Novel use of insect larvae as a substitute model for indomethacin-induced gastric damage

COMPARATIVE IMMUNOLOGY

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Introduction

There is a constant need to develop alternative *in vivo* models to vertebrates for both ethical and financial reasons. The larvae of the greater wax-moth, *Galleria mellonella,* is one potential alternative that boasts low maintenance costs, thermotolerance to 37°C, and high-throughput capacity. These larvae are used routinely as a 'surrogate' model for studying drug toxicity and microbial virulence [1, 2]. The incorporation of insect larvae in biomedicine is increasing in popularity, however, there remains a lack of knowledge regarding their use for studying gut pathobiology. Our aim was to assess the suitability of *G. mellonella* as a novel platform for characterising the gastrointestinal-side effects of biopharmaceuticals.

Methodology

We administered the non-steroidal anti-inflammatory drug, indomethacin [0 – 7.5 µg/larva] to *G. mellonella* via force-feeding and intrahaemocoelic injection (Fig. 1). The toxic side effects were assessed using midgut tissue histopathology and gastric permeability assays – in addition to monitoring survival, development, blood cell (haemocyte) numbers, and detoxification-associated enzyme activities [3].

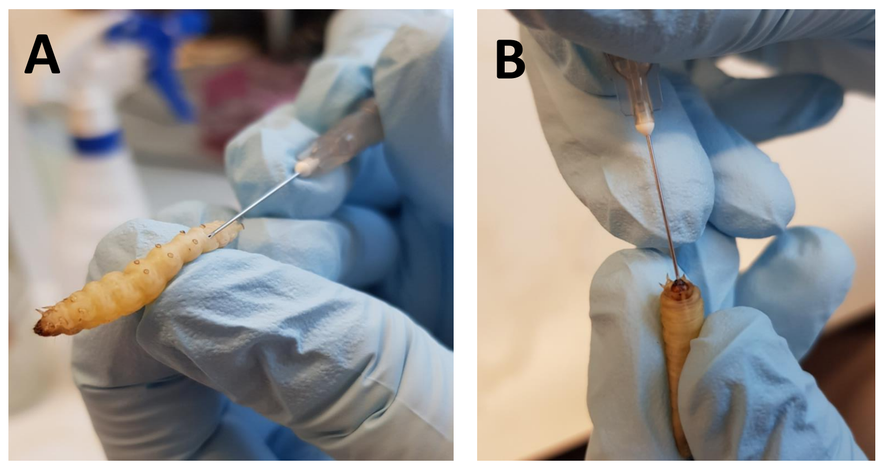

Figure 1. (A) Intrahaemocoelic injection and **(B)** force feeding insect larvae with indomethacin

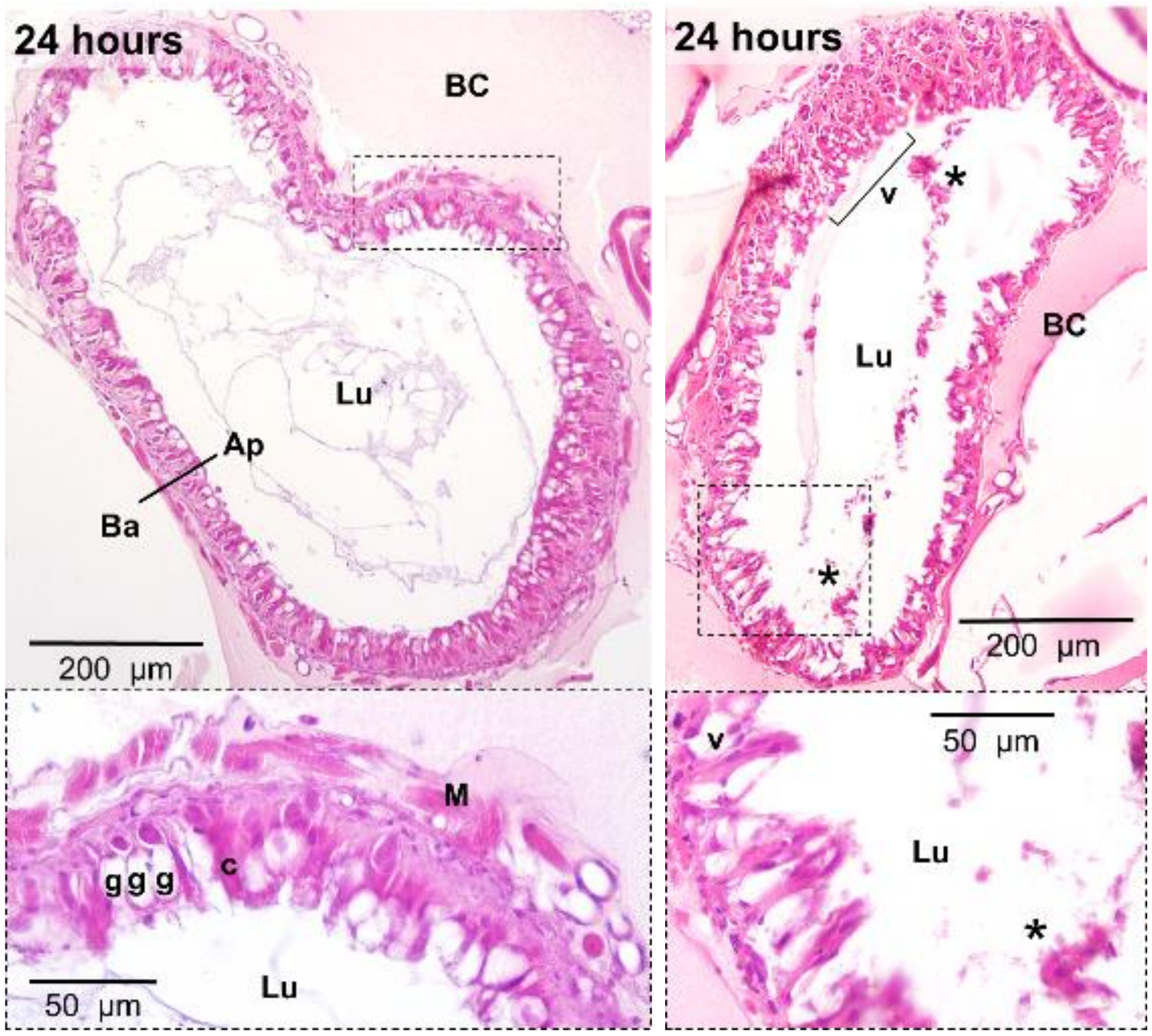

Figure 2. Histopathology of the midgut tissue from *G. mellonella* larvae. Transverse section of larvae mid gut 24 hours post treatment. Larvae force-fed PBS (left panel) show no obvious changes to the structure of goblet cells (g) or columnar cells (c) and no cellular debris in the lumen. Indomethacin-treated larvae (right panel) show tissue deterioration (v - vacuolisation) and displacement into the lumen (Lu).

Results/Discussion

In the absence of indomethacin, the larval midgut is a uniform arrangement of epithelial and goblet cells, with an intact layer of visceral muscle beneath the basement membrane (BM) (Fig. 2). These features are similar to rodent intestines [4]. When larvae were force-fed indomethacin, clear signs of damage such as cell death and blistering were visible. The deterioration of the midgut promoted gut leakiness (Fig. 3). There was a significant increase in the number of latex microspheres in the haemolymph of larvae co-inoculated with indomethacin when compared to those force-fed PBS only.

Indomethacin-induced 'leakiness' of the intestine is well characterised in humans and rodents [5], and herein, we find these symptoms in *G. mellonella* larvae also. Our novel data support the use of insect larvae as a putative model for gut pathobiology.

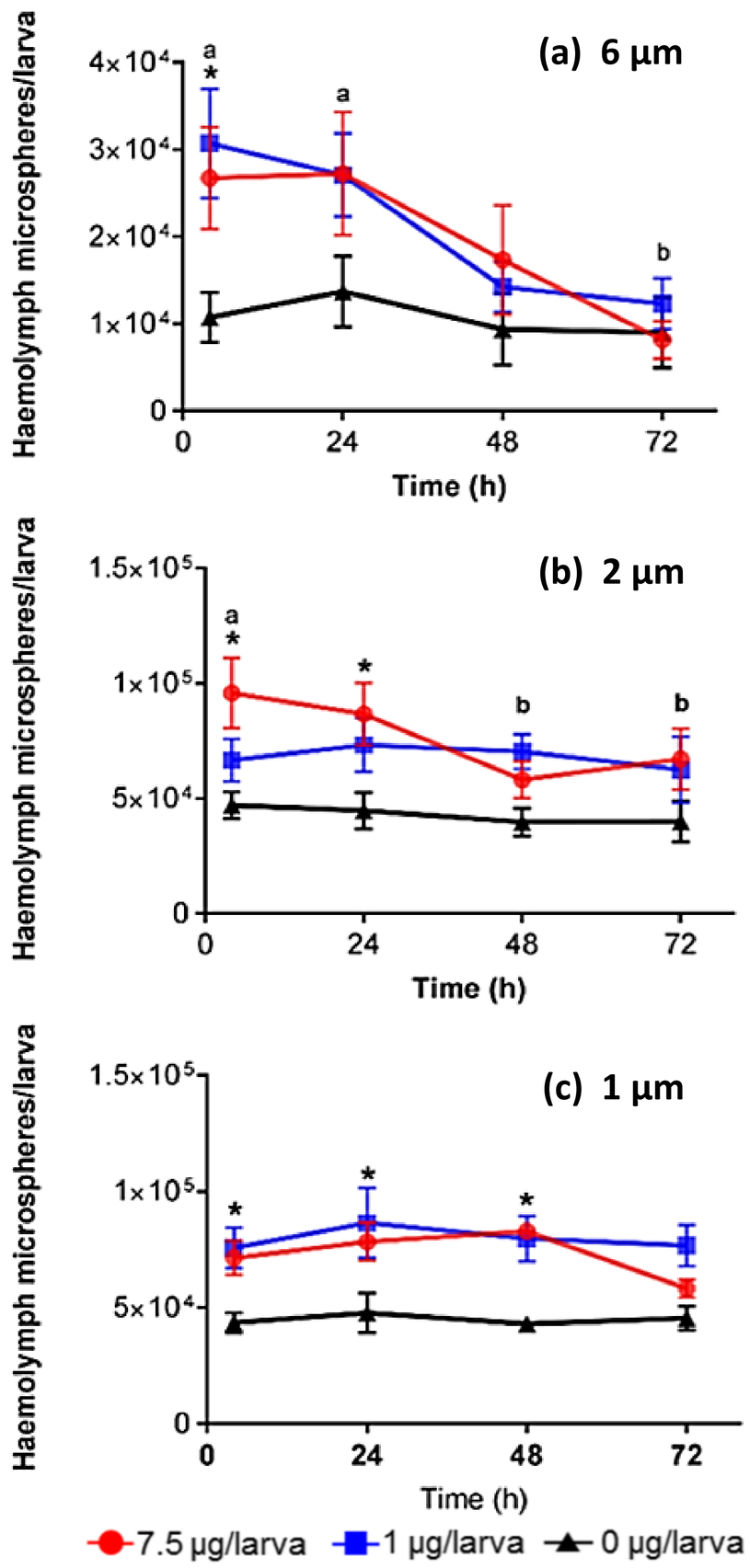

Figure 3. Gut permeability of *G. mellonella* larvae following force feeding of indomethacin. The number of 6 µm (a), 2 µm (b) and 1 µm (c) spheres that leaked into the haemolymph were counted. An asterisk (*) and unshared letters (x, y) represent significant differences ($P \leq 0.05$).

References

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Acknowledgements

H.E. is the recipient of a KESS2 PhD Scholarship. We would like to thank Profs Andrew Rowley and Richard Johnston (Swansea University) for collaborations.