antagonist

1²Laurent Grélot, ³Julien Dapzol, ³Eric Estève, ¹Alain Frugière, ¹Armand L. Bianchi, ²Robert L.G. Sheldrick, ³Christopher J. Gardner & ³Peter Ward
Regurgitation is the expulsion of material from the mouth, pharynx, or esophagus, usually characterized by the presence of undigested food or blood. Regurgitation is used by a number of species to feed their young. This is typically in circumstances where the young are at a fixed location and a parent must forage or hunt for food, especially under circumstances where the carriage of small prey would be subject to robbing by other predators or the whole prey is larger than can be carried to a den or nest. It is in most animals a **normal and voluntary process** unlike the complex vomiting reflex in response to toxins.
CONCLUSION

“(Mini)pigs are much less prone to emesis than dogs?”

NOT ALWAYS!