MEDIAL INJURY AND HYPERLIPIDEMIA IN DEVELOPMENT OF ANEURYSMS OR ATHEROSCLEROTIC PLAQUES

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THE EVOLUTION OF atherosclerotic disease in human arteries is not uniform. Some vessels become obstructed by extensive deposition of intimal plaque, whereas others develop medial atrophy and become aneurysmal, often with thrombus formation and minimal atherosclerosis.

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PERIPHERAL VASCULAR DISEASE

We subjected hypercholesterolemic rabbits to narrow bands of transmural aortic ligation injury to assess the possible roles of endothelial, medial, or plaque disruption in determining differences in the morphogenesis of lesions. The injuries resulted in contrasting effects on the aortic wall depending on the degree of severity of medial damage and the interval between the beginning of cholesterol feeding and operation. Differences in resolution of the injuries include medial atrophy and aneurysm formation with little plaque deposition as well as complete restoration of the media with overlying atherosclerosis.

MATERIALS AND METHODS

Standard 0.3-mm bands of transmural injury were produced in the infrarenal abdominal aorta of 48 New Zealand white rabbits. Three sites of injury were produced in each rabbit by encircling the aorta with a 3-0 silk suture that was tightened to produce subtotal occlusion for 15 minutes. Injury sites and adjacent noninjured aorta were studied at 2, 4, 16, and 32 days by light and electron microscopy after controlled pressure perfusion-fixation of the aorta in situ at 100 mm Hg with 3% phosphate-buffered glutaraldehyde. Sixteen rabbits were fed normal diets; 16 were fed an atherogenic diet containing 0.5% cholesterol and 4% corn oil for one month prior to injury to assess the effects of injury in the presence of hypercholesterolemia before gross lesions are evident; 16 were fed the atherogenic diet for three months prior to injury to assess the effects of injury on an artery with grossly evident plaques. To evaluate endothelial integrity, 1% Evans blue dye (1.0 ml/kg) was administered intravenously 30 minutes before the rabbits were killed.

RESULTS

Serum cholesterol at the time of operation in the rabbits given the normal diet was 75 ± 20 mg/100 ml. In the group without gross lesions at operation serum cholesterol was 1500 ± 300 mg/100 ml, and 1600 ± 200 mg/100 ml in the group with lesions. Levels remained unchanged for each group from operation until the rabbits were killed. Normal diet and prelesion rabbits had no grossly visible aortic plaques at operation whereas rabbits in the manifest lesion group had prominent plaques. Although the standard ligature injury produced transmural necrosis of variable severity, the endothelial surface was denuded over the zone of injury in all rabbits and showed deep staining by the Evans blue dye. Regenerated endothelium impermeable to Evans blue dye covered the injury zone in all rabbits by day 4. In rabbits with intimal lesions already present at operation, plaques also sloughed over the zone of injury.

The media healed completely by day 16 in rabbits given the normal diet, with residual minimal intimal fibrocellular thickening in 44/48 (92%)
of injuries. In four injuries (8%) the media was thinned and trophic and showed aneurysmal dilatation but no intimal thickening. In the hypercholesterolemic rabbits without initial plaques, 40/48 (83%) of the injured medial sites were still disrupted and deformed when the rabbits were killed. Of the 40 injury sites with unrestored medias, 38 (95%) showed no intimal disease despite prominent formation of plaque in the adjacent uninjured aorta; 22 of the 38 (58%) developed aneurysms. The medial injuries healed completely in 36 of 48 (75%) hypercholesterolemic rabbits with plaques already present at operation and were deformed in only 12 (25%). When the rabbits were killed, intimal plaques were prominent at over 24 of the 36 (66%) injury sites with restored medias, but were absent over 11 of the 12 (87%) deformed medial sites; five (42%) of these developed aneurysms.

CONCLUSIONS AND DISCUSSION

In this model the endothelium regenerated completely within four days, regardless of the level of duration of hyperlipidemia. Aneurysm formation occurred when medial disorganization and distortion persisted, but plaques were absent in 95% of such sites. Hyperlipidemia enhanced medial disruption and aneurysm formation, but plaque formation was increased only where the media healed without deformity. Complete restoration of the media and endothelium was apparently necessary for intimal plaque deposition, which is consistent with results of others. In the balloon catheter, endothelial injury model (1,2), plaque formation is greatest where reendothelialization has occurred. Injury of the media without injury to the endothelium may not result in atherosclerosis (3).

Aneursym formation and atherosclerotic intimal deposition may both require hyperlipidemia in this model, but the atherogenic mechanisms for these changes may be different. Lesions in humans tend to be complex, showing evidence of both intimal plaque formation and dilatation, which suggests that the different mechanisms may coexist or occur in sequence.

REFERENCES