ACUTE VASODILATORY EFFECT OF TUMOR NECROSIS FACTOR (TNF) ON THE RABBIT CAROTID ARTERY.

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TNF is believed to be one of the major mediators of sepsis. Decrease in vascular resistances and hyporesponsiveness to contractile agonists are commonly observed in septic shock. We have therefore examined the vascular effects of recombinant human TNF (rTNF) on the precontracted rabbit carotid artery. The two carotids, excised at in vivo length and physiological pressure, were incubated in oxygenated Krebs-Ringer solution at a transmural pressure of 90 mmHg. Changes in diameter were measured using a ultrasonic micromedimeter. Contractions were induced by extraluminal phenylephrine (PE) at 7x10^{-7} M, or KCl at 60 mM. rTNF was then added in the extraluminal solution to give a concentration from 0.01 to 0.7 μg/ml. As shown in the figure, rTNF elicited a dose-dependent relaxation of PE-contracted carotids, with an IC50 of 3.2 nM. This relaxation was immediate, and the mean maximal vasodilation was 79.3 ± 5.9 % of the initial contraction. This effect was almost completely abolished by methylene blue (MB, 10^{-5} M), an inhibitor of the soluble guanylate cyclase. No vasodilatory effect was observed after KCl-inducible contractions. Four carotids were also tested after exposure to N-nomethyl-L-arginine (NMA) at 3x10^{-4} M, an inhibitor of L-arginine pathway, to test whether this effect was mediated by nitric oxide production from L-arginine. Preexposure to NMA did not alter the relaxing effect of rTNF.

This study shows an acute vasodilatory effect of rTNF on the PE-precontracted rabbit carotid, which seems to be due to a direct activation of the guanylate cyclase of vascular smooth muscle. Inhibition of smooth muscle cell contraction by prolonged exposure to Interleukin-1 and TNF has also been reported1,2. These results suggest that cytokines might mediate the vascular tone defect observed in septic shock.

References