

## Effects of type 2 diabetes mellitus on microvascular function

Type 2 diabetes is associated with the development of microvascular dysfunction, but the underlying mechanisms has not yet been fully elucidated. This prompted us to investigate the alterations of the endothelium- and smooth muscle-dependent vasomotor function of the microvessels in animal models of type 2 diabetes. We also set out to characterize the direct vascular effects of OR-1896, a drug that can be beneficial in restoring microvascular function in type 2 diabetes. The key, novel findings of our studies are the followings: 1.) In high fat diet-induced type 2 diabetes mellitus nitric oxide-mediation of endothelium-dependent dilation of rat skeletal muscle arterioles is reduced due to an enhanced xanthine oxidase-derived superoxide anion production. 2.) In a genetic model of type 2 diabetes (db/db mice) arteriolar production of  $H_2O_2$  is enhanced, which leads to increased synthesis of the cyclooxygenase-2 derived constrictor prostaglandins tromboxane  $A_2$ /prostaglandin  $H_2$  in the smooth muscle cells, which in turn enhances basal arteriolar tone. 3.) OR-1896 elicits a substantial vasodilation in skeletal muscle arterioles of the rat by activating primarily  $K_{ATP}$  and  $K_V$  channels.

In summary, our present data suggest that vascular oxidative stress plays a key role in the pathogenesis of arteriolar vasomotor dysfunction and consequently enhanced peripheral resistance in the early and advanced stage of type 2 diabetes. We propose that agents activating potassium channels on microvessels, such as OR-1896 can be useful in the therapy of diabetes by improving microvascular function, decreasing peripheral resistance and arterial blood pressure.