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Novel discoveries in the eicosanoids and other natural products

Abstract:

A simple chemical reaction carried out decades ago in the early stages of the prostaglandin field, that led to an unexpected result initiated my journey into an exciting and productive career in drug discovery that made use of my background in natural products organic chemistry. This result led to my discovery of a new product identified as 6-keto-prostaglandin F1a. A mechanism was proposed suggesting its formation through the first bicyclic intermediate in the prostaglandin field. This intermediate was later chemically synthesised by The Upjohn Co. and called prostacyclin by Vane's group who demonstrated it to be an important unstable highly potent mediator released from the vascular endothelium that inhibited the aggregation of platelets. My subsequent studies in collaboration in part with Yamamoto's group in Japan and Samuelsson's group in Stockholm identified another new pathway involving unstable metabolites of the 12-lipoxygenase pathway named Hepoxilins (HX), a family of C20 hydroxy epoxides which was subsequently shown to be formed by pancreatic islet cells (hence the coined name) and other cell types/tissues although the Hepoxilins were routinely detected as the stable inactive trihydroxy derivatives. To study the biological actions of the native HX, we synthesised their stabilized analogs (PBTs) to study them as prodrugs. The PBTs antagonised HX. The PBTs were shown to possess various biologically positive actions in vitro/in vivo on Calcium translocation on neutrophils, in cancer, on blood coagulation, in inflammation, on diabetes and in ophthalmology. A third research program was embarked in collaboration with J.A Al-Hassan in Kuwait involving lipid products released from catfish skin secretions from the Gulf region demonstrating in vitro actions on cancer, inflammation, and wound healing. (Supported by the MRC, OCRN, CIHR, KFAS). These latter studies supported and extended in vivo and in vitro observations by Al-Hassan's group on the skin secretions and their promising actions in man.

Biography

Cecil Robert Pace Asciak is Emeritus Senior Scientist at the SickKids Research Institute and Emeritus Professor in the Department of Pharmacology and Toxicology at University of Toronto. He is active in research, discovery and commercialization of novel biologically active compounds for development as therapeutics in cancer, inflammation, diabetes, wound healing and pain. He is also a senior member of the Translational Medicine program. He has been involved in lipid research throughout his career, discovering first the changes in prostaglandin synthesis and metabolism LOX derived hepoxilins, and their metabolites and their synthetic analogs.