lotion or surgical removal of the thyroid gland. Following 2 months on a thy-roid suppressive diet, the extent of neointimal regrowth was compared 14 days after balloon injury in hypothyroid rats (Group 1, n = 8, thyroid stimulat-ing hormone (TSH) = 9.6 microIU/ml) and animals maintained on a normal diet (Group 2, n = 8). Neointima formation was significantly attenuated in Group 1: intima/medial ratios were 0.904 ± 0.118 mm² and 1.361 ± 0.061 mm² in Groups 1 and 2, respectively, (p < 0.0). Additional experiments in rats following thyroidec-tomy (n = 3) revealed a similar significant decrease in neointima formation following balloon injury. This inhibitory effect of hypo-thyroidism was maintained in animals who were also made hypercholester-olemic (Group 3, n = 8, TSH = 10.2 microIU/ml), total cholesterol = 752 mg/dl, low-density lipoprotein = 674 mg/dl; intima/medial ratios were 1.361 ± 0.061 mm² and 0.822 ± 0.078 mm², in Groups 2 and 3, respectively, p < 0.02. Prolonged (60 days) cholesterol feeding alone (Group 4, n = 8) as sus-pected, did not result in elevated cholesterol levels, but also did not result in significant differences in intimal thickness when compared to animals in Group 2. These results suggest that thyroid hormone may be an important co-mitogen for the proliferative response of the rat carotid artery to balloon injury and may help partially explain the growth inhibitory effect of hypothy-roidism.

**914-74** Estradiol 17β Protects Against Homocysteine-Induced Vascular Injury in Rat Thoracic Aorta

Michel Y. Farhat, Brenda Dangaia, Michael E. Fader, Peter W. Ramwell. Georgetown University. Washington, DC

Hyperhomocysteinemia produces atherosclerotic lesions with characteristic endothelial desquamation and intimal smooth muscle cell (VSMC) prolif-eration. In vitro, homocysteine is cytotoxic to endothelial cells and recent ob-servations suggest that it may directly stimulate VSMC proliferation. Estro-gens, on the other hand, inhibit VSMC proliferation both in vivo and in vitro. We evaluated the effect of estradiol 17β (E2) on homocysteine-induced VSMC proliferation in arterial segments from the rat thoracic aorta. Seg­ments were placed overnight in Dulbecco’s Minimum Essential Medium, supplemented with gentamicin (25 μg/ml), glutamine (2 mM) and 0.4% fa­tal bovine serum, before incubation for 30 hours with DL-homocysteine thi­olactone (0.1–5.0 mM). Radiolabelled thymidine uptake was assessed in in­tact and deendothelialized arterial segments, in presence of E2 (30 nM) or vehicle (1% ethanol). In deendothelialized segments homocysteine elicited a concentration-dependent increase in 3H-thymidine uptake, expressed as cpm/mg protein. Thymidine uptake increased from a basal value of 8694 ± 1465 to 36336 ± 2025, at 5 mM homocysteine concentration (p < 0.01). Intact arterial segments showed a significantly attenuated response to ho­mocysteine stimulation. On the other hand, incubation of deendothelialized segments with E2 (30 nM) caused a significant inhibition of homocysteine-stimulated response, without affecting basal 3H-thymidine incorporation. These results provide evidence for a direct stimulatory effect of homocys-teine on VSMC proliferation in rat aortic segments. Further, our data show estradiol 17β protects against homocysteine-induced vascular injury, possi­bly via a direct effect on VSMC.

**914-75** The Role of Estradiol 17β on Free Radical Induced Vascular Myointimal Hyperplasia

Sam Cathapermal, Mann Y. Leong-Son, Peter W. Ramwell. Georgetown University. Washington, DC

Oxygen free radicals may be involved in vascular hyperplasia by promot­ing smooth muscle cell proliferation, a response potentiated by endothelial damage. Estradiol 17β protects against vascular injury in experimental arte­riosclerosis and inhibits proliferation of primary cultures of vascular smooth muscle cells. We studied the in vitro effect of estradiol 17β on vascular smooth muscle cell hyperplasia induced by the superoxide anion (O2·−). In­tact and denuded rat aortic segments were incubated overnight at 37° C in 2 ml Eagle’s minimal essential medium supplemented with gentamycin and glutamine, without phenol red. The segments were challenged with either vehicle alone or the O2·− generating system (Xanthine and xanthine oxidase) for 3 (h). We found that O2·− significantly enhanced 3H-thymidine incorpo­ration, an effect potentiated by the absence of the endothelium (Intact ves­sel 8.3 ± 105 ± 0.1 ± 105 vs denuded vessel 2.5 ± 106 ± 1.3 ± 106 p < 0.01). This effect was inhibited by superoxide dismutase. Estradiol 17β (30 nM) significantly inhibited free radical induced 3H-thymidine uptake in both intact and denuded vessels. We conclude that an intact endothelium may protect against free radical induced smooth muscle cell proliferation. Estradiol 17β may also protect against free radical induced vascular proliferation by a mechanism independent of the endothelium.

**915** Coronary Physiology

Monday, March 20, 1995, Noon–2:00 p.m. Ernest N. Morial Convention Center, Hall E

**Presentation Hour: Noon–1:00 p.m.**

**915-76** ATP-sensitive Potassium Channels Contribute to Reactive Hyperemia in Humans

Peter F. Banitt, Paul Smits, Stephen B. Williams, Peter Ganz, Mark A. Cresger. Brigham and Women’s Hospital. Boston, MA

Activation of ATP-sensitive potassium channels (KATP) of vascular smooth muscle causes hyperpolarization of the cell membrane and vasodilatation. The purposes of this study were 1) to determine whether KATP contribute to re­active hyperemia following ischemia in humans, and 2) whether adenosine, a metabolite present in ischemic muscle, activates KATP. Accordingly, we studied the effect of tolbutamide (1 mM), a KATP inhibitor, on reactive hyper­emic forearm blood flow in 12 normal subjects. Forearm blood flow (FBF) was measured by venous occlusion plethysmography. Forearm ischemia was produced by inflating a blood pressure cuff to suprasystolic pressures for 5 minutes. Following cuff release FBF was measured during the reactive hyperemic phase for 5 minutes. After a re-equilibration period the above pro­totocol was repeated during intra-brachial artery infusion of either tolbutamide 1 mM (n = 6) or vehicle (n = 6). Blood flow was plotted vs. time and the area under the curve was calculated after subtracting baseline flow. Tolbutamide did not significantly alter baseline FBF (2.5 ± 0.6 to 2.1 ± 0.0 mll/100 ml/min), or peak reactive hyperemic FBF (21.9 ± 9.2 to 22.7 ± 7.0 ml/100 ml/min) (each p > ns). However, tolbutamide significantly attenuated total hyperemic flow repayment, (166 ± 44 vs. 112 ± 32 ml/100 ml/min, p = 0.02). Vehicle did not impair basal flow, peak reactive hyperemic flow or repayment. Tolbutamide 1 mM did not attenuate adenosine-induced 1500-500 m(M) increases in FBF (n = 6). These data indicate that KATP contribute to vasodilatation during reactive hyperemia in humans. Activation of KATP is not mediated by adenosine.

**915-77** Big ET-1-Infusion in Man Causes Only Renal ET-1-Release but Potent and Long-lasting Systemic, Pulmonary, Renal and Splanchnic Vasocostration

Gunvor Ahlborg, Astrid Ottosson-Seberberger, Anette Hemsén, Jan M. Lundberg. Institution of Clinical Physiology, Huddinge Hospital and Department of Pharmacology, Karolinska Institute, Stockholm, Sweden

Plasma endothelin-1 (ET-1), and the precursor, big ET-1, are demonstrable in healthy man and increase during e.g. myocardial infarction (Miyauchi et al 1989). To study the vascular effects of big ET-1 infusion, and its possi­ble conversion of ET-1, healthy subjects received big ET-1 in doses of 4-8 pmol.kg-1.min-1 intravenously for 20 minutes. Blood samples were taken from systemic arterial and pulmonary arterial as well as jugular, deep fore­arm, hepatic and renal vein catheters for determination of cardiac output, CO, splanchnic (ESBF) and renal (ERBF) blood flows (indicators: cardiogreen and PAH) forearm blood flow (FBF, plethysmography), and Big ET-1 and ET-1 in plasma and tissues extract big ET-1 with fractional extractions of 23±5%. Only the kidney synthesized and released big ET-1. Compared to ET-1 infusion (Weitzberg et al 1991) big ET-1 caused dilatations in these regions. Only the kidney synthesized and released big ET-1. Compared to ET-1 infusion (Weitzberg et al 1991) big ET-1 causes dilatations, despite lower arterial plasma ET-1-L levels, more marked haemodynamic effects as reflected in drops in HR and CO and more marked increase in MAP with more pronounced and long-lasting renal vasocostriction. In addition big ET-1 had no effect on cerebral or skeletal muscle blood flows while ET-1 caused dilatations in these regions.