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Effects of perivascular adipose tissue on sympathetic and sensory perivascular neurotransmission in rat mesenteric arteries

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Introduction: Perivascular adipose tissue (PVAT) can release several vasoactive compounds including adipokines, cytokines, angiotensin II and reactive oxygen species(Szasz and Webb, 2012). It is established that these substances can cause either vasoconstriction or vasodilatation by acting on targets located on either smooth muscle cells or endothelial cells. However, little is known about whether PVAT-derived substances can influence neuronal responses in blood vessels.

Objective: The present study was conducted to investigate the effects of PVAT on sympathetic and sensory perivascular neurotransmission.

Methodology: Male Wistar rats (220-250g, n≥4) were killed by stunning and exsanguination and mesenteric arterial beds (with and without PVAT, removed by careful dissection) were perfused at a constant flow rate of 5 ml min^{-1} with Krebs' solution and stimulated by electrical field stimulation (EFS) in the absence/presence of pharmacological agents. EFS (4-32Hz, 1 ms, 90V, 30s) was applied to examine neurogenic vasoconstrictor responses, while EFS (0.5-12Hz, 0.1ms, 60V, 30s) in the presence of guanethidine and methoxamine (to block sympathetic neurotransmission and pre-constrict the preparations respectively) was applied to study neurogenic vasodilator responses. Effects of PVAT on contractility of mesenteric arteries was also determined using various agonists/antagonists added either into the perfusate (steady-state concentrations) or as bolus injections (50µl) (doses). Vasoconstrictor and vasodilator responses of the preparations were measured as increases and decreases in perfusion pressure (mmHg). All data were analysed by two-way ANOVA with Bonferroni post test. $P<0.05$ was considered significant.

Results: EFS elicited frequency-dependent vasoconstriction of the mesenteric beds. These responses were abolished by guanethidine (5µM), a sympathetic nerve blocker, indicating an involvement of sympathetic nerves. In the absence of PVAT, neurogenic contractile responses were attenuated ($P<0.0001$). There was no significant difference in concentration-dependent contractions to methoxamine (0.1µM-30µM), an α1-adrenoceptor agonist, in preparations with (E_{max} = 178 ± 14 mmHg, pEC_{50} = 5.5 ± 0.13 µM) and without (E_{max} = 172 ± 18 mmHg, pEC_{50} = 5.5 ± 0.17) PVAT. Tyramine (0.1µM-0.3mM), an indirect sympathomimetic agent, produced small concentration-dependent contractions which were not different between preparations with and without PVAT. EFS in the presence of guanethidine and methoxamine, elicited frequency-dependent vasodilatation due to stimulation of sensory nerves. Neurogenic vasodilatation was attenuated in preparations with PVAT removed ($P<0.0001$). In contrast, concentration-dependent vasodilator responses to capsaicin (0.1nM-10nM), an agonist at vanilloid receptor subtype 1 (TRPV1) were not reduced in preparations with PVAT removed. In separate experiments in which capsaicin was applied as bolus doses (1.5x10-12-5x10-9 moles), vasodilator responses to capsaicin were also

comparable between PVAT-intact and PVAT-removed preparations.

Conclusion: The presence of PVAT modulated responses to activation of both sympathetic and sensory nerves. The mechanisms underlying these effects are under investigation.

Szasz T and Webb RC (2012). Clinical science 122:1-12.