Functional remodeling in response to prolonged agonist exposure or elevated pressure delays arteriolar relaxation

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While arteriolar contraction is dependent on Ca^{2+}- induced myosin phosphorylation, other mechanisms including Ca^{2+} sensitisation and time-dependent phenomena such as cytoskeletal and cellular reorganisation may contribute to contractile events. We have hypothesised that if arteriolar smooth muscle exhibits time-dependent behavior that this may be manifested in differences in relaxation following short and long-term exposure to contractile agonists. Consistent with this, isolated skeletal muscle arterioles showed a significantly delayed return to pre-agonist exposure diameter following washout of noradrenaline (5μM) which had been applied for 4 hours as compared to 5 minutes. A similar phenomenon was not observed when contraction was induced by KCl (75 mM) suggesting a possible requirement for receptor activation. As removal of extracellular Ca^{2+} caused a rapid return to passive diameter, the delayed relaxation following 4 h norepinephrine exposure was viewed as being functional in character. The enhanced constrictor response following prolonged norepinephrine exposure was prevented by several tyrosine kinase inhibitors (genistein, PP1 and PD9859; Hill *et al.*, 2003). Arterioles were cannulated onto glass micropipettes and studied *in vitro* using video microscopy, following dissection (4°C) from the cremaster muscle, sampled from anaesthetised rats. Further studies presented here showed that the impaired relaxation is not inhibited in the presence of the Rho kinase inhibitor Y27632. This observation suggests the mechanism is not due to Rho kinase-induced Ca^{2+} sensitisation events contributing to an enhanced constrictor response, while the former implicates events involving a cSrc/p42/44 MAP kinase pathway. In these spontaneously myogenic arterioles, the constrictor stimulus of elevated intraluminal pressure, from 50 to 120 mmHg for 4 hours also results in delayed myogenic vasodilation when the luminal pressure is returned to 50 mmHg. Confocal microscopy studies (using a fluorescein dye exclusion imaging method) aimed at examining smooth muscle cell position within the intact vessel wall suggested that cellular realignment occurs during the 4 hour agonist exposure, consistent with the proposition that early remodelling events are occurring during this 4 hour time course. In particular, an increase in the extent of overlap between neighbouring vascular smooth muscle cells was observed after the prolonged agonist exposure period. Collectively, these data are consistent with the action of prolonged constrictor stimuli, either noradrenaline exposure or elevated luminal pressure, resulting in an early functional remodelling process that involves tyrosine kinase-dependent processes and results in impaired relaxation on removal of the stimulus.

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