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PROTEIN KINASE C ACTIVATION MAY CONTRIBUTE TO TESTOSTERONE INDUCED RELAXATION IN HUMAN INTERNAL MAMMARY ARTERY.

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Testosterone (T) induces vasodilatation in human internal mammary artery in vitro. It has been shown that testosteron-induced relaxation is higher than dihydrotestosterone (a nonaromatisable testosterone). Whether the remaining relaxation induced by testosterone could be attributed or not to estrogen is not known.

The study was performed using internal mammary artery (IMA). The strips were suspended in an organ bath filled with Krebs-Henseleit solution at 37 degrees C (pH 7.4) and continuously aired with 95% oxygen and 5% carbon dioxide. Changes in isometric tension of the specimens were measured with a force-displacement transducer and recorded with a polygraph.

After precontration with prostaglandin F2a (10 mM) T. propionate induced relaxation. While tamoxifen (10-4 M) partly inhibited the relaxation induced by T, letrozol (10-4 M) had no effect.

Tamoxifen is a non-steroidal estrogen agonist-antagonist that is widely used for treatment of breast carcinoma. Tamoxifen is also an effective PKC inhibitor. In the present study, the lack of effect of letrozol, an aromatase inhibitor, suggests that not partial aromatisation of testosterone into estrogen but PKC inhibiton may contribute to relaxation effect of testosterone in IMA.

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TESTOSTERONE RELAXES HUMAN INTERNAL MAMMARY ARTERY IN VITRO.

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Testosterone (T) has contradictory effects on vascular tone in animals in vitro, i.e, endothelium-dependent or independent vasodilatation and vasoconstriction. In clinical studies, T has beneficial effects on ischemia and coronary vasomotion in human. However, there is no study on in vitro effect of T in human isolated arteries.

The responses in human internal mammary artery (IMA) were recorded isometrically by a force-displacement transducer in isolated organ baths. T. Propionate (10 nM-100 mM) was dissolved in alcohol and added to organ baths either at rest or after precontraction with KCl (68 mM) and prostaglandin F2a (10 mM). T -induced relaxations were tested in the presence of cyclooxygenase inhibitor indomethacin (10 mM), nitric oxide synthase inhibitor L-NAME (1 mM), large conductance Ca2+-activated K+ channel inhibitor tetraethylammonium (TEA, 1 mM), ATP-sensitive K+ channel inhibitor glibenclamide (GLY, 100 mM) and voltage-sensitive K+ channel inhibitor 4-aminopyridine (4-AP, 1 mM). In addition, concentration-response curves to CaCl2 (10 mM - 30 mM) were obtained in absence and presence of T (100 mM).

T produced potent relaxation in human IMA (Emax: 33.29+4.49% and 41.12+6.13%; pEC50: 4.47+0.05 and 4.80+0.19 for KCl and % PGF2a, respectively). Vehicle had no significant relaxant effect. Except TEA, the relaxation at low concentrations is not affected by neither K+ channel inhibitors (GLY and 4-AP), nor cyclooxygenase and nitric oxide synthase inhibitors. Pre-treatment of the arteries with high concentration T (100 mM) inhibited CaCl2 induced contractions. These results show that T relaxes IMA via potassium channel opening and calcium antagonistic action.

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