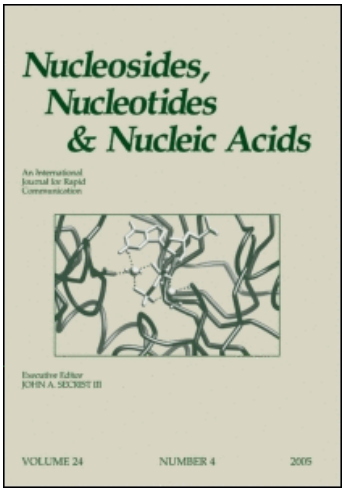

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Adenosine-induced dilation of rat thoracic aorta is mediated by cyclic GMP and is age-dependent

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Adenosine-induced dilation of rat thoracic aorta is mediated by cyclic GMP and is age-dependent

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Abstract Contrary to the established concept that the effects of adenosine are mediated by cAMP, we found that the vasodilator effect of adenosine is in part mediated by cGMP, and decreased with age.

Adenosine induced dilation of aorta from rats of 4 weeks old. From the order of potencies of adenosine derivatives in inducing dilation, adenosine-receptors mediating the dilation is suggested to be of the A_2-subtype. N^G-monomethyl L-arginine (10 μM), hemoglobin (10 μM) and methylene blue (30 nM), or removal of the endothelium partly reversed or attenuated the adenosine-induced dilation, without affecting that induced by the cAMP-phosphodiesterase inhibitor cilostamide.

The dilation was attenuated with an increase in age of the rats to 8 weeks old, and was not detected with aorta from rats of 20 weeks old. Between the age of 4 and 60 weeks, the concentration-response curves for NECA shifted about 3 orders of magnitude, whereas the dilator responses to the A_1-agonist S-PIA showed little change.

[^{3}H]NECA bound to aortic membranes from rats of 4 weeks old, and its binding was displaced more effectively by NECA and the A_2-ligand CV-1808 than by the A_1-ligand S-PIA. The number, but not the affinity of specific binding sites for [^{3}H]NECA decreased considerably with an increase in age of rats to 8 weeks, and scarcely any binding of [^{3}H]NECA was detected in preparations from rats of 20 weeks old.

Adenosine (10 μM) caused marked increase in cGMP production, but did not induce an increase in the cAMP level. This increase in cGMP

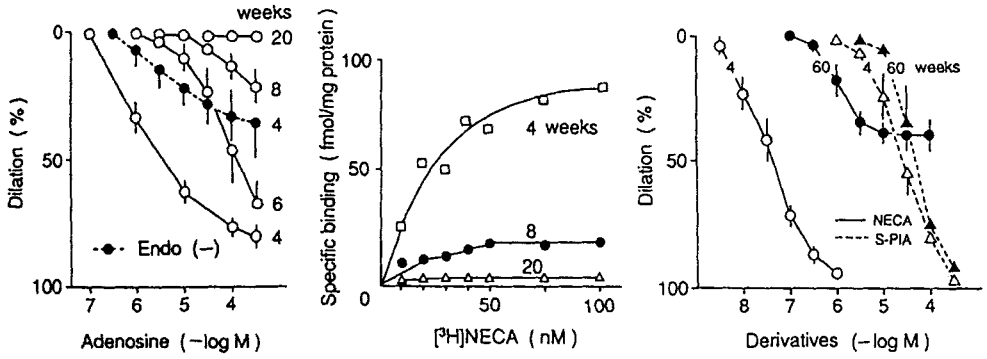

FIG. 1. Age-associated changes in adenosine-induced dilation (left) and [^{3}H]NECA binding (middle), and effect of aging on A_1- and A_2-mediated dilations (right). Age of rats are shown in weeks. Endo (-), without endothelium.

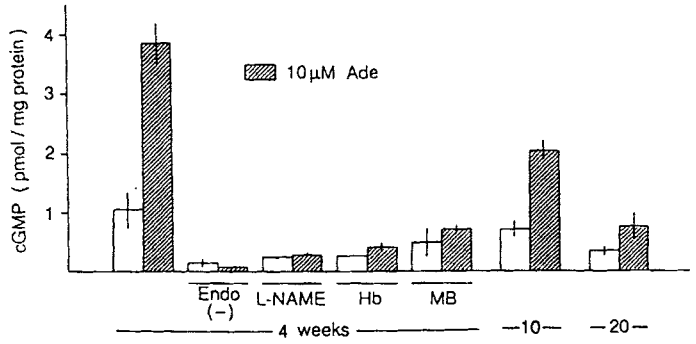

FIG. 2. Effects of hemoglobin, N^G-monomethyl L-arginine, methylene blue, and removal of the endothelium on adenosine-stimulated cGMP production in thoracic aorta from rats of 4 weeks old, and effect of aging on the A_1- and A_2-mediated dilations. Amounts of cGMP was measured after incubation with or without 10 μM adenosine for 15 sec. Hb; with 0.1 μM hemoglobin; MB, with 1 μM methylene blue.

production was abolished by N^G-monomethyl L-arginine, hemoglobin or methylene blue, or by removal of the endothelium. The age-associated decrease in adenosine-induced dilation was found to be associated with reduction in formation of cGMP.

The present results suggest that adenosine causes dilation mainly via A_2-receptors in the endothelium by stimulating production of EDRF, which in turn stimulates soluble guanylate cyclase, and so increases production of cGMP, and that aging affects these functions or steps.