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The modulation of vascular smooth muscle BK channel activity by nitric oxide

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Vascular smooth muscle cells (VSMCs) are responsible for tuning the vessel diameter and therefore possess an exceptionally important physiological role in the regulation of vascular resistance, and consequently blood flow as well as blood pressure. This resistance is greatly influenced by the large conductance calcium-activated potassium channel (BK channel), which is a potassium channel that is present in VSMCs and regulates their membrane potential. The channel is activated by membrane depolarization and by an increase of the intracellular calcium concentration. In addition, nitric oxide (NO) is one of the functionally most powerful regulators of BK channel activity and is thought to stimulate the BK channel via the activation of soluble guanylate cyclase (sGC), which generates cyclic guanosine monophosphate (cGMP), which in turn activates the cGMP-dependent protein kinase (PKG). However, there is also some evidence that suggests that NO can deactivate the BK channel. Because only very few studies have addressed the latter mechanism, the contribution of this pathway to vessel contractility is unknown. Considering the physiological importance of the interaction between NO and the BK channel, this is a significant gap in our understanding. Thus, the goal of this study was to investigate whether NO activates or deactivates the BK channel, and to what extent this depends on the contractile state of the vessel.

The effects of NO-donors on saphenous as well as caudal arteries of the rat were observed using isometric wire myography and Fura-2 calcium-fluorimetry. Isometric wire myography is a technique in which the force of isometric contractions of the smooth muscle of isolated artery ring segments is measured while applying different substances to the vessel under investigation. Fura-2 calcium-fluorimetry uses a calcium binding fluorescent dye to detect intracellular calcium ions and then – using the changes in the fluorescence – to assess changes in intracellular calcium concentration. To investigate the effects of NO on the BK channel, the selective BK channel blocker iberiotoxin (IbTX), different NO-donors, as well as substances that inhibit different steps of the NO/sGC/PKG pathway were used. The blood vessels were constricted with the α_1-agonist methoxamine (MX) from full relaxation to maximal contraction. This is a new approach in investigating and analyzing the effects of NO on the BK channel. It simulates the continuous exposition of blood vessels to NO with a following acute action of a constrictor stimulus, which is a prevalent physiological scenario.

The experiments showed that NO deactivates the BK channel in VSMCs when the blood vessel is in a contractile state where BK channels are active. This seems to be mediated via an inhibition of the MX-induced influx of extracellular calcium, but not of the calcium release from intracellular stores. When the blood vessel is in a contractile state where BK channels are only marginally active, NO activates the BK channel. These two effects both seem to be mediated by the sGC/PKG pathway, leading to the conclusion that the pathway branches up into a BK channel-deactivating arm prevailing at lower levels of contractility, and into a BK channel-activating arm prevailing at higher levels of contractility.

These findings provide new insight into the physiological role of the vascular smooth muscle BK channel in the context of modulation thereof by NO and the pathways involved. However, further research needs to be conducted in order to explore the details of the specific pathway responsible for the inhibition of extracellular calcium influx.