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Investigation of Directly and Indirectly Mediated Cardiovascular Actions of Stimulants

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The stimulants cathine and cathinone (from Khat leaves) and methylhexanamine (MeHex) produce adrenoceptor mediated tachycardia and vasopressor actions that are probably the result of direct receptor stimulation and displacement of noradrenaline from nerve terminals. Given the widespread use of these agents, and the resultant adverse effects, we wished to establish the importance of indirect actions in the overall cardiovascular effects of these agents in vivo.
Male Wistar rat were anaesthetized with pentobarbitone (60mg/kg, i.p.). Studies were approved by the HPRA and by the RCSI Research Ethics Committee. Some rats were sympathectomised with 6-hydroxydopamine (40mg/kg i.p., day 1 & 4, used on day 5 or 6). Dose-response curves were obtained to test drugs given i.v.. Data is presented as mean±S.E.M., (n animals), and analysis was performed using ANOVA and Dunnett's test.
In anaesthetised rats, cathine, cathinone, MeHex and tyramine (all 0.001-1mg/kg) produced marked tachycardia, and cathine, MeHex and tyramine produced marked pressor responses. In sympathectomised rats, the tachycardia to all agents was markedly attenuated. Blood pressure effects of cathine, MeHex and tyramine were also markedly attenuated by sympathectomy.
The results demonstrate that chemical sympathectomy greatly reduces responses to all agents investigated, demonstrating that all act as indirect sympathomimetics.

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Deletion of SIRT1 in perivascular adipose tissue accelerates obesity-induced endothelial dysfunction

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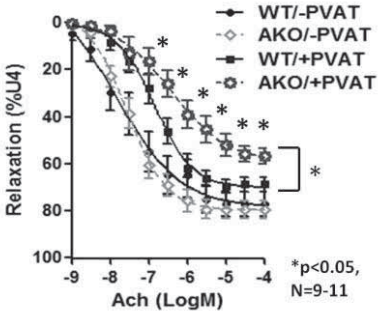

Introduction. Perivascular adipose tissue (PVAT) exhibits brown adipose features and its dysfunction is implicated in cardiovascular diseases. SIRT1 is key to adipocyte phenotypes and metabolism.
Aims. In the present study, we aim to investigate the role of SIRT1 within PVAT in modulating obesity-evoked endothelial dysfunction.
Methods. Wild type (WT) and adipocyte-specific SIRT1 knockout mice (AKO) were fed with standard chow or westernized diet for 12 weeks. Endothelium-dependent relaxation (EDR) in aortic rings with or without PVAT was assessed by wire myograph. DHE staining was used to measure superoxide.
Results. In the presence of PVAT, the EDR was significantly impaired in aorta from obese mice, and such an impairment was further exacerbated in obese AKO mice. In accompany, AKO mice exhibited exacerbated atherosclerosis in apoE-/- background. PVAT in lean WT mice displayed a brown phenotype, whereas SIRT1 deficiency augmented obesity-induced brown-to-white transition. In WT mice, chronic cold exposure (4ºC for 1 week) reversed obesity-induced attenuation of brown phenotypes, thereby leading to improved vascular reactivity by reducing superoxide and increasing adiponectin. However, all these beneficial effects of chronic cold exposure were abrogated in AKO mice..
Discussion. The brown phenotype of PVAT is associated with increased endothelial functions. SIRT1 plays a pivotal role in controlling PVAT browning, which in turn causes decreased superoxide production and increased adiponectin to protect vascular injury.