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CHS President's Report

A Year of Evolution for the Canadian Hypertension Society

By Richard Lewanczuck; Presented at the CHS Annual Business Meeting, October 24, 2005 in Montreal, Quebec

The Canadian Hypertension Society (CHS) has been in existence for more than 25 years. However, in this current era of new antithrombotic agents, novel inflammatory mediators, and more sophisticated cardiac interventions, some might think that hypertension, as a field of study, is becoming a bit dated. Nowadays, we infrequently see new major hypertension trials being published. As a matter of fact, in a totally unscientific survey, I found that in a literature search for our therapeutics sub-committee of the Canadian Hypertension Education Program (CHEP), review and meta-analytical articles on hypertension outnumbered novel clinical research by a ratio of 50 to one. Thus, some might wonder whether the study of hypertension is becoming irrelevant.

Quite the contrary! The number-one cause of mortality worldwide, regardless of country, is cardiovascular disease. And the number-one risk factor for cardiovascular disease is hypertension, far outdistancing other risk factors such as smoking or dyslipidemia. Thus, if anything, the study and treatment of hypertension is gaining in importance.

A few weeks ago, a high-school student asked me, "What is the cause of high blood pressure?" Although I could explain the physiology and the vascular pathology, despite decades of research we still can't answer this student's question. The study of hypertension is not dead by any estimation, but is critically dependent upon the efforts of societies such as ours to continue to forge ahead in the study and treatment of this pervasive disease. It is thus with great pride that I present this year's report.

CHS Lends Expertise to Canadian Public Health and Research Policy

My predecessor, Tim Reudelhuber, characterized his presidency of the CHS as a year of consolidation. I would characterize this past year as one of evolution or

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President's Report

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transformation. In the past, the CHS has supported hypertension research, introduced the evidence-based guidelines concept to the world, and concentrated on therapeutic advances. This year, we have taken a step forward, becoming more involved in the realm of public policy. Because hypertension is now recognized as a major contributor to cardiovascular morbidity and mortality, and as a significant chronic disease in its own right, the CHS has been sought out to provide input regarding matters of public health policy.

For example, Health Canada established a chronic-disease working group in order to facilitate infrastructure development for the management of three key chronic diseases: diabetes, chronic renal failure and hypertension. The CHS was invited to be part of this process as the official voice of hypertension in Canada. In addition, various non-profit societies and granting agencies have sought CHS participation in the area of policy development around cardiovascular disease. Finally, our members have been called upon by provincial governments to provide input into health policy decisions. Thus, the CHS has been involved in setting the health and research policy agenda in Canada.

Permanent Office Established

As a further evolution, the CHS has now established a permanent office, courtesy of Queen's University in Kingston. And we now have our first permanent employee, Kathy Christmas, whom many of you know from the Ontario Hypertension Society. In the past, the CHS office has resided with the Secretary-Treasurer. However, after having personally wit-



nessed the incredible amount of work that our Secretary-Treasurers have to do, it is only fair to ease their burden by having someone who is experienced to handle many of the routine activities involved in the running of the CHS. Further details, such as the office's address and contact numbers, will soon be made available.

Another exciting feature of having a permanent office is that discussions are underway to share the office with CHEP and Blood Pressure Canada (formerly known as the Canadian Coalition for High Blood Pressure Prevention and Control). This will allow all three organizations to better coordinate our efforts. In fact, an important milestone was achieved this year when it was agreed that CHEP would generally focus its efforts on hypertension detection and treatment using a variety of strategies, while Blood Pressure Canada would focus on public issues and the CHS would concentrate on research, education and public policy. Thus, the three organizations representing hypertension in Canada are working collaboratively for the benefit of all Canadians.

CHEP Maintains Independence

Although the CHS instituted the evidence-based guidelines approach to hypertension many years ago, the involvement of other organizations—and the need to maintain independence—led to the formation of CHEP. Further to the independence issue, it was recently felt that direct fundraising by CHEP could potentially put it in a position of conflict of interest. Accordingly, by agreement, the CHS has taken over CHEP's finances, providing arm's-length funding and auditing functions to ensure that the independence of CHEP is maintained.

Partnerships and Collaborations with the CIHR

The CHS has continued to be at the forefront in defining Canadian Institute of Health Research (CIHR) partnerships. This year, the executive met with representatives of the Institute of Circulatory and Respiratory Health to review our partnerships and to define future areas of collaboration. This was a very fruitful meeting, resulting in an

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agreement that allows us to even more efficiently utilize our Rx&D partner funds to support hypertension research and training in Canada.

Another CIHR-related collaboration has been the National Chair for High Blood Pressure Prevention and Control. As mentioned, we are at the vanguard of unique CIHR partnerships and, because of this, the various sides got off to a bit of a "false start" in the competition for this Chair. Because of its novel terms of reference, there was some confusion surrounding the selection process. This has now been sorted out, and the process to select a Chair has been re-established. It is anticipated that an announcement of award will be made by the end of this calendar year.

CHS Members are Key to Ongoing and Future Initiatives

The CHS has been busy in a number of other areas over the past year. We

continue to support the Vancouver 2010 committee in its organization of the International Society of Hypertension (ISH) meeting. Our website continues to expand and prove its practical usefulness, thanks in large part to Denis Drouin. Martin Myers and his committee have been busy sorting out the status of various blood-pressure-measurement technologies in Canada. Our CHEP mem-

bers continue to garner international accolades by extending their efforts to guideline implementation and adherence.

Overall, this has been a fulfilling year for the CHS, and we are certainly counting on the continued involvement of our members. Many thanks to all those who have contributed to various CHS projects this year. A special thanks to Michael Adams, Venkat Gopalakrishnan and their respective administrative staffs for organizing an outstanding and record-setting meeting. And thanks to all the members who continue to support the CHS in its endeavors. I feel confident that I leave the CHS in good hands as I hand over to our incoming President, Marcel Lebel.

*Richard Lewanczuk, MD, FRCPC, PhD
President, Canadian Hypertension Society.*



New Investigator 2005

RGS Proteins: A New Weaponry Class in the War Against Cardiovascular Disease?

By Scott P. Heximer

Heterotrimeric G-proteins: Master Regulators of the CV System

The cardiovascular (CV) system relies on regular communication between its various component tissues to maintain homeostatic control of blood pressure (BP) in response to rapidly changing physiologic stimuli. CV tissues have co-opted heterotrimeric G-protein signaling as a primary means of sensing and responding to changes in physiologic status. Proper function of this highly integrated network is maintained by controlling the precise release of neurotransmitters and circulating hormones capable of exerting their effects through G-protein coupled receptors (GPCRs) on peripheral vascular smooth muscle cells (VSMCs) and cardiomyocytes within end-effector cardiovascular organs.

G-proteins Relay Physiologic Signals for VSMC Contraction

BP is controlled via coordinated regulation of cardiac output and constriction of peripheral VSMCs. In peripheral arterioles, the blood vessels that regulate resistance to arterial blood flow, G-protein signaling is critical for relaying physiologic information to the contractile machinery. The signal relay mechanism between GPCRs to the contractile machinery is known as pharmacomechanical coupling. The physiologic sensor molecule at the level of the contractile machinery is MLC_{20} , the myosin light chain moiety. MLC_{20} is positioned on the myosin thick filaments and its phosphorylation by myosin light chain kinase (MLCK) facilitates productive actin-myosin cross-

bridge formation to promote vasoconstriction. The phosphorylation state of MLC_{20} is determined by the opposing actions MLCK and myosin phosphatase, the activities of which are coordinately regulated by GPCR signaling pathways.

GPCRs that couple to $Gq/11\alpha$ and $G12/13\alpha$ can regulate the activation of MLCK and inactivation of myosin phosphatase, respectively, through distinct signaling pathways. The result is a cooperative increase in MLC_{20} phosphorylation and contractile function. Most of the classical vasoconstrictor agonists, including norepinephrine, angiotensin II and vasopressin, exert their effects through Gq-coupled receptors. Upon receiving a vasoconstrictive stimulus, Gq-mediated activation of Phospholipase C β (PLC β) leads to production of inositol phosphate (IP_3) and subsequent IP_3 -mediated release of intracellular Ca^{2+} from sarcoplasmic reticulum stores. The resulting increase in cytosolic Ca^{2+} facilitates Ca^{2+} /calmodulin-dependent activation of MLCK and contractile force generation. In addition, $G12/13$ -coupled receptors can inhibit myosin phosphatase through the direct engagement of RhoGEF effectors to result in activation of Rho/Rho kinase signaling pathways. Established mediators of VSMC function, including thrombin and sphingosine-1-phosphate, exert their effects through this signaling pathway. Activated Rho kinase phosphorylates myosin light chain phosphatase (MLCP) to inhibit its function. Reduction of MLCP activity results in accumulation of phosphorylated MLC_{20} and leads to greater VSMC contraction. Thus, synergistic Gq- and $G12/3$ -mediated regulation of MLC_{20} on the contractile machinery

plays a key role in maintenance of normal vascular tone and function.

The relevance of these signaling pathways to the treatment of patients with hypertension is evident when one considers that chronic hypertension is often associated with increased activity of vasoconstrictor hormones and neurotransmitters that work through GPCRs. Furthermore, chronic elevation of G-protein-mediated pathways is associated with pathophysiologic changes in the cells of the blood-vessel wall (cellular hypertrophy, cellular hyperplasia) and vascular remodeling. It should not be surprising, therefore, that some of the drugs most widely used to lower BP (*i.e.*, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists) and reduce pathophysiologic remodeling of arterial vessels act upstream or at the level of GPCRs on VSMCs to reduce intracellular signal throughput. My research is focused on characterization of intracellular mechanisms that normally attenuate G protein signaling in VSMCs, with the ultimate goal of discovering new molecular strategies for the treatment of hypertension and its associated pathophysiologic effects on the heart and vasculature.

RGS Proteins are Potent Regulators of G-protein Activity

The quiescent heterotrimeric G-protein complex is coupled to the intracellular surface of the GPCR. Receptor activation by agonists such as norepinephrine results in the exchange of GTP for GDP on the $G\alpha$ subunit and the dissociation of GTP-bound $G\alpha$ from the $G\beta\gamma$ heterodimer. This condition marks the acti-



vated (“ON”) state during which time the $G\alpha$ and $G\beta\gamma$ subunits are free to engage appropriate downstream effectors such as $PLC\beta$. Effector signaling is terminated following $G\alpha$ catalysed hydrolysis of GTP and reformation of the quiescent (“OFF”) receptor-coupled heterotrimer. If there is still sufficient agonist present to elicit receptor activation, another cycle of G-protein activation will be initiated. Importantly, the intrinsic rate of GTP hydrolysis by $G\alpha$ subunits (the rate limiting step for signal termination) is very slow. Thus, to regulate the rapid increases and decreases in G-protein signaling activity observed during cardiovascular function in vivo, there must be additional regulation of GTP hydrolysis in the form of specific GTPase activating proteins (GAPs).

RGS proteins are a newly appreciated mammalian family of > 30 GAPs for $G\alpha$ subunits. They can increase the rates of intrinsic GTP hydrolysis by up to 2,000 times compared to those observed for purified $G\alpha$ subunits. Such inhibitory activity is predicted to have two important effects on the physiologic responses to GPCR activation. First, RGS proteins promote faster signal termination kinetics following clearance of physiologic stimuli. Second, by inhibiting activated G-proteins before they can engage downstream effector pathways, RGS proteins can also decrease the sensitivity of GPCRs for specific agonists. Accordingly, we predict that a specific set of RGS proteins is required to coordinate the G-protein signaling and contractile status of VSMCs during normal BP homeostasis. We have identified a number of RGS proteins expressed in vascular tissues and have begun to investigate the effects of RGS protein deficiencies on vascular G-protein signaling in genetically altered mice.

Multiple RGS Family Subtypes Are Expressed in VSMCs

All of the RGS protein family members are characterized by an ~180

amino acid GAP domain that is required for G-protein inhibition. The family can be subdivided into small RGS proteins (RGS1, RGS2, RGS3, RGS4, RGS5, RGS8, RGS13, RGS16, RGS17, RGS18, RGS19), including those that contain minimum sequences outside the GAP domain and a set of much larger RGS proteins (RGS6, RGS7, RGS9, RGS11, RGS12, RGS14, p115-RhoGEF, LARG, PDZ-RhoGEF) that contain multiple modular intracellular signaling domains potentially capable of directing these proteins to specialized signaling domains within the cell.

A rather interesting relationship exists between the RhoGEF containing RGS proteins and regulation of contractile machinery. This subclass of RGS

proteins mediates the activation of Rho/Rho kinase by G12/13-coupled receptors (see above). Thus, they are capable of acting as both inhibitors and effectors of vasoconstriction, depending on the relative activities of their GAP and RhoGEF domains. Examination of RGS protein mRNA expression in vascular tissue expression indicates that several members of both the small and large RGS protein subclasses are present. Of particular interest to us is the relatively high expression of the RGS protein genes whose products are capable of inhibiting vasoconstrictor agonist-mediated Gq signaling and modulating G12/13-dependent activation of Rho/Rho kinase. The contribution of these molecules to vascular function in normal and disease conditions is the focus of present and future work in my laboratory.

RGS2-deficient Mice Show Marked Hypertension with Prolonged Vasoconstriction

We previously identified RGS2 as one of the strongest potential candidates for mediators of BP regulation. The *rgs2* gene is expressed in virtually all tissues involved in BP regulation, including the nervous system, kidney, and VSMCs, where its expression is induced by angiotensin II as a potential inhibitory feedback mechanism. Furthermore, it is unique among all the RGS protein family members in its ability to selectively attenuate Gq-coupled pathways.

We predicted that mice deficient in RGS2 function would show prolonged responses to potent Gq-coupled vasoconstrictors including norepinephrine, angiotensin II, endothelin-1 and throm-

BP is controlled via coordinated regulation of cardiac output and constriction of peripheral VSMCs. In peripheral arterioles, the blood vessels that regulate resistance to arterial blood flow, G-protein signaling is critical for relaying physiologic information to the contractile machinery.

bin. In support of these hypotheses, *rgs2^{+/-}* and *rgs2^{-/-}* mice are strongly hypertensive with chronic peripheral vasoconstriction and prolonged responses to acute administration of vasoconstrictor agonists. Treatment with an angiotensin II receptor antagonist normalizes BP in these mice, suggesting a key role for the renin-angiotensin system in this phenotype. Ongoing work in my lab is aimed at characterizing the contribution of vascular and nonvascular tissues to the hypertensive condition in these animals.

Can Modulation of RGS Protein Activity be Used in the Treatment of CV Diseases?

RGS proteins are potent regulators of GPCR signaling that may provide new pharmacologic targets for the regulation of vascular cell function. Depending on their normal role as inhibitors or effec-

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CHS Presidential Lecture

Hypertension is a Disease of Carbohydrate and Lipid Metabolism

CHS President Dr. Richard Lewanczuk introduced this year's Presidential Lecture speaker, Dr. Gerald M. Reaven, by reviewing Dr. Reaven's many accolades in the fields of cardiovascular and diabetes medicine and presenting him with the 2005 CHS Presidential Lectureship award.

Dr. Reaven, Emeritus Professor in the Division of Cardiovascular Medicine at Stanford University, was called upon to speak about his research relating to the role of insulin resistance in essential hypertension. Specifically, Dr. Reaven's presentation was aimed at: 1) describing the metabolic and vascular abnormalities in patients with essential hypertension that increase the risk of cardiovascular disease (CVD); 2) presenting evidence that CVD risk is significantly accentuated in the subset of patients with essential hypertension who are also insulin resistant; and 3) reviewing potential mechanistic links between insulin resistance (and compensatory hyperinsulinemia) and the development of hypertension.

Measurement and Regulation of Insulin Resistance

Dr. Reaven began his lecture with an overview of insulin resistance (IR), in terms of how the condition is defined, measured and regulated. Since the late 1960s, he noted, a method of measuring IR has been to quantify insulin-mediated glucose uptake. Using this method, researchers are able to measure subjects' steady-state plasma glucose concentration (SSPG), identifying those with higher values as being more insulin resistant and those with lower values as more insulin sensitive.

Dr. Reaven presented data showing

deciles of SSPG across a population of apparently healthy subjects. These data, he noted, illustrate that there is a continuous distribution of insulin action across such populations. Moreover, he continued, the deviation from lowest to highest decile is between 600% and 800%—a difference which does not exist for any other well known variable among apparently healthy people.

Having established that insulin action can vary significantly between individuals, Dr. Reaven went on to discuss the factors that regulate this action. One factor, he said, is how overweight an individual is. The relationship between body mass index (BMI) or waist circumference (both markers of adiposity) and SSPG has been recognized, with higher adiposity being associated with higher likelihood of IR.

The other major variable regulating insulin action, Dr. Reaven continued, is how fit an individual is. Measuring fitness by maximal aerobic capacity (expressed as VO_2 max), Dr. Reaven was able to show that higher levels of fitness are associated with higher levels of insulin sensitivity.

In other studies designed to control for each of these variables ("fatness" and fitness), Dr. Reaven showed that each variable accounted for approximately 25% of the observed person-to-person variation in insulin action. In a very recent study, in fact, each of these factors was shown to predict diabetes to about the same extent.

With approximately 50% of the person-to-person variation in insulin action being accounted for by "lifestyle" factors (overweight and fitness), researchers are working to better understand the other factor(s) involved. Much focus has been

on possible genetic or familial relationships. In one study (of Pima Indians), significant aggregation of in vivo insulin action (at the high insulin infusion rate) was observed among siblings, and family membership independently accounted for about 34% of the variance observed between individuals.

Overall, Dr. Reaven said, based on these and other data, we can conclude that 50% of insulin action is determined by lifestyle factors, while the other 50% seems clearly related to family history and is very likely genetic (though the specific genes involved have yet to be determined). As well, there are very powerful ethnic differences: one study showed SSPG levels roughly twice as high in South Asian Indians compared to well matched subjects of European ancestry.

IR and Hypertension

Dr. Reaven went on to discuss the relationship between IR, compensatory hyperinsulinemia and essential hypertension, pointing out that patients with IR who are not diabetic must be hyperinsulinemic.

He presented data showing results of glucose-tolerance tests in a "normal" population, a group of patients with untreated hypertension, and a group receiving antihypertensive treatment. Plasma glucose levels, he showed, were slightly higher in both groups of hypertensive patients, while plasma insulin levels were much higher in these two groups compared to the normal group. Together, this glucose intolerance and hyperinsulinemia strongly suggest IR in the hypertensive patients. In another study, measuring glucose levels and insulin levels throughout the day in normotensive and



hypertensive subjects (matched for all other important variables), in response to “mixed meals,” showed that the hyperinsulinemia observed in hypertensive patients is not simply a function of the glucose-tolerance test but in fact present throughout the day. Hypertensive patients were shown to have IR as a group, regardless of whether or not they were receiving antihypertensive therapy.

As well, Dr. Reaven showed that there is a significant increase in IR levels in those who are first-degree relatives of people with essential hypertension. This observation has been made even in relatively young, normotensive first-degree relatives, illustrating the importance of family history of essential hypertension in determining IR.

Inversely, Dr. Reaven presented data from several prospective studies showing that insulin (and the surrogate measure of IR) can predict the presence or development of hypertension, and is therefore considered a significant risk factor for hypertension.

A common question based on these types of data, Dr. Reaven said, is what proportion of people with IR might develop hypertension. In a prospective study, Dr. Reaven and colleagues divided subjects into quartiles of baseline grade of IR. The group in the highest quartile of IR level had roughly twice the risk of developing essential hypertension (compared to the lowest quartile). It is important to understand, however, that not all patients with essential hypertension have IR. In the same population, Dr. Reaven and colleagues estimated that approximately 50% of subjects with essential hypertension had IR and hyperinsulinemia. This estimate, Dr. Reaven said, has been supported by other findings, which have generally ranged between 40% and 60%.

IR and CVD Risk

Next, Dr. Reaven examined the relationship between IR, compensatory hyperinsulinemia, and CVD. To explore this,

Dr. Reaven and colleagues divided the hypertensive individuals from the study mentioned above into a group with IR and a group without IR. Patients with IR were observed to have some degree of glucose intolerance, with much greater plasma glucose response to oral glucose challenge. Not surprisingly, these patients also had a much higher plasma insulin level. Therefore, it was clear that the two groups of hypertensive patients, while matched for all important variables, were metabolically very different.

Approximately half of patients with essential hypertension, Dr. Reaven con-

As well, Dr. Reaven showed that there is a significant increase in IR levels in those who are first-degree relatives of people with essential hypertension. This observation has been made even in relatively young, normotensive first-degree relatives, illustrating the importance of family history of essential hypertension in determining IR.

tinued, also have been consistently shown to have dyslipidemia, with elevated triglycerides (TG), low HDL cholesterol (HDL-C), and an increased LDL:HDL ratio (a known marker of CVD risk). Looking back at the data discussed earlier for relatively young, normotensive first-degree relatives of people with essential hypertension, Dr. Reaven noted that these people (compared to a matched cohort without such a family history) demonstrate higher TG levels, slightly lower HDL-C, higher non-HDL-C (also a known marker of CVD risk), and higher LDL:HDL ratios.

Dr. Reaven and colleagues further examined the association between CVD risk and IR by dividing a population of hypertensive subjects into one group with EKG abnormalities consistent with myocardial ischemia and another group with normal EKG findings. A control group of healthy (normotensive) volunteers was also analyzed. Glucose levels were not significantly different between the groups (being slightly higher in the hypertensive group with abnormal EKGs

compared to the normal-EKG and control groups), while insulin levels were slightly higher in the normal-EKG hypertensives and much higher (by 2-3 fold) in the abnormal-EKG hypertensives (compared to control). Hypertensive patients with abnormal EKGs were also significantly more dyslipidemic (with higher plasma TG levels and lower HDL-C concentrations) compared to controls and hypertensives with normal EKGs.

Dr. Reaven then presented data from the Copenhagen Male Study, in which investigators divided their study population on the basis of fasting plasma TG and

HDL-C concentrations. Three groups were created: a “high TG low HDL-C” group whose TG and HDL-C was in the upper third or lower third, respectively, of the whole population (*i.e.*, dyslipidemia characteristic of IR); a “low TG high HDL-C” group whose TG and HDL-C were in the lower and upper thirds, respectively; and an “intermediate” group whose lipid values did not qualify them for either of the two extreme groups. The investigators then defined interactions between TG-HDL-C groups and four conventional CVD risk factors (smoking, sedentary lifestyle, hypercholesterolemia, and essential hypertension).

In the essential-hypertension analysis, the investigators further divided subjects based on the presence or absence of high BP and tracked the development of ischemic heart disease over time. Normotensive subjects with normal lipid metabolism formed the “baseline” for this analysis. The investigators found that, even in normotensive subjects, the presence of IR-related dyslipidemia (high TG and low HDL-C), was associ-

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New Investigator 2005

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tors of G-protein signaling, pharmacologic regulation of RGS proteins could be used to potentiate or attenuate the actions of endogenous agonists. As we begin to unravel the specific cell signaling pathways controlled by each RGS protein in vivo, we will have a much clearer picture of the potential physiologic effects expected from their pharmacologic manipulation.

One potentially relevant therapeutic target in the treatment of hypertension is RGS2, a molecule for which ablation of

one gene copy results in BP elevation in mice. In this case, identifying drugs that increase RGS2 function would be of potential interest. In other cases, such as for the RhoGEF containing RGS proteins, blocking their ability to engage the Rho/Rho kinase pathway may provide the key to lowering BP.

Lastly, a major challenge of drug development for the treatment of hypertension is finding unique signaling targets whose manipulation will be efficacious but not toxic to other tissues in the body. Therefore, it might be beneficial to study RGS proteins that are only expressed in smooth muscle

cells of the resistance vasculature. In this regard, it is interesting that RGS5 expression is restricted to arterial VSMCs and microvascular pericytes in adult mice. Future studies will hopefully reveal the G-protein pathways that are selectively attenuated by RGS5 function, and whether its activity can be pharmacologically upregulated to decrease arteriolar tone in hypertensive individuals.

*Scott P. Heximer, PhD,
Canada Research Chair, Physiology,
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CHS/Biovail New Investigator.*

CHS Presidential Lecture

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ated with a significant increase in risk of coronary heart disease (CHD). Hypertensive subjects in the "low TG high HDL-C" group were not at significantly greater risk for CHD, while those with essential hypertension in the "high TG low HDL-C" group demonstrated by far the greatest risk.

To further explain the mechanisms by which IR might contribute to CVD risk, Dr. Reaven pointed out that the first step in the process of atherogenesis is the binding of mononuclear cells to the endothelium. In general, higher mean arterial pressure is associated with mononuclear cells that are more adherent to the endothelium. Further dividing subjects by degree of IR, it is clear that degree of IR has an even stronger correlation with mononuclear cell adherence. Hypertension combined with IR is therefore associated with the greatest degree of mononuclear-cell binding to the endothelium.

Similarly, Dr. Reaven continued, it has been shown that plasma concentration of

asymmetric dimethylarginine (ADMA; an endogenous inhibitor of nitric oxide synthase), which is a known predictor of CVD, is increased in normotensive and hypertensive subjects with IR.

Finally, Dr. Reaven discussed what he considers one of the least understood links between IR and compensatory hyperinsulinemia and the genesis of hypertension. He emphasized that not all tissues in the body are insulin resistant, and that many of the negative effects of IR are the result of compensatory hyperinsulinemia acting on normally insulin-sensitive tissues, such as those found in the sympathetic nervous system (SNS) and the kidneys. In the SNS, hyperinsulinemia acts through various mechanisms to increase BP. There is evidence that insulin enhances SNS activity, and heart rate (HR) is a known predictor of IR. Dr. Reaven presented data showing that greater levels of IR are associated with increased HR.

In terms of the action of hyperinsulinemia on the kidneys, Dr. Reaven and colleagues found that subjects given a high-sodium diet retained salt and water only in the presence of IR (and that degree of

IR was therefore associated with the amount of weight subjects gained). In this same study, it was not surprising to see that subjects who gained more weight were also more likely to have significantly increased BP.

Conclusions

Dr. Reaven concluded his presentation by restating that: 1) IR and associated metabolic abnormalities are increased in prevalence in patients with essential hypertension; 2) similar changes are seen in normotensive first-degree relatives of people with essential hypertension; 3) IR and compensatory hyperinsulinemia predict the onset of essential hypertension; 4) IR and associated abnormalities are present in no more than 50% of patients with essential hypertension; 5) CHD occurs primarily in the subset of patients with essential hypertension who also have IR and hyperinsulinemia (with the associated metabolic consequences); and 6) enhanced SNS activity and renal sodium retention in people with IR and hyperinsulinemia increase the risk of developing essential hypertension.

Readers of Hypertension Canada are invited to visit the CHS homepage at www.hypertension.ca and submit suggestions on its improvement.

