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Vascular protective effects of selective PKCb inhibitor with Ruboxistaurin in Murine models

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Although a growing body of evidence from animal and human studies indicates beneficial effects of protein kinase C β (PKCβ) inhibition on microvascular parameters, our studies have examined the effects of PKCβ inhibitor, ruboxistaurin, on macrovascular disease in the experimental murine models of atherosclerosis, restenosis, myocardial ischemia, and lung ischemia. Wild type C57BL6 and apoE-/- male mice were maintained on normal rodent chow and then fed normal chow containing the PKCβ inhibitor, ruboxistaurin (LY333531) or vehicle chow without inhibitor. Mice were rendered diabetic (D) (defined as plasma glucose >250 mg/dl) by injection of streptozotocin (65μg/g weight) for five consecutive days at age 6 weeks. Our data provide the first evidence that key species and stresses implicated in vascular injury, such as modified lipoproteins, glucose and diacylglycerol (DAG), acute physical stress, hypoxia and ischemia/reperfusion transduce their key pathogenic effects, at least in part, via rapid and, in certain settings, chronic recruitment of PKCβ signaling pathway. This work raises the possibility that blockade of the PKCβ by a pharmacologic inhibitor, ruboxistaurin, may attenuate neointimal expansion or organ dysfunction and damage triggered by acute mechanical injury, chronic atherosclerosis, or ischemia-reperfusion stress. In addition, based on the bioavailability and tolerability of ruboxistaurin in diabetes and our findings in euglycemia and diabetic atherosclerosis, we speculate that blockade of PKCβ signaling pathway may hold promise as a therapeutic intervention in treating macrovascular disease involving the heart and large vessels in both diabetes and non-diabetes, although this remains to be proven in clinical trials.

Biography

Shi-Fang Yan, MD, has completed postdoctoral training from Physicians and Surgeons College of Columbia University. She is an Associate Professor at the Department of Medicine and Pharmacology, New York University School of Medicine. She has published more than 100 research/review articles in medical journals, including Nature Medicine, Journal of Clinical Investigation, PNAS, Circulation Research, FASEB, JBC, Atherosclerosis and etc. She was the Winners of the Council's 2000 Cournand and Comroe Young Investigator Award and a best poster award (2005) at the American Heart Association. She has been serving as an editorial board member, a grant reviewer at American Heart Association Cardiac Bio BCT 1 study section.