Hyperpolarising effect of perivascular adipose tissue in rat mesenteric artery myocytes: stimulation by \( \beta_3 \) adrenoceptor activation

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Rat mesenteric arteries are surrounded by white perivascular adipose tissue (PVAT) which, in most in vitro pharmacological investigations, is removed to improve drug access to the artery and to prevent complications due to drug absorption by lipids within the adipocytes. However, recent studies have demonstrated that PVAT has a vasorelaxant effect which has been ascribed partially to endothelium-dependent nitric oxide release with subsequent \( K^+ \) channel opening (Gao et al., 2007). Greenstein et al. (2009) proposed that the ‘factor’ was likely to be adiponectin which activates endothelial nitric oxide synthase and stimulates the release of nitric oxide. Thus, the aim of the present paper was to investigate whether PVAT \textit{per se} and/or adiponectin do indeed hyperpolarise the myocytes and, if so, to identify the underlying mechanisms involved.

Using sharp micro-electrodes, myocyte membrane potential was recorded in myocytes in third-order mesenteric artery branches (approx. 250 \( \mu \)m diameter) dissected from male Wistar rats (approx. 280-320g) previously killed by stunning and cervical dislocation (Schedule 1; UK Animals (Scientific Procedures) Act, 1986).

In the absence of the endothelium, 10 \( \mu \)M CL-316,243, a \( \beta_3 \) adrenoceptor agonist, produced a PVAT-dependent hyperpolarisation of 11.2 ± 1.1 mV, \( n=4 \). Iberiotoxin (100nM) abolished the response, suggesting that the hyperpolarisation had resulted solely from the opening of large-conductance \( Ca^{2+} \)-sensitive \( K^+ \) channels (BK\( _{Ca} \)). One downstream pathway of a ubiquitously-expressed adiponectin receptor (AdipoR1) involves activation of the AMP-activated kinase (AMPK; Yamauchi et al., 2007). Both adiponectin (5 \( \mu \)g/ml) and the AMPK activator A769662 (5 \( \mu \)M) hyperpolarised the vascular myocytes in the absence of PVAT or endothelium (by 10.8 ± 0.5 mV, \( n=4 \), and 9.2 ± 0.6 mV, \( n=4 \), respectively). Hyperpolarisations to adiponectin, A769662 and CL-316,243 were each inhibited to a similar extent (approximately 70\%) by the AMPK inhibitor dorsomorphin (1\( \mu \)M) and essentially abolished by clotrimazole (30\( \mu \)M). In contrast, the hyperpolarisation induced by the BK\( _{Ca} \) opener NS1619 (33 \( \mu \)M; 15.1 ± 0.5 mV, \( n=4 \)), which was abolished by 100 nM iberiotoxin, was not affected by either clotrimazole or dorsomorphin.

In healthy rats, we conclude that stimulation of adipocyte \( \beta_3 \) adrenoceptors releases a factor which acts indirectly to activate myocyte BK\( _{Ca} \) channels. We speculate that the factor is adiponectin (which interacts with myocyte adipoR1 receptors to activate AMPK). Further investigations are in progress to determine whether AMPK activates a plasmalemmal channel to allow \( Ca^{2+} \) entry and thus provoke BK\( _{Ca} \) opening. Adipocyte-dependent myocyte hyperpolarisation is likely to be physiologically important in the modulation of arterial blood pressure and its modification in obesity (in which serum concentrations of adiponectin are reduced; see Chiarugi & Fiaschi, 2010) may be a contributory factor in obesity-induced hypertension.


