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Intestinal epithelial permeation enhancers: High content screening reveals sub-lethal cellular effects of sodium caprate

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Abstract

The medium chain fatty acid, sodium caprate (C_{10}), is a component of clinical trial solid dose formulations to facilitate intestinal epithelial permeation of peptides. There is debate over its mechanism of action and the relative contribution of paracellular and transcellular pathways at the high concentrations, well above its critical micellar concentration (~20 mM), that are required to enhance permeation *in vivo*. In addition, as a mild surfactant, there may be safety concerns arising from its reversible membrane perturbation effects following repeat administrations, although there is little evidence to date that it facilitates passage of bystander pathogens. At an *in vitro* level, we have re-examined its effects on Caco-2 monolayers grown on 96 well plates and filters using an InCell®-1000 High Content Analysis (HCA) system, based on sensitive quantitative fluorescent microscopy. We tested sub-lethal effects of C_{10} on multiple cell parameters using fluorophores incubated with live monolayers over time. On monolayers on filters exposed to C10 for 60 min, 1mM increased nuclear area, while 8.5 mM increased plasma membrane permeability (PMP), intracellular calcium, mitochondrial membrane potential, and nuclear intensity. 15 mM caused cell sloughing and decreased cell number. 8.5 mM was the threshold for increasing fluxes of mannitol and FITC-dextran 4000 across these monolayers. HCA data on Caco-2 monolayers grown on wells gave a similar pattern at slightly higher concentrations. In a comparison of C_8-C_{12}, increases in chain length hydrophobicity were associated with increased intracellular calcium and PMP, which predicted the capacity to increase fluxes across monolayers through membrane perturbation.

Biography

David Brayden is Associate Professor of Advanced Drug Delivery at University College Dublin (UCD), Ireland. He is also the Director of Science Foundation Ireland's '*Irish Drug Delivery Network*' research cluster (2007-2013). David is the author / co-author of over 150 publications covering his time as a senior scientist at Elan Corp (1991-2001) as well as at UCD. His lab specializes in oral peptide delivery technologies and bioassays and he consults for the biotech companies. He was made a Fellow of the Controlled Release Society in 2012.