Response to "Diffusion versus convection"

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Thank you for the comments on our recent paper (Jin et al., 2013) about convective effects that impair drug targeting to surface-exposed sites on intestinal crypts (see Lucas in this issue).

We acknowledge that the magnitude of basal secretion by intestinal crypts remains unclear, but point out that the evidence for cryptal secretion in secretory diarrheas, the subject of our model, is compelling. As Dr. Lucas points out, it has been proposed that basal secretion may have an antibacterial role in which bacteria are flushed out of the cryptal lumen by convection. Our model would not support such a conclusion, as bacterial diffusion would greatly dominate over convection at low basal secretion rates. We thank Dr. Lucas for pointing out an important implication of our model that we did not think about.

Dr. Lucas questioned the choice of certain model parameters and requested to see computations using different parameter values. With regard to the high fluid secretion rate in cholera, our values should be quite accurate, as they derive from experimental data and daily stool volumes. Figs. 3–5 in our paper (Jin et al., 2013) show the dependence of convective effects on fluid secretion rate.

With regard to linear viscosity in crypt fluid, the limited available data support an inhibitor diffusion coefficient ~10-fold less than that of water. The parameters for linear viscosity used in our paper were based on photobleaching measurements in rat colonic crypts (Thiagarajah et al., 2001) and are consistent with other studies on diffusion in intestinal mucus, as well as other data from our laboratory on diffusion in luminal airway mucus (Livingston et al., 1995; Flemström et al., 1999; Crater and Carrier, 2010; Derichs et al., 2011).

Model predictions, as expected, are quite sensitive to drug diffusion in cryptal fluid, as increased diffusion results in increased access of drug to the cryptal epithelial surface, which in turn reduces cryptal fluid secretion. Using parameters corresponding to fluid secretion in cholera in mid-jejunum, Fig. 1 shows attenuated convective effects with increasing inhibitor diffusion coefficient. However, based on the experimental evidence mentioned above, it is unlikely that the diffusion coefficient is much greater than 2×10^{-10} m^2/s in intestinal mucus, both because of the intrinsic viscous properties of mucus and the likelihood of drug binding to mucins, which would further reduce drug diffusion. It would be informative, though challenging, to make good measurements of viscosity in surface and cryptal mucus in the intestine in vivo.

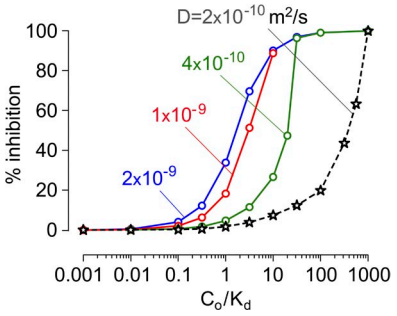

Figure 1. Influence of inhibitor diffusion coefficient on convective washout. Computations done for human mid-jejunal anatomy as in Fig. 3 A of our original paper (Jin et al., 2013), for J_v^o of 7×10^{-2} $\mu L/cm^2/s$. Percentage inhibition of net secreted fluid compared as a function of C_o/K_d for indicated values of inhibitor diffusion coefficient.

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