Nonlinear relationship between hyperpolarisation and relaxation enables long distance propagation of vasodilation *in vivo*

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Spread of vasodilation from arterioles to feed arteries enables large increases in blood flow due to the rapid spread of hyperpolarization along the vessels. However, dilations encompass larger distances than can be explained by passive spread. We hypothesized that the unattenuated spread of vasodilation results from a nonlinear relationship between hyperpolarisation and relaxation. Membrane potential and diameter were recorded simultaneously after blockade of nitric oxide synthase and cyclooxygenase in the cremaster microcirculation in vivo. Superfusion of acetylcholine (1μM, 10μM), evoked concentration-dependent hyperpolarisation (−11±1mV, −23±2mV, from −28±1mV) but maximal relaxation (90±2%, 96±2%, n=7). Inhibition of voltage-dependent calcium channels with nifedipine (1μM) also evoked maximal relaxation (97±2%) with submaximal hyperpolarisation (−10±2mV, n=6). Hyperpolarisation beyond −38mV was always accompanied by maximal relaxation. Conduction of dilation was studied following ionophoresis of acetylcholine. Locally induced hyperpolarisations (−17.5±4mV) decayed with distance (1500μm: −7±1mV) while dilation remained intact (105±16% of local response, n=7). Selective destruction of the endothelium (light dye treatment) prevented conduction of dilation without impairment of the local response. Using a computational model of the vessel wall, we could correctly predict the spread of vasodilation by applying a voltage threshold for maximal relaxation. We conclude that long distance spread of local dilations is facilitated by spread of supramaximal hyperpolarisations through the endothelium, due to a saturating relationship between hyperpolarisation and dilation that minimizes the impact of electrotonic decay. Our data suggest that changes to vasodilatory control will result rapidly from functional deficits in potassium channels or shifts in the voltage sensitivity of calcium channels.