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## Factors regulating the time-course of the relaxation of rabbit aorta strips after contraction by angiotensin II

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It has been shown (Regoli & St-Louis, 1975) that the myotropic response of rabbit aorta strips (RAS) to angiotensin II is diminished in the absence of $Ca^{2+}$ and restored when $Ca^{2+}$ (1.5 mM) is readmitted to the physiological salt solution (PSS). The effect of $Ca^{2+}$ upon the angiotensin II response is still observed for several minutes after the angiotensin II infusion has been stopped, showing that angiotensin II continues to stimulate the receptors for several minutes after washing. Some factors regulating this continued myotropic response have now been investigated.

Helical RAS 2 cm long were equilibrated for 3 h under 3 g tension in a cascade system and superfused with a tris buffered PSS (van Breeman, Farinas, Gerba & McNaughton, 1972) maintained at 37°C. The drugs were applied by infusion in the PSS and isometric contractions were recorded by a Grass FTO3C force transducer.

A steady submaximal contraction was elicited with angiotensin II ($4.5 \times 10^{-9}$ M) and the rate of relaxation of the subsequent tension decrease was observed when angiotensin II or $Ca^{2+}$ or both were removed from the PSS. $RT_{50}$ values (time for 50% relaxation, Kalsner, 1975) were $7.1 \pm 0.3$ min following angiotensin II removal; $4.5 \pm 0.2$ min following $Ca^{2+}$ removal; and $3.8 \pm 0.2$ min following simultaneous removal of both ($n=8$). Regoli & St-Louis (1975) have shown that changes in calcium concentration do not alter the receptor binding of angiotensin II but interfere with the magnitude of the contraction. The present results therefore show that interference with the contractile mechanism can increase the rate of relaxation.

When a 100-fold excess ($5 \times 10^{-7}$ M) of a potent competitive angiotensin II antagonist (8-Gly-angiotensin II; Regoli, Park & Rioux, 1974) was added during the angiotensin II infusion, there is again a decrease in $RT_{50}$ to $3.8 \pm 0.1$ min ($n=12$). Hence the $RT_{50}$ value can also be decreased by promoting the dissociation of angiotensin II from its receptor (Rioux, Park & Regoli, 1975).

When the steady contraction was caused by analogues of angiotensin II (Regoli *et al.*, 1974) the $RT_{50}$ value for the relaxation after removing the compound from the PSS was correlated with the $pD_2$ value of each compound. When the antagonist 8-Gly-angiotensin II was added, the $RT_{50}$ values for these analogues were markedly reduced and were well correlated with the $pD_2$ value of each compound, $r=0.928$ ($n=6$ to 8 for each compound). The response to $Ca^{2+}$ readmission 30 s and 4 min after interrupting the infusion of these same analogues of angiotensin II in $Ca^{2+}$ free PSS, decreased with decreasing $pD_2$ value of the compounds. These last results suggest that the relaxation, and the residual contraction observed after adding $Ca^{2+}$ to the PSS, are highly dependent on the rate of dissociation of the agonist compound from the angiotensin II receptor.

The results presented here support the conclusion of Regoli & St-Louis (1975) that angiotensin II continues to stimulate the receptors several minutes after washing, and suggest that the dissociation of angiotensin II from its receptors is a rate-limiting step for the decrease in tension when angiotensin II is removed from the superfusing PSS.

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