Diet-induced obesity alters sympathetic neurotransmission in rat small mesenteric arteries

R.E. Haddock and C.E. Hill, Neuroscience Program, John Curtin School of Medical Research, ACT 0200, Australia.

In pressurized rat small mesenteric arteries, ATP released from sympathetic nerves, activating smooth muscle purinoceptors, constitutes the major mechanism underlying neurally-evoked vasoconstriction. However, during obesity, increased contractility has been linked to adrenergic hyperactivity, while the role of purinergic signalling in diet-induced obesity remains unexplored. In the present study, adult male Sprague-Dawley rats were fed either normal or high fat diet and small mesenteric arteries (341±10μm diameter, n=33) were isolated and pressurized (80 mmHg). Sympathetic nerves were activated with electrical field stimulation (1-10Hz), while intracellular recordings were made with sharp microelectrodes (120-185 MΩ), filled with fluoroscein to identify impaled cells, and simultaneous changes in vessel diameter monitored (DIAMTRAK). While resting membrane potential did not vary between groups (control: −41.7±0.6mV; obese: −40.2±1.3mV, n=33), ATP-mediated excitatory junction potentials (EJPs) were increased in amplitude in obese arteries (13.0±3.5mV; control: 8.2±0.5mV, n=4, $P<0.05$), with decrease in rise time (28.5±1.4ms; control: 66.5±2.5ms, n=4, $P<0.05$) and rate of decay (28.5±1.4ms; control: 66.5±2.5ms, n=4, $P<0.05$). Repetitive nerve stimulation (1 Hz, 30s) caused significantly greater vasoconstriction (obese: 4.3±1.3%D/Dmax; control: 1.7±1.9%D/Dmax) and larger EJPs in obese arteries (9.5±1.0mV; control: 7.2±0.8mV; n=6, $P<0.05$). Desensitisation with α,β-methylene ATP (0.1μM) abolished EJPs and vasoconstriction in both arteries ($P<0.05$). Increasing stimulation frequency (3, 5, 10Hz) increased constriction amplitude; the effects being greater in obese arteries (n=6, $P<0.05$). Intracellular recordings revealed EJPs superimposed on a slow depolarization. We conclude that sympathetic nerve-mediated vasoconstriction is augmented during diet induced obesity and that ATP plays a significant role. Data suggest that this occurs due to increased neurotransmitter release, perhaps accompanied by postsynaptic receptor alterations. Investigation of the underlying mechanisms may help to reduce and control obesity related cardiovascular disease.