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Investigation of segmental differences of the gastrointestinal tract of rats

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Learning objectives:

1. Discuss different methods to investigate the gastrointestinal tract of rats.
2. Identify important characteristics of rat gastric and intestinal fluids.
3. Explain the ideas behind the use of rat simulated fluids *in vitro*.

INTRODUCTION: For predicting oral bioavailability of drugs, it is important that *in vitro* data are generated under conditions as close to the *in vivo* situation as possible. Several simulated gastrointestinal (GI) fluids have been developed to accommodate this need, but they are based on the composition of GI fluids in humans or dogs (1). The aim of the current study was to investigate pH, osmolality, bile salt and phospholipid concentrations in different segments of the GI tract in rats, with the overall aim of producing media simulating gastric and intestinal fluids in rats.

METHODS: Seven Sprague Dawley rats weighing 297 ± 9 g were fasted overnight prior to the experiments. Six rats were sacrificed to measure pH and collect fluid samples and one rat was sacrificed for matrix-assisted laser desorption ionization mass spectrometry (MALDI MS) imaging. The rats were anesthetized, and the abdomen was opened. The pH was measured with a micro electrode through a small incision in six different segments of the GI tract (Fig. 1), and fluid samples were collected for subsequent analysis. The osmolality was measured, and the concentration of bile salts and phospholipids were determined using a fluorometric and colorimetric enzymatic assay kit, respectively. The types of bile salts and phospholipids present were imaged using MALDI MS imaging of the small intestine.

RESULTS: The measured pH values and concentrations are shown in Table 1. The pH and osmolality were observed to increase from the stomach through the small intestine. The bile salt concentration was determined to be 24.4 ± 10.5 mM in the proximal part of the small intestine and increased to 46.8 ± 15.2 mM in the distal part. The phospholipid concentration was similarly higher in the proximal part of the small intestine (2.5 ± 1.7 mM) than in the distal part, where it was hardly detected (0.3 ± 0.3 mM). Both bile salts and phospholipids were scarcely measurable in the stomach. MALDI MS images of the rat small intestine showed taurocholic acid, cholic acid and beta-muricholic acid to be the most abundant bile salts, whereas lysophosphatidylcholine was present as phospholipid.

CONCLUSIONS: Different segments of the GI tract of rats were investigated regarding pH, osmolality and bile salt and phospholipid type and concentration. Based on these findings, media simulating gastric and intestinal conditions in rats were prepared, which may lead towards better *in vitro in vivo* correlation in the future.

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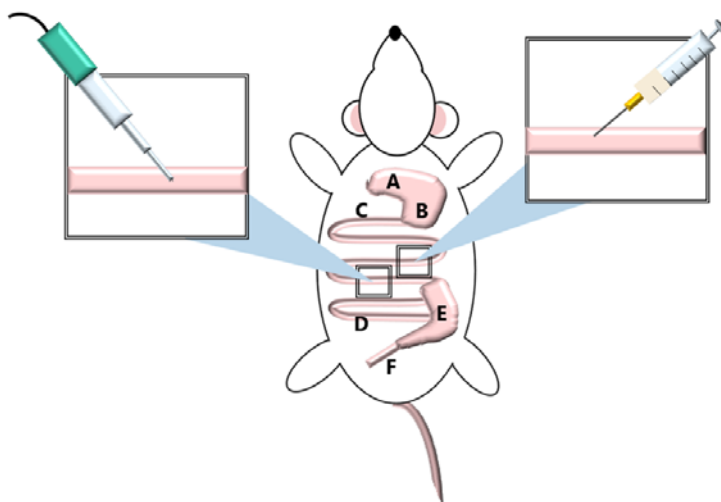


Fig. 1: Schematic of the sampling and pH measurements in the GI tract of a rat in A: Forestomach, B: Glandular stomach, C: Proximal small intestine (5 to 20 cm distal to the stomach), D: Distal small intestine (5 to 20 cm proximal to the caecum), E: Caecum and F: Colon.

Table 1: pH values, bile salt and phospholipid concentrations and osmolalities measured in the GI tract of fasted rats (mean ± SD, n= 3-6).

| | Forestomach | Glandular stomach | Proximal small intestine | Distal small intestine | Caecum | Colon |
|-----------------------------|-------------|-------------------|--------------------------|------------------------|-----------|-----------|
| pH | 1.9 ± 0.3 | 2.9 ± 0.7 | 7.5 ± 0.3 | 7.8 ± 0.3 | 7.6 ± 0.2 | 7.6 ± 0.2 |
| Bile salts (mM) | 1.5 ± 0.9 | | 24.4 ± 10.5 | 46.8 ± 15.2 | - | - |
| Phospholipids (mM) | 0.7 ± 0.3 | | 3.0 ± 1.4 | 0.3 ± 0.3 | - | - |
| Osmolality (mOsm/kg) | 237 ± 19 | | 313 ± 13 | 328 ± 13 | - | - |