Common pathways of hypercholesterolemia and hypertension leading to atherothrombosis: the need for a global approach in the management of cardiovascular risk factors

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Abstract: In the last years there has been increasing evidence suggesting that the treatment of cardiovascular risk factors must be done on a global rather than on a separate approach, because they have additive effects and share common pathways leading to atherothrombosis. Of special interest is the relationship between hypertension and dyslipidemia. An excessive activity of the renin-angiotensin system (RAS), that plays an important role in hypertension, contributes to endothelial dysfunction, vascular inflammation and thrombosis. Dyslipidemia induces the same effects through similar mechanisms. In fact, combined therapy with statins and RAS modulators shows synergic beneficial effects in the treatment of atherosclerosis. Then, in the future, the traditional hypertension and dyslipidemia units should probably evolve into global cardiovascular risk management Units. Also, polypills combining antihypertensive and lipid-lowering drugs will make easier the treatment of these conditions. These changes would provide us the necessary tools to treat our patients in accordance with the current strategies of cardiovascular therapy and prevention.

Keywords: Angiotensin, atherosclerosis, endothelium, hypercholesterolemia, hypertension, inflammation

Many years ago, the Framingham study and other studies began to identify a number of different risk factors as potential causes of atherothrombotic events (Kannel et al 1961; McGill 1996). Treating these risk factors emerged then as a capital task in the fight against cardiovascular disease. However, this approach has evolved notoriously in the last years. In the initial era, cardiovascular risk factors (CRF) were assessed and treated separately, but later, the avalaible information has shown us that this work has to be done based on a global approach. Clinical studies have demonstrated that CRF act in a synergistic way. In addition, we have learned from pathophysiological studies that there are mechanistic links between the pathways through which different CRF cause atherothrombosis. In this regard, of special interest is the relationship between the pathophysiology of hypertension and dyslipidemia.We will focus on the clinical and pathophysiological data relating to the development of these two factors, to support the concept of a global management of the patient with CRF.

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Combined antihypertensive and lipid lowering therapies in the clinical practice

A large number of clinical trials has demonstrated that treatment of either hypercholesterolemia or hypertension leads to a reduction in the incidence of cardiovascular

events. Also, statins and angiotensin converting enzyme (ACE) inhibitors demonstrated an additive effect reducing the incidence of cardiovascular events (Yusuf et al 2000; Heart Protection Study Collaborative Group 2002).

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) studies have shed new light into this matter. The ASCOT-BPLA (Blood Pressure Lowering Arm) analyzed 19,257 patients with hypertension and at least three other cardiovascular risk factors, which were randomized to therapy with amlodipine, adding perindopril when necessary, or to atenolol, using bendroflumethiazide as a second drug (Dahlof et al 2005). By the end of the trial, 78% of patients were taking the second antihypertensive drug, and the amlodipine/perindopril regimen was superior to atenolol in terms of all-cause mortality, stroke, total cardiovascular events and procedures and new-onset diabetes.

When several variables of the ASCOT-BPLA were analyzed, blood pressure reduction was not the only contributor to the amlodipine/perindopril decrease in cardiovascular events (Poulter et al 2005). Interestingly, although blood pressure was the most important variable associated with the incidence of stroke, differences in HDL cholesterol were more important for coronary events. Furthermore, full adjustment for these variables as well as for bodyweight, and glucose, triglycerides, creatinine and potassium serum levels explained only 50% and 40% of the differences in coronary and stroke events, respectively, leaving the remaining percentages to be potentially explained by other variables not considered in this analysis. These data suggest that blood pressure reduction is not the only mediator in the beneficial effect of antihypertensive drugs. Accordingly, several vasculoprotective mechanisms have been demonstrated for anti-hypertensive drugs, the most important of which have been described for those that modulate the renin-angiotensin system (RAS). The same holds true for statins, which have been claimed to exert a part of their beneficial actions by cholesterol-independent mechanisms (Blanco-Colio et al 2003; Ray et al 2005).

The ASCOT-LLA (Lipid Lowering Arm), published in 2003, showed data of further interest (Sever et al 2003). Ten thousand three-hundred five patients from the ASCOT-BPLA study with total cholesterol concentrations of 6.5 mmol/L or less were randomized to atorvastatin 10 mg/d or placebo. Treatment with the statin reduced the incidence of non-fatal myocardial infarction or fatal coronary heart disease and that of stroke, cardiovascular and coronary events. Thus, using statins in patients with moderately increased or even normal cholesterol levels, but at risk of cardiovascular events because of accompanying hypertension and other CRF, improved their clinical evolution. Remarkably, in the ASCOT-BPLA, an optimal prevention of cardiovascular events was reached in patients randomized to atorvastatin and the amlodipine/perindopril treatment, with a reduction of 48% in the risk of fatal myocardial infarction and non-fatal coronary heart disease and 44% in the incidence of stroke (http://www.broadshow.com/ascot/press-material.php).

Dyslipidemia and hypertension share common pathways leading to atherothrombosis

Three findings are of special interest in the above-mentioned data. First, a statin, a cholesterol-lowering drug, is beneficial in the treatment of patients who are at risk of cardiovascular events because of the coexistence of several risk factors for atherothrombosis, even when their cholesterol levels are normal or only moderately elevated. Second, blood pressure control and lipid lowering seem not to account for all the reduction achieved by antihypertensive and statin treatments respectively. And, third, the combination of a statin and an effective antihypertensive regimen leads to the best prevention results.

These facts suggest that the pathophysiologic pathways that link hypertension and dyslipidemia to atherothrombosis may share common mechanisms, and this may be similar for other cardiovascular risk factors. This idea is supported by clinical data showing that statins may diminish blood pressure levels (Glorioso et al 1999). However, most evidence supporting this possibility comes from basic research. In this setting, the enhanced activity of the RAS, which plays an important role in hypertension, can activate similar mechanisms to dyslipidemia in endothelial dysfunction, inflammation and thrombosis.

Endothelial dysfunction in the crossroad between hypertension and dyslipidemia

All major atherothrombotic risk factors induce endothelial dysfunction. The key feature in this disorder is a reduced availability of nitric oxide (NO) due to both a decrease in its synthesis and to an enhanced degradation. Hypercholesterolemia plays an important role in this setting,

as oxidized LDL diminishes the expression of endothelial NO synthase (eNOS) (Laufs et al 1998). Furthermore, in hypercholesterolemia there is an increase of asymmetric dimethylarginine levels, an eNOS endogenous inhibitor (Ito et al 1999). Angiotensin (Ang) II may also downregulate eNOS expression via protein-kinase C (Harrison et al 1995), thus leading to a decrease in NO production. In addition, both hypercholesterolemia and Ang II can participate in NO degradation. Oxidized LDL contributes to oxidative stress, where superoxide anion is generated by endothelial oxidase enzymes. Superoxide reacts with NO yielding peroxynitrite ($ONOO^-$), a compound which, in high amount, works as a strong oxidant and is toxic to proteins (Ischiropoulos et al 1995). On the other hand, Ang II is a powerful oxidant agent that increases superoxide anion production through NADH/NADPH in vivo an in vitro via AT1 receptors (Rajagopalan et al 1996). Angiotensin II can generate reactive oxygen species (ROS), which activate different intracellular signaling cascades, including mitogen-activated protein kinases (MAPK) and the transcription factor NF-κB (Hernández-Presa et al 1997; Ushio-Fukai et al 1998). Statins are able to counterbalance the effect of oxidative stress, and decrease the NF-κB activity induced by superoxide anion (Ortego et al 1999).

In the setting of endothelial dysfunction, there is an increase in vascular permeability to LDL, which becomes oxidized in the arterial wall where the macrophages uptake them evolving into foam cells. These processes are promoted by AT1 receptor activation (Keidar et al 1997). In fact, the expression of the oxidized LDL receptor LOX is enhanced through AT1 activation (Morawietz et al 1999). Moreover, the expression of this receptor is induced by LDL in vascular smooth muscle cells, and is enhanced in experimental models of atherosclerosis (Nickenig et al 1997; Warnholtz et al 1999). In addition, ACE is present in greater amounts in atherosclerotic plaques (Diet et al 1996). Thus, lipid-lowering drugs are not the unique strategy to lessen these LDL-related biological processes. In agreement with these data, angiotensin receptor blockers (ARBs) have been shown to decrease atheroma formation (Warnholtz et al 1999).

According to all this evidence, multiple studies in the literature have demonstrated that both statins and RAS inhibitors improve the endothelial function in human beings (Mancini et al 1996; O'Driscoll et al 1997; Tuñón et al 2004; Ceriello et al 2005). Furthermore, there is an additive effect of hypertension and dyslipidemia. The infusion of Ang II in patients with hypercholesterolemia increases blood pressure and AT1 expression more than twice as compared with healthy subjects, and these responses are normalized by treatment with statins (Nickenig et al 1999). Finally, the combination of a statin and an ARB are superior to each drug alone in reducing the extent of atherosclerosis and the expression of LOX-1 and p38 MAPK in the apo-E knockout mice (Chen et al 2006). This fact reinforces the idea of the interplay between the atherothrombotic pathways of the RAS and hypercholesterolemia.

Common pathways to inflammation for Ang II and dyslipidemia

Another important feature in the pathophysiology of atherothrombosis is inflammatory cell recruitment into the vascular wall. This phenomenom is due to the expression of adhesion and chemoattractant molecules by the endothelium, which is regulated, among others, by the transcription factor NF-κB (Barnes et al 1997). This transcription factor plays a key role in the atherothrombotic process, since it also controls the expression of many other proinflammatory and prothrombotic proteins, including that of tissue factor, the trigger of thrombosis in the atheroma plaque. The activation of NF-κB is enhanced, among other stimuli, by ROS and oxLDL, and inhibited by HDL (Barnes et al 1997; Xu et al 1999; Robbesyn et al 2003). In this regard, we have shown that statins decrease NF-κB activity in vitro and in a rabbit model of atherosclerosis (Bustos et al 1998; Ortego et al 1999). However, we have also demonstrated that Ang II is able to induce NF-κB activity in cultured monocytic and vascular smooth muscle cells (Hernández-Presa et al 1997). In this effect, Ang II-induced ROS generation may play an important role, as it was inhibited by pyrrolidinedithiocarbamate (Ortego et al 1999). In fact, ARB treatment diminishes free radical generation and NF-κB binding in mononuclear cells of healthy subjects (Dandona et al 2004).

In addition, Ang II induces leukocyte-endothelial cell interactions and upregulates the expression of several adhesion molecules and chemoattractant cytokines, including MCP-1 (monocyte chemoattractant protein-1), IL-6 (interleukin-6), and IL-8, mainly through AT1 receptors (Hernandez-Presa et al 1997; Schieffer et al 2000; Ito et al 2002; Riaz et al 2004). In addition, RAS inhibitors decrease inflammation in human beings and in experimental models of atherosclerosis (Hernández-Presa 1997, 1998; Cipollone et al 2004; Fliser et al 2004). For instance, the ARB irbesartan reduces macrophage infiltration, and the expression of the proinflammatory enzyme cyclooxygenase-2 (COX-2) and metalloproteinases in human carotid plaques (Cipollone et al 2004). Also, olmesartan has demonstrated recently to

diminish plasma levels of C reactive protein, TNF-α, IL-1 and MCP-1 in patients with arterial hypertension and micro-inflammation (Fliser et al 2004).

With regard to statins, there is a huge amount of information showing that they may downregulate the NF-κB pathway, decreasing the expression of adhesion molecules, chemoattractant cytokines, that of the proinflammatory enzyme COX-2 and plasma levels of several inflammatory markers (Bustos et al 1998; Hernández-Presa et al 1998; Ortego et al 1999; Blanco-Colio et al 2003). In this regard, we have demonstrated that atorvastatin decreases NF-κB activity, MCP-1 expression and macrophage infiltration in human atherosclerotic plaques in only one month of treatment (Martín-Ventura et al 2005). Of interest, the expression of metalloproteinases is enhanced by Ang II in smooth muscle cells and reduced by statins (Luan et al 2003; Luchtefeld et al 2005). Furthermore, statins are able to inhibit the Ang II-induced expression of MCP-1 and IL-8 in vascular smooth muscle cells (Ortego et al 1999; Ito et al 2002), confirming the interaction between the inflammatory pathways triggered by dyslipidemia and the RAS. Finally, the combination of atorvastatin and irbesartan reduced C-reactive protein and IL-6 levels more effectively than each of two drugs alone in diabetic patients (Ceriello et al 2005).

There are other crosslinks between RAS and statins in inflammation. Vascular permeability is augmented by Ang II via AT1 receptors, while it is decreased by statins (Bonetti et al 2002; Victorino et al 2002). Ang II and dyslipidemia share also their effects on fibrosis, the part of the inflammatory process that repairs the damaged tissue, but that in atherosclerosis also results in plaque growth. In this sense, the expression of PDGF (platelet-derived growth factor), TGF-β1 (transforming growth factor-β1) and CTGF (connective tissue growth factor), that mediate the growth-promoting effect of Ang II, is reduced not only by ARBs and ACE inhibitors, but also by statins (Grandaliano et al 1993; Wong et al 1997; Kim et al 2000; Iwanciw et al 2003; Rupérez et al 2003). Moreover, these drugs are able to decrease Ang II-induced expression of CTGF (Iwanciw et al 2003).

Lipids, RAS and thrombosis

Thrombosis is a critical component of the atherosclerotic disorder, and leads to acute coronary syndromes and ischemic stroke. It begins with platelet adhesion and aggregation, followed by activation of the coagulation cascade. Tissue factor activation is the first step of the cascade coagulation in vascular thrombosis, and this factor is present in the lipid core component of the atherosclerotic plaques (Toschi et al 1997). Platelets express AT1 receptors, and ACE inhibitors and ARBs have been demonstrated to inhibit platelet aggregration (James et al 1988; Crabos et al 1993; Schieffer et al 2004). Also, losartan works as a competitive antagonist of thromboxane A_2, a compound derived from COX-1 activity which induces platelet aggregation (Corriu et al 1995). Statins also interfere with these pathways, as they diminish platelet aggregation, thromboxane A_2 synthesis and thrombin-induced tissue factor expression in endothelial cells (Davi et al 1992; Notarbartolo et al 1995; Eto et al 2002). Moreover, Ang II induces tissue factor expression in human monocytes via the protein kinase C pathway, and ARBs decrease tissue factor activity in hypertensive patients (Koh et al 2004; He et al 2006). Also, RAS is involved in the regulation of the endogenous fibrinolytic system. Ang II induces the expression of the inhibitor of spontaneous thrombolysis PAI-1 (plasminogen activator inhibitor type 1), and RAS inhibitors decrease PAI-1 plasma levels, which are enhanced following a myocardial infarction (Wright et al 1994; Koh et al 2004). Moreover, ACE inhibitors block bradykinin degradation, and this peptide induces the expression of t-PA (tissue plasminogen activator) (Vaughan et al 1995). Similarly, statins increase the synthesis of t-PA and decrease PAI-1 (Essig et al 1998; Bourcier et al 2000). Very recently, we have observed that intensive treatment with atorvastatin after an acute coronary syndrome enhances the expression of annexin II, a receptor for tissue plasminogen activator and plasminogen, in circulating monocytes (Tuñón et al 2007). In conclusion, Ang II and dyslipidemia also act through common mechanisms to promote thrombus formation, which is ultimately responsible for acute ischemic events in atherothrombosis. Combining adequately RAS modulators with statins may reduce the probabilities of developing cardiovascular events by interfering with these actions.

Clinical implications

Several pathways of the essential biological processes in atherothrombosis are shared by dyslipidemia and Ang II, and these mechanisms are targets for RAS modulators and statins. Then, the isolated approach to the treatment of separated risk factors for atherothrombosis seems to be over, since evidence from basic and clinical research clearly indicates that the pathways by which multiple risk factors lead to this disorder are strongly interrelated. In fact, cur-

rent practice guidelines for the management of hypertension and dyslipidemia take into account the existence of other risk factors to advice the intensity of antihypertensive and cholesterol-lowering therapy. Moreover, polypill combinations of antihypertensive and lipid-lowering drugs are already available in one tablet, such as amlodipine and atorvastatin (CADUET), and others, such as ARB and statins, will be probably coming soon. It follows that the next step for this approach should be the evolution of the traditional hypertension and dyslipidemia Units into cardiovascular risk management departments. These changes would provide the necessary tools to treat our patients in accordance with the current strategies of cardiovascular therapy and prevention.

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