Effects of sunitinib perfusion on vascular function in the rat mesenteric arteries.

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Background: Sunitinib, the multikinase inhibitors (MKIs) is used extensively for treatment of human tumors. It has become a clinical problem with sunitinib-induced hypertension, which is one of most common adverse effects related to MKI treatment. Our previous study have investigated that acute treatment of sunitinib perfusion in the rat mesenteric arteries significantly promoted both vasoconstrictor and vasodilator responses to periarterial nerve stimulation (PNS) and vasoactive agents. However, the detailed mechanisms have been unknown. The aim of this study is to demonstrate the mechanism of increased vascular function caused by sunitinib.

Methods: The mesenteric vascular beds were isolated from pentobarbital-anesthetized rats and perfused with Krebs solution at a constant flow rate of 5 ml/min with a peristaltic pump. Changes in perfusion pressure were measured with a pressure transducer.

Results: In rat mesenteric vascular beds treated with sodium deoxycholate (SD) to remove vascular endothelial cells with active tone, acetylcholine (ACh)-induced vasodilation was markedly inhibited. PNS (1 to 4 Hz) and sodium nitroprusside (SNP) increased adrenergic nerve-mediated vasoconstriction and vasodilation respectively, compared with that of control group. Sunitinib (1 nM) perfusion decreased PNS-induced vasoconstriction, which is inhibited by ruthenium red (1 uM), the transient receptor potential channel Vanilloid 1 (TRPV1) channel blocker, or capsaicin (1 uM) treatment. However, ACh, CGRP, SNP and PNS-induced calcitonin gene-related peptide (CGRP) ergic vasodilations had no change, compare with that of SD-treated group.

Conclusion: These results suggest that sunitinib has facilitatory action on CGRPergic nerve mediated by TRPV1.