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PERSPECTIVES

The epithelial glycine transporter GLYT1: protecting the gut from inflammation

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L-Glycine is a simple, non-essential amino acid that consists of a single carbon atom attached to an amino and a carboxyl group. While glycine is established as an inhibitory neurotransmitter in the central nervous system, ample evidence has been generated demonstrating that glycine has efficacy as an anti-inflammatory and cytoprotective agent. Administration of glycine is protective in experimental models of ischaemia–reperfusion injury, shock, transplantation, alcoholic hepatitis, hepatic fibrosis, arthritis, tumour and drug toxicity (Zhong *et al.* 2003). While the mechanism(s) responsible for the protective effects of glycine are unclear, they are likely to be multi-factorial involving direct effects on target cells, inhibition of glycine-gated chloride channels and/or inhibition of inflammatory cell activation. In the intestine, studies indicate protection by glycine from damage caused during mesenteric ischaemia is by inhibition of apoptosis (Jacob *et al.* 2003), while others have shown that glycine protection against intestinal IR injury is by a mechanism consistent with glycine uptake (Lee *et al.* 2002). Glycine is a substrate for a number of membrane transport systems in the intestine that may facilitate cellular uptake. One of these receptors, GLYT1, is localized predominantly at the basolateral membrane of enterocytes and functions primarily to import glycine into the cell, suggesting a role in meeting essential requirements of the enterocyte, rather than in nutrient absorption (Christie *et al.* 2001).

In this issue of *The Journal of Physiology*, Howard *et al.* (2010) used human intestinal epithelial cell lines to investigate the role of GLYT1 in the cytoprotective effect of glycine against oxidative stress. Exogenous glycine protected Caco-2 and HCT-8 cell lines against the oxidative agent tert-butylhydroperoxide and reduced the intracellular concentration of reactive oxygen species, when applied prior to but not concomitant with the oxidative stressor. Glycine given prior to oxidative challenge preserved intracellular glutathione levels without affecting the rate of glycine uptake. Protection was dependent on specific GLYT1 activity, supporting a requirement for intracellular glycine accumulation. Interestingly, the protective effect of glycine occurred in the absence of any change in gene transcription of GLYT1 or glutathione synthesizing enzymes, suggesting transcriptional regulation is not involved. The authors concluded that the protective effect of glycine was mediated, at least in part, by preservation of intracellular glutathione content. This contrasts with studies in kidney and liver where glycine cytoprotection appears to be independent of glutathione levels (Dickson *et al.* 1992; Weinberg, 1992). Furthermore, these observations differ from those of Katayama & Mine (2007) who demonstrated increased glutathione content and glutathione reductase activity in oxidatively stressed Caco-2 cells pre-treated with alanine but showed no cytoprotection, indicated by a reduction in IL-8 secretion, by glycine. In addition to different culture conditions between the two studies, the conflicting conclusions emphasize the importance of testing a variety of parameters of inflammation in a cell type specific manner.

Of direct relevance to the findings in this study, glycine has been shown to protect against intestinal injury in well-established chemical models of colitis induced by dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS) (Tsune *et al.* 2003). Both of these models involve epithelial irritation and damage prior to influencing activation of different immune cell populations. These authors noted that in studies using rat intestinal epithelial cells, glycine was unable to inhibit TNF-α induced chemokine expression, in contrast to effects on a macrophage cell line, thus suggesting that epithelial cells were not involved in the anti-inflammatory effects of glycine in these models. However, the study by Howard *et al.* raises the possibility that direct effects of glycine on intestinal epithelial cells could exert a specific impact on the overall inflammatory status of the intestine, by virtue of altering redox status, that is distinct from anti-inflammatory effects of glycine on different molecular targets in other mucosal cell populations, i.e. cytokine production by macrophages. Howard *et al.* identified that the anti-oxidant effect of glycine was dependent on accumulation of glycine within the cell prior to oxidative challenge. This mechanism may restrict the therapeutic as opposed to preventive efficacy of glycine with respect to epithelial involvement. Moreover, Tsune *et al.* (2003) identified that dietary glycine given 2 days after TNBS administration was also effective in reducing inflammation, thus indicating therapeutic as well as prophylactic benefit of glycine. While these observations do not necessarily exclude a role for epithelial specific effects in the therapeutic potential of glycine, particularly since the TNBS model features epithelial ulceration, they do suggest that the timing of glycine administration may play a critical role in modulating cytoprotective *vs.* anti-inflammatory effects.

The capacity of glycine to modulate multiple cell types further emphasizes the difficulty in dissecting the multiple modes of action of glycine in restricting inflammation and injury. However, given the efficacy of glycine administration in protecting against a number of intestinal inflammatory conditions, further studies to identify specific roles for glycine receptors on epithelial *vs.* immune cells would serve not only to increase our understanding of the mechanisms responsible for the anti-inflammatory and cytoprotective effects of glycine, but also to identify cell type specific signalling targets that might provide greater therapeutic specificity in treating intestinal inflammatory conditions.

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