



Physiology and pharmacology of the brushtail possum gastrointestinal tract: Relationship to the human gastrointestinal tract[☆]

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Abstract

Oral formulations are typically based on studies from eutherian animal models. This review introduces information relating to oral formulations for a marsupial species, the Australian brushtail possum (*Trichosurus vulpecula*) that has arisen from research into new methods for controlling this species — a major vertebrate pest in New Zealand. Morphologically, the gastrointestinal tract of the brushtail possum is similar to that of hindgut fermenting eutherian species, but there are some striking differences in function. Limited data suggests that the pharmacokinetics and bioavailability of administered drugs are similar to that in eutherian species, but there is some evidence that possums may have specific mechanisms for handling the intake of plant toxins and xenobiotics. The development of oral formulations for a free-ranging pest species presents several challenges above those encountered in the development of therapeutic formulations for humans and domestic animals. Use of a marsupial animal model may lead to new strategies for oral formulations in humans.

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Keywords: Oral delivery; Marsupial; Caecum; LHRH; Gastrointestinal pH; Transit time; *Trichosurus vulpecula*

Contents

1.	Introduction	1122
1.1.	The common brushtail possum	1122
1.2.	The brushtail possum in New Zealand	1122
1.3.	Developing oral delivery formulations for possums	1122
2.	Gastrointestinal tract physiology	1122
2.1.	Morphology	1122
2.2.	Gastrointestinal transit	1123
2.3.	Gastrointestinal pH	1124
2.4.	Microflora	1125
3.	Barriers to oral delivery of peptides and proteins	1125
3.1.	Proteolytic activity	1125
3.2.	Permeability	1126
3.3.	Epithelial cell function	1127

Abbreviations: CSM; colonic separating mechanism; GI gastrointestinal; ^{99m}Tc; radiolabeled technetium; BSA; bovine serum albumin; LHRH; luteinizing hormone releasing hormone; DGGE; denaturing gradient gel electrophoresis; EDTA; ethylenediamine tetra-acetic acid; SDA; sodium deoxycholic acid; DTT; dithiothreitol; PSM; plant secondary metabolite.

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4. Pharmacology	1127
4.1. Metabolism of ingested toxins	1127
4.2. Drug pharmacokinetics in possums	1128
5. Conclusions	1129
References	1129

1. Introduction

1.1. The common brushtail possum

The common brushtail possum (*Trichosurus vulpecula* Kerr) is a nocturnal, arboreal, marsupial endemic to Australia with an adult body weight of between 1.5 and 3.0 kg. Marsupials are a separate lineage of mammals that diverged from eutherian¹ mammals about 130 million years ago [1]. Marsupials radiated in Australasia and the group includes many anatomically diverse species such as kangaroos (*Macropus* spp.) and the koala (*Phascolarctos cinereus*). The common brushtail possum, one of 28 possum species in Australia (Family Phalangeridae), is distinct from the American opossums (genus *Didelphis*, Family Didelphidae).

Although the brushtail possum is usually considered to be a generalist folivore, there is increasing evidence that they obtain additional energy and/or nutrients from other sources. Brushtail possums are amongst the smallest folivorous mammals and thus face severe problems in meeting their energy requirements from a leaf diet alone [2]. There is evidence that possums, at least those in New Zealand, predate on birds eggs and fledglings [3], invertebrates [4] and molluscs [5]. In our own possum colony, where possums are housed as groups [6], brushtail possums frequently kill and eat sparrows [7]. The brushtail possum is therefore, an opportunistic folivore that eats a wide range of foliar and non-foliar foods, including a variety of animals [8].

1.2. The brushtail possum in New Zealand

The brushtail possum was deliberately introduced into New Zealand during the mid-1800s and is now the country's most significant vertebrate pest [9]. It is a major ecological threat to New Zealand's indigenous biodiversity [10] and an economic threat as a vector for bovine tuberculosis [11]. Current control methods rely largely on poisons, for example sodium monofluoroacetate (compound 1080 [12]). However, the use of poisons is becoming increasingly unpopular for welfare reasons and for the impact of poisons on non-target species. In addition, the scale of the possum problem in New Zealand is so large that poisons alone have a limited effect on reducing the population of brushtail possums on a national level. Consequently, a number of novel biocontrol strategies are currently being investigated [13–15], including contraceptives and sterilants to

interfere with reproduction and lethal toxins that may be specific to possums or to marsupials in general.

There are no reliable methods of determining a population of brushtail possums, but it has been estimated that there may be as many as 70 million possums in New Zealand, spread across more than 90% of the land mass, including remote and inaccessible bushland. Consequently, the oral route of delivery (in the form of a bait) is the most prudent strategy to administer the biocontrol agent to this widespread, free-ranging, feral animal. For contraceptive and sterility agents at least, it is highly likely that the biocontrol agent will be in the form of a peptide or protein molecule. Therefore, appropriate formulation of the bioactive will be essential, due to the inherently low bioavailability of protein and peptide bioactives, especially if delivered via the oral route. Thus, oral delivery will be a major hurdle to overcome in the development of a new biological control strategy for this species, as it is in eutherians.

1.3. Developing oral delivery formulations for possums

Approaches used in the pharmaceutical industry to design efficacious drug delivery systems for humans and domestic animals can be applied to the design of delivery systems for biocontrol agents for use in wildlife management, including the brushtail possum. However, until very recently there has been little information on the function of the brushtail possum gastrointestinal (GI) tract or on the stability or absorption of drugs following oral delivery in this species. This review presents information on the function of the brushtail possum GI tract, on peptide and protein stability within the GI tract and permeability across the epithelial cell layer. Comparisons will also be made with each feature in humans.

2. Gastrointestinal tract physiology

2.1. Morphology

The organization of the GI tract of the common brushtail possum is in general, similar to that of other mammals including humans. However, due to differences in digestive strategies, the brushtail possum has some specialised adaptations. The morphology of the GI tract of the common brushtail possum was first described in detail by Lönnberg [16]. This animal is a hindgut fermenter and the morphology of its GI tract is an important adaptation to the nutritionally-poor diet of *Eucalyptus* leaves that the brushtail possum evolved to utilize in Australia [2,17]. In particular, the caecum and proximal colon (collectively referred to as the hindgut) represents a greater proportion of the GI tract in this species than it does in humans

¹ Eutherians are a sub-class of mammals that includes placental mammals (e.g. humans). Marsupials belong to the sub-class Metatheria. This classification is based on reproductive features.

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