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Endothelium is involved in the vasorelaxation by an ATP-sensitive K^+ channel opener, NIP-121

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Abstract

Possible involvement of endothelium was examined in the vasorelaxation of rat aorta in response to NIP-121 ((+)-7,8-dihydro-6,6-dimethyl-7-hyroxy-8-(2-oxo-1-piperidinyl)-6*H*-pyrano[2,3-*f*]benz-2,1,3-oxadiazole), an ATP-sensitive K^+ (K_{ATP}) channel opener. The NIP-121-induced vasorelaxation was greater in endothelium-intact preparations than in endothelium-denuded ones. In the presence of glibenclamide, which inhibits K_{ATP} channels, NIP-121-induced vasorelaxations were of a similar extent in both endothelium-intact and -denuded preparations. These findings suggest that the presence of endothelium plays a role in the vasorelaxation in response to K_{ATP} channel openers. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: K^+ (K_{ATP}) channel, ATP-sensitive; Endothelium; Aorta, rat

NIP-121 ((+)-7,8-dihydro-6,6-dimethyl-7-hyroxy-8-(2-oxo-1-piperidinyl)-6*H*-pyrano[2,3-*f*]benz-2,1,3-oxadiazole) is a derivative of cromakalim and shows ATP-sensitive K^+ (K_{ATP}) channel opening activity in cardiovascular tissues, including arteries (Masuda et al., 1991; Yamashita et al., 1995). The primary site of actions of K_{ATP} channel openers, in conjunction with the vascular relaxation they induce, is generally thought to be plasmalemmal K_{ATP} channels in vascular smooth muscle cells (Cook, 1988), activation of which leads to plasma membrane hyperpolarization that limits Ca^{2+} entry through L-type voltage-gated Ca^{2+} channels, and thus, decreases cytoplasmic Ca^{2+} concentration and vascular smooth muscle relaxation. In the present study, we determined whether endothelium, which plays important roles in the regulation of vascular smooth muscle tonus and vascular smooth muscle cell membrane excitability, contributes functionally to the vascular relaxation induced by NIP-121 in the isolated rat aorta.

Fig. 1 shows concentration–response curves for NIP-121-induced relaxation of rat aorta preconstricted with phenylephrine (3×10^{-7} M). The NIP-121-induced relaxation was greater in endothelium-intact preparations than in endothelium-denuded ones: the pEC_{50} values of NIP-121 with 95% confidence limits, for inducing vasorelaxation of rat aorta were 8.26 (7.97–8.54) ($n = 9$) and 7.80 (7.63–7.96) ($n = 12$) in the preparations with and without endothelium, respectively, and they were significantly different from each other ($P < 0.05$). The vascular relaxation by phentolamine (3×10^{-7} M), an α-adrenoceptor antagonist, against phenylephrine-induced contraction did not differ in endothelium-intact and in endothelium-denuded preparations. In the presence of glibenclamide (10^{-6} M), the concentration–response curves for NIP-121-induced vasorelaxation were almost identical: pEC_{50} values were 6.95 (6.71–7.19) ($n = 3$) and 6.81 (6.59–7.03) ($n = 3$) for endothelium-intact and -denuded preparations, respectively ($P > 0.05$). These findings suggest that the endothelium-dependent component of NIP-121-induced vasorelaxation is attributable to specific activation of K_{ATP} channels possibly existing on endothelial cells.

One possibility to explain the present findings is that activation of K_{ATP} channels of endothelial cells by NIP-121, with possible subsequent membrane hyperpolarization, enhances Ca^{2+} entry through Ca^{2+}-permeable non-specific cation channels due to a driving force increased by

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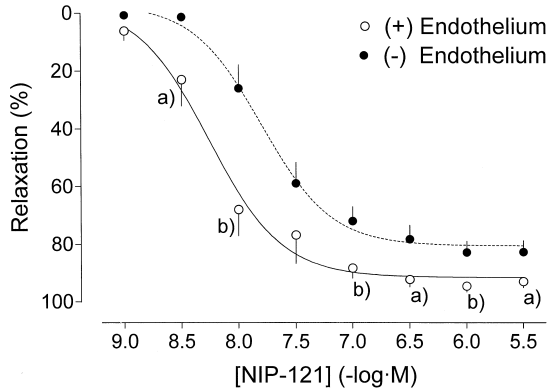

Fig. 1. Concentration–response curves for the relaxation by NIP-121 of rat aorta with and without endothelium. Rat aorta with (open circles) or without (filled circles) endothelium was preconstricted with phenylephrine (3×10^{-7} M) and NIP-121 was applied cumulatively. Acetylcholine (10^{-5} M)-induced vasorelaxation was observed only in endothelium-intact preparations. (a) $P < 0.05$ and (b) $P < 0.01$ show significant differences from endothelium-denuded preparations.

membrane hyperpolarization to move Ca^{2+} across the plasma membrane from the extracellular space (Busse et al., 1988), thus enhancing production and release of nitric oxide. Another possibility is that the endothelial cell membrane hyperpolarization, induced by the opening of K_{ATP} channels due to NIP-121, is transferred electrotonically to underlying vascular smooth muscle cells via endothelium–vascular smooth muscle cell junctions, which subsequently induces membrane hyperpolarization of vascular smooth muscle cells (Bény and Brunet, 1989). In any event, the present findings are the first indication that endothelium may significantly contribute to the vascular relaxation induced by K_{ATP} channel openers.

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