The L-type Ca^{2+} channel agonist BayK8644 selectively augments the α_{1A}-adrenceptor-mediated component of nerve-evoked contraction in rat tail artery

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Modified neural control of cutaneous blood flow following spinal cord injury (SCI) results in poor thermoregulation and may contribute to the increased risk of pressure sores and impair wound healing (Mathias & Frankel, 1999). While SCI severs bulbospinal inputs to sympathetic preganglionic neurons, the spinal reflex pathways caudal to the lesion remain intact and are unopposed by inhibitory inputs from the brainstem. As a result somato-sympathetic reflexes produce pronounced decreases in skin blood flow below the level of the injury. Studies in patients suggest that this hyperreflexia is in large part due to an increased responsiveness of cutaneous arterial vessels to neural activation (Wallin & Stjernberg, 1984). This augmentation of neurovascular transmission has been confirmed in the tail artery of SCI rats (Yeoh, McLachlan & Brock, 2004), a thermoregulatory vessel that supplies blood to tail skin. In recent studies we have demonstrated that this effect of SCI on neurovascular transmission is mediated by a selective increase in the contribution of L-type Ca^{2+} channels to activation of the vascular muscle and that it is mimicked by application of the L-type Ca^{2+} channel agonist BayK8644 (Al Dera *et al.,* 2011).

Here we have investigated the postjunctional mechanisms that underlie the BayK8644-induced increase in neurovascular transmission. Tail arteries were dissected from male Sprague Dawley rats that had been deeply anaesthetized with isoflurane and killed by exsanguination. Artery segments were mounted in wire myographs for assessment of contractions evoked by electrical activation of the perivascular sympathetic axons or by contractile agents. Both in the absence and in the presence of BayK8644 (0.1 μM) nerve-evoked contractions were unaffected by the P2X1-purinoceptor antagonist NF449 (10 μM, n = 4; $P > 0.4$). At this concentration NF449 abolished contractions to the P2X-purinoceptor agonist α,β-methylene-ATP (1 μM). In the absence of BayK8644, blockade of α_2-adrenoceptors with idazoxan (0.1 μM, n = 8) reduced contractions to 100 stimuli at 1 Hz by ~50%, whereas in the presence of BayK8644 the blockade produced by idazoxan was greatly reduced. In contrast, blockade of α_1-adrenoceptors with prazosin (10 nM, n = 6) reduced the contractions to 100 stimuli at 1 Hz by ≥ 85% both in the absence and in the presence of BayK8644. Taken together these findings suggest that BayK8644 selectively augments the α_1-adrenoceptor-mediated component of nerve-evoked contraction.

In rat tail artery, concentration-contraction curves for the α_1-adrenoceptor agonist phenylephrine were shifted to the right both by the α_{1A}-adrenoceptor antagonist RS100329 (0.1 μM, n = 6) and by the α_{1D}-adrenoceptor antagonist BMY7378 (0.1 μM, n = 6), but the magnitude of this effect was much greater for RS100329. Similarly, RS100329 produced a greater blockade (~90%, n = 6) of contractions to 25 stimuli at 1 Hz than did BMY7378 (~50%, n = 6). These findings suggest that α_{1A}-adrenoceptors are the predominant subtype of α_1-adrenceptor in the rat tail artery but that α_{1D}-adrenoceptors also contribute to activation of this vessel.

BayK8644 (0.1 μM) produced a leftward shift in the phenylephrine concentration-contraction curve and this effect was abolished in the presence of RS100329 (n = 6) and was reduced in the presence of BMY7378 (n = 6). However, the facilitatory effect of BayK8644 on nerve-evoked contractions was markedly reduced in the presence of RS100329 (n = 6) but was not significantly changed in the presence of BMY7378 (n = 6). These latter findings suggest that BayK8644 selectively increases the α_{1A}-adrenoceptor-mediated component of nerve-evoked contraction.

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