Do K^+ channels play a role in noradrenergic signalling in vascular smooth muscle?

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The mechanisms underlying depolarization of arterial smooth muscle by nerve-released noradrenaline (NA) remain largely unknown. In isolated vascular smooth muscle cells, applied NA produces an inward current by activating Ca^{2+}-activated Cl^- channels (Hogg *et al.*, 1994) and transient receptor potential (TRP)-like cation ion channels (Albert & Large, 2006). In rat iridial arterioles (Gould and Hill, 1996) and guinea-pig mesenteric veins (Van Helden, 1988), nerve-released NA produces a transient depolarization that is mediated by Ca^{2+}-activated Cl^- channels. However, there is no evidence that TRP-like cation channels contribute to nerve-evoked depolarization. In rat tail artery and guinea-pig mesenteric vein, nerve-released NA produces a slow phase of depolarization that is associated with a decrease in membrane conductance, indicating closure of K^+ channels (Cassell *et al.*, 1988; Van Helden, 1988). During ongoing nerve activity, this slow synaptic potential produces 15-20 mV of depolarization and contributes to constriction of the tail artery (Brock *et al.*, 1997). We have been investigating the mechanisms that underlie this depolarization.

Tail arteries were isolated from rats that had exsanguinated under deep anaesthesia (80 mg/kg pentobarbitone, i.p.). Artery segments were mounted in a recording chamber and the perivascular axons were electrically stimulated. Intracellular recordings were made from the smooth muscle cells. In rat tail artery, short trains of stimuli evoke both ATP-mediated excitatory junction potentials (EJPs) and a slow NA-mediated depolarization (NAD). Application of the α_1-antagonist prazosin (0.1 μM) slowed the rising phase of the NAD but did not change its amplitude. In contrast, the α_2-antagonist rauwolscine (1 μM) did not change the onset of the NAD but it did reduce its amplitude. In the presence of prazosin, the NAD was completely blocked by the K_{ATP} channel blockers, glybenclamide (10 μM, n = 6) and PNU 37883A (5 μM, n = 6). These agents also produced membrane depolarization. The α_2-adrenoceptor-mediated component of the NAD is produced by closure of K_{ATP} channels.

The NAD remaining when α_2-adrenoceptors were blocked with rauwolscine (1 μM) was increased in amplitude by glybenclamide (10 μM, n = 5). In rat tail artery, the time constant of decay of the EJP (τEJP) is determined by the membrane time constant (Cassell *et al.*, 1988). The τEJP of EJPs evoked at the peak of the rauwolscine-resistant NAD was prolonged (relative change 1.16, $p < 0.01$, n = 6). Similarly, the τEJP was prolonged during depolarization induced by the α_1-agonist, phenylephrine (0.5-1 μM, n = 5). These findings indicate a decrease in membrane conductance, suggesting that α_1-adrenoceptor-mediated depolarization is also produced by closure of K^+ channels. The rauwolscine-resistant NAD was unaffected by the Cl^- channel blockers, 9-anthracene carboxylic acid (100 μM, n = 5) and niflumic acid (10 μM, n = 5) or by the non-selective cation channel blocker, SKF 96365 (10 μM, n = 4).

Broad-spectrum K^+ channel blockers (tetraethylammonium, 4-aminopyridine, Ba^{2+}) did not inhibit the rauwolscine-resistant NAD. In CNS neurones, NA produces depolarization by closing the two-pore domain K^+ channel, TASK-1, but the selective blocker of these channels, anandamide (10 μM, n = 5), did not change the NAD. In heart, NA closes a Na^+-dependent K^+ channel that is blocked by quinidine. Quinidine (10 μM, n = 5) produced depolarization, slowed the τEJP and reduced the NAD. However, quinidine is reported to be an α_1-adrenoceptor antagonist.

These findings indicate that the NAD has two components: one of which is due to activation of α_1-adrenoceptors and the other to activation of α_2-adrenoceptors. The α_2-adrenoceptor-mediated component is produced by closure of K_{ATP} channels whereas α_1-adrenoceptor-mediated component is most likely mediated by closure of another type of K^+ channel.

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