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MOUSE SOLUTIONS TO HUMAN PROBLEMS

OLIVER SMITHIES

Department of Pathology and Laboratory Medicine. University North Carolina at Chapel Hill, NC, USA

Essential hypertension probably results from combinations of genetic variations, not necessarily the same in all afflicted persons, which individually may not cause sufficient deviation from normality to be significantly harmful.

Genes contributing to hypertension are being sought by analytic experiments aimed at identifying candidate genes that segregate with the phenotype, and by synthetic experiments in which changes are made in candidate genes in animals and their effects on blood pressure are determined.

We have used gene targeting to vary angiotensinogen (AGT) and angiotensin converting enzyme (ACE) synthesized from the corresponding genes (Agt and Ace). These «gene titration» experiments establish that changes in Agt gene expression directly cause changes in the blood pressures of mice with normal homeostatic mechanisms. Surprisingly, quantitative changes in Ace gene expression over a four-fold range do not affect blood pressures.

Computer simulations with a simple version of the renin-angiotensin system predict that changes in Agt function alter the steady-state levels of both angiotensin I (ANGI) and angiotensin II (ANGII). In contrast, modest changes in Ace function alter ANGI levels considerably but scarcely affect ANGII levels. Simulations of more drastic changes in ACE levels, as would occur with an ACE inhibitor, predict that ANGII levels decrease only when ANGI levels have plateaued.

Comparison of the computer simulations with our genetic experiments and with prior work of others using wide dose ranges of ACE inhibitor shows a satisfactory agreement, helps reconcile the apparent contradictions between the genetic and pharmacological experiments.