SEW-2871 is Toxic to Renal Epithelial Cells at Therapeutic Doses

Paul Weisman, Jason Kirby, Lois Arend
Department of Pathology, University of Cincinnati

SEW-2871 is a specific agonist for the $S1P_1$ receptor, one of five G-protein coupled receptors whose endogenous ligand is sphingosine-1-phosphate (S1P), a potent, bioactive lysosphingolipid with both intracellular and extracellular effects. SEW-2871 is currently in pre-clinical trials for its ability to protect the kidney against acute ischemia/reperfusion (I/R) injury, presumably due to an indirect, immunosuppressive mechanism. Typical SEW-2871 dosages used in these trials range from 2 to 12μM. Using MDCK cells, which are canine renal epithelial cells, we found that SEW-2871 caused a dose-dependent cytotoxic effect when the cells were cultured in medium containing increasing concentrations of SEW-2871 (from 0.5 to 10μM). Moreover, using pertussis toxin as an inhibitor of the Gi protein coupled to this receptor, we found that this cytotoxic effect is likely not mediated by the $S1P_1$ receptor. We conclude that SEW-2871, when used at doses currently employed in pre-clinical trials to produce an immune-mediated protective effect in the kidney *in vivo*, is directly toxic to cells of the renal epithelium *in vitro* via a mechanism that does not include binding to the $S1P_1$ receptor. If this result can be reproduced *in vivo*, our findings may represent an important side effect of this drug that, to the best of our knowledge, has not been reported in the literature to date. The significance of our findings is underscored by the ability of the kidneys to concentrate the tubular fluid, exposing the cells of the renal epithelium to even higher solute concentrations than are found in the plasma and potentiating the toxic effects of the pharmacological agents found therein.