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Resistant Hypertension, Elevated Aldosterone/Renin Ratio and Reduced RGS2: A Pathogenetic Link Deserving Further Investigations?

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1. Introduction

Hypertension control is unsatisfactory in most countries and it carries an unacceptably high cardiovascular risk and death toll (Mancia et al., 2007) The reasons for the poor blood pressure control are different and interrelated (motivation of patients and physicians, costs, compliance, access to health care, secondary and resistant hypertension). Among them, resistant hypertension is receiving considerable attention, as it may be caused by unrecognized secondary hypertension, mainly primary aldosteronism (PA).

We have recently shown in patients with resistant hypertension elevated aldosterone / renin ratio (ARR) and reduced RGS2 expression. We, therefore, hypothesize that in many patients resistant hypertension is secondary to disproportionate aldosterone secretion caused by blunted inhibition of angiotensin II (Ang II) cellular effects due to low RGS2 expression.

2. Resistant or uncontrolled hypertension

Resistant hypertension is defined as blood pressure remaining above the goal levels in spite of the concurrent use of three antihypertensive agents of different classes at the same time, with diuretic as one of the three agents and all agents prescribed at optimal dose (Calhoun et al., 2008). This implies that also patients whose blood pressure needs four or more drugs to be controlled should be considered resistant to treatment. Resistant hypertension identifies patients who are at a high risk of having secondary and reversible causes of hypertension or patients who may benefit from further diagnostic and therapeutic work up. Uncontrolled hypertension is not synonymous of resistant hypertension as uncontrolled hypertension includes patients who do not reach blood pressure control due to poor adherence or an inadequate treatment regimen, as well as patients with true treatment resistance.

2.1 Prevalence

The prevalence of resistant hypertension is unknown, even if according to the literature it is not an uncommon condition: the majority of studies indicate that less than 40% of elderly

patients reach a goal blood pressure with drugs. Among high risk populations and, in particular with application of the lowest blood pressures goal recommendation of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) for patients with diabetes mellitus or chronic kidney disease, the percentage of uncontrolled hypertensive patients is even higher.

2.2 Prognosis

Prognosis of patients with resistant hypertension compared with patients with drug controlled hypertension is likely to be worse due to the long history of poorly controlled or uncontrolled hypertension and the presence of commonly associated cardiovascular risk factors, such as obstructive sleep apnea, diabetes, left ventricular hypertrophy and chronic kidney disease. Yet, no clinical trial has been conducted to specifically evaluate its associated increased risk.

The cardiovascular risk reduction associated to the treatment of resistant hypertension is unknown. The benefits of effective treatment, however, are supposed to be substantial, as suggested by several outcome studies, and, therefore, achievement of goal pressure levels should always be urged.

2.3 Patient characteristics

Populations who are at the highest risk of developing resistant hypertension have been investigated. The strongest predictors of treatment resistance are chronic kidney diseases, obesity and diabetes mellitus. Differences between races and genders have been reported, since blacks and women are at higher risk of resistant hypertension.

Blood pressure is considered uncontrolled most often because of persistent elevation of systolic values as patients treated with antihypertensive drugs reach correct diastolic more easily than systolic values. This diversity in systolic versus diastolic blood pressure control worsens with increasing age of patients, as arterial stiffness (strongly related with age) is the main cause of isolated systolic hypertension. This explains why the strongest predictor of the lack of blood pressure control is old age. High baseline systolic pressure was associated with increased risk of never reaching goal blood pressure (Lloyd-Jones et al., 2002). Other strong predictors of poor systolic blood pressure control are the presence of left ventricular hypertrophy and obesity (that is, body mass index [BMI] greater than 30 kg/m2). The prevalence of resistant hypertension is predicted to increase in older and heavier cohorts in association with the growing prevalence of diabetes and chronic kidney disease.

In terms of poor diastolic pressure control, the strongest negative predictor is obesity, with goal blood pressure reached one third less often in obese than in lean patients.

2.4 Genetics / pharmacogenetics

The genetics of hypertension is complex and there is no known single gene playing a major role, but rather many different genes contributing all together with different environmental factors in rising blood pressure. Due to its particular type, it is reasonable that in resistant hypertension genetic factors may play an even greater role than in the general hypertensive population. However, in resistant hypertensive population, genetic studies are limited and

based on a very small number of patients, even if identification of genetic influences on resistance to current therapies might lead to development of new therapeutic targets. Gene variants of ENaC (epithelium sodium channel) (Hannila-Handelberg et al., 2005) and of CYP3A5 enzyme (11β-hydroxysteroid dehydrogenase type 2) (Givens et al., 2003; Ho et al., 2005) have been demonstrated, focusing attention on sodium homeostasis, and on cortisol and corticosterone metabolism but the clinical relevance of these mutations is unclear.

2.5 Pseudoresistance

Pseudoresistance is the condition of poor blood pressure control with no real treatment resistance and no coexisting factors causing persistently high blood pressure values. There are many causes of pseudoresistance that can be related either to medical or to lifestyle factors. These conditions should be kept in mind and carefully searched in resistant hypertensive patients to avoid incorrect classification of hypertension.

Among the medical related causes of pseudoresistant hypertension, the most frequent are poor blood pressure measurement techniques, poor adherence to therapy, white-coat effect and drug-related causes.

Poor blood pressure technique consists in inaccurate measurement of blood pressure, resulting falsely high. Blood pressure should be measured only after the patient has been sitting quietly for a few minutes and with the use of adequate size cuff, not too small as it often happens. (Pickering et al., 2005) Poor adherence to therapy is probably the main cause of the lack of blood pressure control (Yiannakopoulou et al., 2005): near 40% of newly diagnosed hypertensive patient discontinue therapy during the first year of drug treatment (Caro et al., 1999; Mazzaglia et al., 2005) and 60 % of patients at five and ten year follow up show poor adherence to the suggested treatment (Van Wijk et al., 2005) . It should be noticed that the percentage of poor adherence to therapy falls from 40 to 15 % when the patients are seen in hypertension specialist clinic rather then at primary care.

White-coat effect consists in clinic blood pressure values persistently elevated while out-of-office values are normal or significantly lower (Brown et al., 2005) . The prevalence of this condition is similar in patients with resistant hypertension and in the general hypertensive population, with values in the range of 20% to 30%. It can be identified with ambulatory blood pressure recording showing normal out of office blood pressure values (Redon et al., 1998; Muxfeldt et al, 2003; Pierdomenico et al., 2005).

Drug-related causes are due either to incorrect antihypertensive drug assumption or to drug interactions. Identification of poor adherence is clinically relevant to stop useless continuous modification of the treatment regimens and further investigations. Drug interactions should always be looked for, in particular in those patients assuming complex combination therapies. Several classes of drugs can increase blood pressure and contribute to treatment resistance:

- stimulants (dextroamphetamine, amphetamine, methamphetamine, methylphenidate, dexmethylphenidate) ;
- sympathomimetic agents (like nasal decongestants, diet pills and cocaine);
- NSAIDs - Nonsteroidal antiinflammatory agents, including selective COX-2 inhibitors;
- alcohol;

- glucocorticoids (such as prednisone);
- corticosteroids (mainly the ones with the greatest mineralcorticoid effect such as cortisone and hydrocortisone);
- oral contraceptives;
- cyclosporine and calcineurine inhibitors;
- erythropoietin;
- Natural products such as licorice (common in oral tobacco products) or herbal compounds (ephedra or ma huang).

The effect of these agents is highly variable with most patients manifesting little or no effect and other individuals showing severe blood pressure elevations (Radack et al., 1987; Conlin et al., 2000). Due to large use and wide distribution, non narcotic analgesics are probably the most common interacting medicaments with antihypertensive drugs (Dedier et al, 2005; Forman et al., 2005). NSAIDs induced blood pressure increase is modest but predictable, apart from patients with significant fluid retention and/or acute kidney disease in which there is subsequent sodium and fluid retention and rebound pressure relevant increase due to inhibition of renal prostaglandin production.

Among lifestyle factors the most relevant are obesity, excessive dietary salt and alcohol intake. Obesity is associated with the need for an increased number of antihypertensive medications, a more severe hypertension and increased probability of difficult achieving or never achieving appropriate blood pressure control (Bramlage et al., 2004). Mechanisms of obesity-induced hypertension are multiple, complex and not fully understood: activation of the renin-angiotensin-aldosterone system, impaired sodium excretion and increased sympathetic nervous system activity (Hall et al., 2003). As a consequence, obesity is a common feature of patients with resistant hypertension (Nishizaka et al., 2005).

Excessive dietary salt intake sustains resistant hypertension both by increasing blood pressure directly and by decreasing the effect of most classes of antihypertensive agents (Weinberger 1988; He & MacGregor, 2004; Luft & Weinberger, 1988;). These effects are mainly found in salt-sensitive patients, like the elderly, those suffering from chronic kidney disease (Boudville et al, 2005) and both African and American races.

Alcohol intake at high doses is associated with increased risk of hypertension and resistant hypertension. Epidemiological studies have shown a direct relationship between alcohol intake and blood pressure, which is particularly evident when 28 g of ethanol per day are exceeded (Henningsen et al., 1980; Aguilera et al., 1999; Wildman et al., 2005). All the subpopulations that have been analyzed (males, females, Caucasian and African race) show a blood pressure increase related to alcohol consumption, but the African race shows a blood pressure greater raise compared to Caucasians at the same intake. Chronic daily intake of alcohol it is not required for the hypertensive effect, since it has been proven that also consumption confined to only a few days a week is associated with increased blood pressure. Prospective studies have demonstrated that cessation of heavy alcohol ingestion reduced 24-hour ambulatory systolic blood pressure.

2.6 Secondary causes

Secondary causes of hypertension are common among patients with resistant hypertension, mainly in older patients due to high incidence of sleep apnea syndrome, renal parenchymal

disease, diabetes mellitus, renal artery stenosis and primary aldosteronism. Uncommon causes of secondary resistant hypertension include pheochromocytoma, Cushing's syndrome, hyperparathyroidism, aortic coarctation.

2.6.1 Obstructive sleep apnea

Obstructive sleep apnea is strongly associated with hypertension. In normotensive subjects it predicts development of hypertension, and it is very common in patients with resistant hypertension (Nieto et al., 2000; Peppard et al., 2000). There is a significant gender distribution, with males more affected than females. The more severe and untreated is sleep apnea syndrome, the less likely is blood pressure controlled despite the use of polymedications (Grote et al., 2000; Lavie & Hoffstein, 2001) Sleep apnea seems to create and maintain hypertension by increasing sympathetic nervous system (SNS) activity generated by intermittent hypoxemia; the SNS hyperactivation increases cardiac output, peripheral vascular resistances and fluid retention (Grassi et al., 2005).

2.6.2 Renal parenchymal disease

Renal parenchymal disease is both cause and complication of uncontrolled hypertension. Serum creatinine higher than of 1.5 mg/dL is a strong predictor of failure to achieve blood pressure goal, due to increased sodium and water retention and intravascular volume expansion (Klahr et al., 1994; Buckalew et al., 1996).

2.6.3 Diabetes

Diabetes and hypertension are commonly associated, in particular in patients with resistant hypertension. Diabetes associated insulin resistance is supposed to contribute to the development of hypertension directly through sympathetic nervous activity, vascular smooth muscle cell proliferation, and increased sodium retention with intravascular volume expansion (Bakris, 2001) .

2.6.4 Renovascular disease

Renal artery stenosis is a common finding in resistant hypertension, with several studies suggesting a percentage of renovascular disease in resistant hypertension between 12 and 15%. More than 90% of renal artery stenoses have an atherosclerotic origin, with increased incidence in smokers, older patients, and widespread atherosclerotic disease (Aqel et al., 2003; Cuckson et al., 2004). Less than 10% of renal lesions are fibromuscular in etiology, developing particularly in young women. Specific diagnostic studies should be performed when renovascular disease is suspected, such as ultrasound, magnetic resonance angiography (MRA), renal scintigraphy, and computed tomography angiography (Leiner et al., 2005).

2.6.5 Pheochromocytoma

Pheochromocytoma accounts for a small number of secondary causes of resistant hypertension. Its prevalence is 0.1% to 0.6% among hypertensive patients, and even if the prevalence as a cause of resistant hypertension is unknown, it has to be underlined that 95% of pheochromocytomas show hypertension at clinical onset and 50% have resistant

hypertension (Omura et al., 2004; Sinclair et al., 1987). It should be suspected in every hypertensive patient with headaches, palpitations, and sweating, typically occurring in an episodic way; not all pheochromocytomas show up with these typical symptoms, and this is the reason why there is often a delay between the initial symptoms and the final diagnosis, with an average delay of three years. Moreover, pheochromocytoma is characterized by increased blood pressure variability due to inconstant catecholamine release, which represents an additional independent risk factor beyond increased blood pressure itself for cardiovascular morbidity and mortality (Kikuya et al., 2000; Björklund et al., 2004; Zelinka et al., 2005).

2.6.6 Cushing's syndrome

The mechanism that causes hypertension in Cushing's syndrome is overstimulation of the nonselective mineralocorticoid receptor by cortisol (Moneva & Gomez-Sanchez, 2002; Ferrari, 2003) , even if other factors contribute to hypertension in this disease, such as sleep apnea and insulin resistance (McFarlane et al, 2001) .

Cortisol is the hormone which is mainly increased in Cushing syndrome and hypertension is present in 70-85% of patients suffering from this syndrome. Hypertension is often resistant because of the cortisol dependent pressor activity: the most common therapeutic agents (renin-angiotensin system blockers, calcium channel antagonists, adrenergic blockers, and diuretics) are frequently ineffective. The most effective antihypertensive agents are mineralocorticoid receptor antagonists (such as spironolactone or eplerenone), but frequently only surgical removal of an adrenocorticotropic hormone (ACTH) or another cortisol-producing tumor allows effective blood pressure control. Target organ damage and overall cardiovascular risk in Cushing's syndrome is more severe than in primary hypertension, because the disease is associated with other cardiovascular risk factors such as metabolic syndrome, diabetes mellitus, obesity, sleep apnea syndrome, and dyslipidemia (Sacerdote et al., 2005).

3. Primary aldosteronism and resistant hypertension

Primary aldosteronism (PA) is a clinical condition sustained by overproduction of the mineralocorticoid hormone aldosterone by the adrenal glands. The overproduction is relatively independent by the renin-angiotensin system (RAS) activity, and non suppressible by sodium loading. PA was considered to be a rare cause of secondary hypertension until recently. Early epidemiologic studies have claimed the prevalence of PA to be less than 1% of hypertensive patients. On the contrary, there is evidence from several recent studies that PA is a much more common cause of resistant hypertension than had been suspected before, and particularly common in patients with resistant hypertension, its prevalence being between 10 and 15% among patients with severe hypertension (Gordon et al., 1994; Fardella et al., 2000; Mosso et al., 2003). Several authors have suggested a direct role of aldosterone autonomy as a mechanism for drug resistance and have recommended the search for primary aldosteronism in cases of severe or drug resistant hypertension as primary aldosteronism was found in 20% of patients with resistant hypertension. Primary aldosteronism is, therefore, the most common cause of secondary hypertension.

Bilateral idiopathic hyperaldosteronism (IHA) and aldosterone-producing adenoma (APA) are the most common subtypes of primary aldosteronism. A rarer cause of primary aldosteronism, unilateral hyperplasia or primary adrenal hyperplasia, is generated in a single adrenal gland by hyperplasia of the zona glomerulosa. Two forms of familial hyperaldosteronism (FH) have been described: FH type I and FH type II. FH type I, or glucocorticoid-remediable aldosteronism, is autosomal dominant in inheritance and associated with variable degrees of hyperaldosteronism, high levels of hybrid steroids (e.g. 18-hydroxycortisol and 18-oxocortisol), ameliorated by exogenous glucocorticoids. FH type II refers to the familial occurrence of APA or IHA, or both (Young, 2003) .

A number of studies demonstrate that primary aldosteronism is strongly associated with target organ damage and elevated rate of cardiovascular events. Indeed, hyperaldosteronism produces oxidative stress with oxidative damage to DNA, inflammation, and nongenomic effects (with cardiovascular remodeling, hypertrophy, fibrosis, endothelial dysfunction and increased arterial stiffness). This reflects in increased cardiovascular events, such as impaired systolic and diastolic ventricular function, atrial fibrillation, microalbuminuria, increased incidence of ischemic and hemorrhagic stroke, pulmonary edema and myocardial infarction. (Takeda et al., 1995; Rocha et al., 2002; Farquharson & Struthers, 2002; Sechi et al., 2006; Rossi et al., 2008; Schupp et al., 2010).

3.1 Diagnosis

Diagnosis of PA is made by a three step approach: screening; confirmation / exclusion; subtype diagnosis. Serum potassium level cannot be used as an indicator of the presence of hidden primary aldosteronism due to high prevalence of normokalemic PA, and the prevalence of hypokalemia increasing with severity of hypertensive disease. These data suggest that hypokalemia is a late manifestation of the disorder following the onset of hypertension.

3.1.1 Screening test

Resistant hypertension is enlisted among the subtypes of hypertension which should undergo a screening test for primary aldosteronism (Funder et al, 2008) .

There is general consensus that ARR is the most reliable available mean for primary aldosteronism screening, a validated and assured index of inappropriate aldosterone activity, and a valid screening assay even without discontinuation of antihypertensive medications (Gallay et al., 2001). ARR provides the best parting of patients with primary aldosteronism from essential hypertensive subjects. However, there is no agreement on the ARR cut-off value and on whether the absolute aldosterone level should also be taken into account. It should be noted that the optimal ARR cut-off value (as well as the aldosterone level after confirmatory test) is dependent on the assay used to measure aldosterone. Different assays, although demonstrating good overall correlation with one another, often show significant differences in absolute aldosterone concentrations (Pizzolo et al., 2006). In order to compare results from different studies and to use the same cut-offs for screening and confirmation, aldosterone assays thus need to be standardized. Moreover, ARR is strongly dependent on plasma renin activity (PRA), so that anyone with suppressed PRA will have increased ARR: this implies that ARR needs to be interpreted in light of

aldosterone plasma level (>15 nd/dL) and the lowest detectable level of PRA. Another debated issue is the use of direct active renin assay instead of PRA. PRA and direct renin are closely and strongly correlated, but the correlation is weaker for the low range of values compared with the high/normal range of values (Hartman et al., 2004) .

3.1.2 Confirmatory testing

Because of the high prevalence of low renin hypertension, it is important to stress that increased ARR is not diagnostic of PA by itself, and a confirmatory test is most often required. This is to avoid a large number of hypertensive patients inappropriately undergoing costly and potentially harmful procedures. The choice of the test remains a matter of debate and there is currently insufficient direct evidence to recommend one in particular. The most widely used and approved by the guidelines tests are: fludrocortisone suppression test (FST), intravenous saline load test (SLT), oral sodium loading test (OLT) and captopril challenge (CC). FST, SLT and OLT include the administration of salt and thus should be considered preferable to CC for confirming PA (Mulatero et al., 2010). CC has the advantage of being relatively cheap, safe, well tolerated and easy to perform. Because of the high rate of false positive diagnoses to which it is related, it should only be used in patients at risk of volume expansion.

3.1.3 Subtype differentiation

All patients affected by PA should undergo an adrenal HTCT scan as the initial study for subtype differentiation in order to rule out an adrenocortical carcinoma. Magnetic resonance offers no advantage over CT, and adrenal scintiscan with [6 -131I] iodomethyl-19-norcholesterol has a low sensitivity and specificity for APA. CT scanning should be performed by an expert and motivated radiologist to diminish inadequacy of CT scanning to distinguish between APA and IHA because of small size of some adenomas. The Endocrine Society Guidelines recommend that all patients for whom the surgical treatment is practicable and desired should undergo adrenal venous sampling (AVS) as the gold standard to differentiate unilateral from bilateral disease (Young & Stanson, 2009)

3.1.4 ARR to identify disproportionate aldosterone production

High aldosterone secretion may play a role in the pathogenesis of increased blood pressure in resistant hypertensives even when PA cannot be diagnosed by clinical and instrumental criteria. We have shown that a mild elevation of ARR and plasma aldosterone, which are not reduced to a significant extent by oral captopril administration during CC, predict poor blood pressure response to antihypertensive agents. The clinical features and outcome of these patients with high ARR were indistinguishable from those of hypertensive patients with clinically diagnosed IHA: both reached blood pressure goal in a smaller fraction and in a longer time than patients with ARR in the normal range (Sartori et al., 2006). The cause(s) of the disproportionately high aldosterone levels which are not inhibited to a significant extent by the inhibition of Ang II production by captopril remain(s) unknown but they may be related to abnormal regulation of aldosterone production by Ang II (see below). ARR should be, therefore, performed in all patients with resistant hypertension to demonstrate a disproportionate aldosterone secretion and encourage treatment with aldosterone antagonists to achieve a more effective blood pressure reduction.

3.2 Treatment of primary aldosteronism

Surgical treatment should be offered to eligible patients with unilateral adrenal disease; it consists in unilateral adrenalectomy. It has been shown to improve blood pressure control. In patients who are unable or unwilling to undergo surgery, or with a bilateral adrenal disease, treatment with a mineralcorticoid receptor antagonist should be started. Treatment of aldosterone excess either with spironolactone or with unilateral adrenalectomy was found to reduce the high cardiovascular risk of this patient group (Milliez et al., 2005). The benefit of controlling PA is also demonstrated after a long period of therapy: treated patients with PA had similar rates of cardiovascular events as hypertensive patients without PA after a 12-years follow up. The best cardiovascular outcome was seen in younger patients and in those with a shorter duration of disease. These results stress the need of early recognition and treatment to reverse the adverse effects of aldosterone excess.

3.2.1 Mineralocorticoid receptor antagonists

Spironolactone is a direct antagonist of the mineralcorticoid receptor and it is a powerful add-on agent to the antihypertensive regimen in patients with resistant hypertension. When added to a regimen of three drugs including a diuretic, spironolactone lowers blood pressure significantly, with achievement of blood pressure control in a high percentage of patients. This effect is similar in patients with or without evidence of aldosterone excess, with no gender or ethnic difference. Indeed, similar degrees of blood pressure reduction were achieved regardless of baseline plasma aldosterone or PRA values. This underscores the contributory role of relative aldosterone excess to treatment resistance, such that even those with presumably low levels of aldosterone benefit from mineralcorticoid receptor antagonists use. (Nishizaka et al., 2003; Sartori et al., 2006; De Souza et al., 2010) This is in contrast with other studies that showed that high ARR predicted the antihypertensive efficacy of spironolactone (Eide et al., 2004); these contrasting results may be explained by the considerably higher spironolactone dose administered in patients with demonstrated PA, generating a strong difference in the two populations.

The importance of relative aldosterone excess in promoting treatment resistance is emphasized also in another recent study: spironolactone was added either to an ACE-I or to an ARB theraphy and compared to ACE-I plus ARB combined therapy. Greater blood pressure reduction was achieved when spironolactone was added to an ACE inhibitor or an ARB versus dual RAS blockade (Alvarez-Alvarez et al., 2010). These results suggest that aldosterone excess plays a major role in the pathogenesis of treatment resistance, and that hypersecretion of aldosterone is relatively autonomous of the RAS activity, so that the amplitude of blood pressure lowering is greater in patients given the mineralcorticoid receptor antagonist compared to those on dual blockade. Furthermore, since the study excluded patients with PA, the results show that resistant hypertensive patients in general have an element of relative aldosterone excess, even if aldosterone falls within the normal range. (Acelajado & Calhoun, 2011).

Mineralcorticoid receptor antagonists are also anti-proteinuric: reduction of albuminuria was demonstrated in patients with diabetes or chronic kidney disease, nephropathy, or persistent microalbuminuria. In case of chronic kidney disease, spironolactone alone was able to reduce proteinuria and slow down renal progression (Bianchi et al., 2006).

Treatment with mineralcorticoid receptor antagonists not only controls blood pressure levels and proteinuria, but also reverses or attenuates the cardiovascular injury mediated by aldosterone excess. This is particularly true for the nongenomic effects, which lead to tissue fibrosis, arterial stiffness, and increased oxidative stress. In patients with resistant hypertension spironolactone reduces left ventricular mass index after 3 and 6 months of therapy, both in patient with PA and in those with normal renin - angiotensin- aldosterone levels (Gaddam et al., 2010) . The extent of regression of the left ventricular mass index achieved with spironolactone treatment is greater for patients with PA compared to those without.

If patients with both resistant hypertension and PA are selected, further interesting benefits of therapy with spironolactone are shown on nongenomic effects. Spironolactone significantly decreases brain natriuretic peptide (BNP), an effect that was not seen in those with normal or low aldosterone levels; this indicates a prominent diuretic effect even when administered on top of chronic thiazide diuretic treatment. In another study on resistant hypertension and PA, flow-mediated dilation of the brachial artery increased with spironolactone treatment as an indication of reduced arterial stiffness and improvement of endothelial function, and this effect was independent of the change of blood pressure (Nishizaka et al., 2004) .

3.2.2 Adverse effects

Adverse effects of spironolactone use are breast tenderness, gynecomastia, erectile dysfunction, and menstrual irregularities, as a result of the binding of spironolactone to androgen receptors, preventing their interaction with dihydrotestosterone. All these major adverse effects warrant monitoring (Marrs, 2010). The incidence of these effects is rare (2–9%) and they are all reversible after discontinuing treatment. If a more selective MR antagonist is used (such as eplerenone), no or less antiandrogen effects is shown, given its lower affinity for progesterone and androgen receptors. A comparison between spironolactone and eplerenone in patients with primary hypertension and bilateral adrenal hyperplasia showed that the two agents achieved similar degrees of blood pressure lowering in patients with PA (Karagiannis et al., 2008). A direct comparison of these two agents in patients with resistant hypertension has not been conducted so far. Furthermore, eplerenone has not yet been specifically evaluated for the treatment of resistant hypertension and it is not available in several countries.

Hyperkalemia can also be a side effect of treatment with mineralcorticosteroid antagonists, especially when multidrug therapy, including renin – angiotensin system blockers, is prescribed or in patients with chronic kidney diseases. This effect can be reversed by discontinuing the drug or reducing the dose.

4. RGS2

The above mentioned studies, showing benefits of aldosterone antagonists in patients with resistant hypertension, strongly support a role of aldosterone excess, beyond true primary aldosteronism, as a major cause of treatment resistance. Furthermore, data from our laboratory have shown that disproportionately high aldosterone levels associated to poor response to inhibition of Ang II production by captopril are prevalent in resistant

hypertension (Sartori et al., 2006). Therefore, we have investigated the signal transduction pathways of Ang II to clarify whether the inappropriately high aldosterone levels are caused by abnormal regulation of aldosterone production by Ang II in the adrenals.

The pressor effects of Ang II action are mediated by stimulation of G protein-coupled receptors (GPCRs), which are mediators of the activity of several other important cardiovascular neurotransmitters and hormones, including noradrenaline, adrenaline, endothelin, thrombin, vasopressin, acetylcholine, serotonin and sphingosine-1-phosphate (S1P). G-proteins are widely expressed throughout the cardiovascular system and thus play an important role in the physiological regulation of the cardiovascular system.

Signaling by hormones and neurotransmitters that activate G protein-coupled receptors (GPCRs) maintains blood pressure within the normal range despite large changes of cardiac output that can occur within seconds. The blood pressure regulation requires, therefore, precise kinetic control of GPCR signaling. Alteration of GPCR signaling is a salient feature of hypertension and its associated cardiovascular complications and hypertension is often associated with increased activity of GPCR-mediated signaling in the heart and blood vessels. Accordingly, these pathways are common targets of inhibitors used to treat hypertension and heart disease (angiotensin-converting enzyme -ACE- inhibitors - and Ang II receptor antagonists) (Rockman et al., 2002).

4.1 G-Protein structure and function

The G-protein heterotrimer is composed of a GDP bound Gα subunit and a G$\beta\gamma$ heterodimer. Different gene families consisting of 16α, 6β and 12γ genes encode the three subunits that can form heterotrimeric complexes in various combinations. It is the Gα subunit families (Gs, Gq, Gi etc.), however, that define the signaling context of the heterotrimer via its ability to couple selectively to a limited number of seven-transmembrane domain receptors and effectors. In the absence of extracellular ligand (inactive state -OFF state-), the G-protein heterotrimer is coupled to the intracellular surface of the receptor. Binding of receptor ligand induces the exchange of GTP for GDP on the Gα subunit and the subsequent dissociation of Gα from the G$\beta\gamma$ heterodimer. This condition marks the activated (active state -ON state-) state and during this time the Gα and G$\beta\gamma$ subunits are free to engage the appropriate downstream effector pathways (Clapham & Neer, 1997; Hamm 1998). Effector signaling is terminated by the Gα-subunit catalyzed hydrolysis of GTP and reformation of the quiescent receptor-coupled heterotrimer. Thus G-proteins act as molecular time switches that control the onset and lifetime of cellular responses to extracellular signals.

4.2 RGS proteins promote rapid termination of G-protein mediated signals

G-protein signaling pathways are tightly coupled to rapid ON–OFF kinetics of the cell physiological effectors, including membrane ion channels. As the intrinsic rate of Gα-mediated GTP hydrolysis is very slow, GTPase-activating proteins (GAPs) are needed to achieve the rapid ON–OFF kinetics of G-protein signaling observed *in vivo*. Regulators of G protein signaling (RGS) proteins contain a 120 amino acid GAP domain (Berman et al., 1996) that increase the rate of Gα-mediated GTP hydrolysis by up to 2000 times (Ross & Wilkie, 2000). Accordingly, RGS proteins attenuate GPCR-mediated signaling by promoting faster

signal termination kinetics following removal of a GPCR agonist and decreasing GPCR agonist sensitivity (higher agonist concentrations are needed to achieve the same degree of signaling). In addition, the RGS protein GAP domain can inhibit signaling by blocking G*a* binding to downstream effector molecules (Ceolotto et al., 2001). Three RGS proteins, RGS2, RGS4, and RGS5, are among the most highly expressed proteins in the heart and blood vessels. The genes encoding these three proteins are located within the region on chromosome 1 associated with blood pressure variation.

4.3 RGS2

Regulators of G-protein Signaling (RGS) proteins are a large family of important endogenous regulators of GPCR signaling: RGS proteins have an established role as inhibitors of G-protein signaling in cardiovascular tissues and, therefore, are important endogenous regulators of blood pressure.

4.3.1 RGS2 inhibits G*α*q and adenylatecyclase-mediated signaling

RGS2 is unique owing to its preferential interaction with G*a*q/11 (and Gas) and its low affinity for G*a*i (Heximer et al., 1999; Cladman et al., 2002). RGS2 binds either directly (M1 muscarinic receptor, or a1A- and b2-adrenoceptors) or indirectly via interaction with a scaffold protein (a1B-adrenoceptor) to GPCRs. Through its unique G protein selectivity for G*a*q/11, RGS2 appears to play a key role in cardiovascular pathophysiology, in which deleterious processes are often initiated via G*a*q/11-coupled GPCRs; for example, in blood vessels, many contractile responses are mediated via G*a*q (Wieland et al., 2007) .

Activation of G*a*q-mediated vasoconstrictor signaling pathways in vascular smooth muscle cells (VSMCs) mediates the action of several vasoconstrictor agonists, including noradrenaline, Ang II, vasopressin and endothelin. RGS2 is a selective and potent inhibitor of G*a*q signalling that is ubiquitously expressed throughout the cardiovascular system. The biological significance of RGS2 in cardiovascular physiology is evident from blood pressure studies carried out in mice and humans. Several studies have shown that RGS2-null mice are hypertensive (Tang et al., 2003; Gross et al., 2005), with altered G-protein signaling in a number of tissues. These mice have agonist-dependent increases in G*a*q signaling in VSMCs compared with wild-type controls. Moreover, RGS2-null mice also have increased pressor responses to infusion of Ang II and *a*-adrenergic receptor agonists compared with wild-type controls. This effect may be partly explained by increased myogenic vasoreactivity to G-protein-mediated stimuli of the RGS2-null mice (Hercule et al., 2007). RGS2 has also been shown to be highly integrated within the NO mediated vasodilator pathway. Specifically, the N-terminal of RGS2 is phosphorylated by PKG (cGMP-dependent protein kinase), resulting in plasma membrane translocation and increased function as an inhibitor of vasoconstrictor signaling (Tang et al., 2003). Results from knockout animal studies also suggest that abnormal function of the autonomic nervous system contributes to the hypertensive phenotype, since they have increased urinary noradrenaline and altered baroreflex sensitivity. Moreover, through the ability of its N-terminal domain to directly inhibit specific adenylate cyclase isoforms (Gu et al., 2008b; Salim et al., 2003), RGS2 may attenuate signaling via receptors for dopamine and vasopressin in the kidney. Consistent with this suggestion, RGS2 was shown to regulate vasopressin responses in cortical collecting duct segments *in vivo* (Zuber et al., 2007).

4.3.2 RGS2 and Ang II action

There is increasing evidence of a reciprocal association between RGS2 activity and Ang II signaling. RGS2 has been shown to modulate signaling through the AT1 receptor (Ang II type 1 receptor) in several reports mentioned above. However, it has also been shown that RGS2 mRNA expression is increased by Ang II signaling in several cell lines, suggesting that RGS2 is an important part of a negative-feedback loop for this pathway. Indeed, the Ang II-stimulated expression of RGS2 has been shown to be able to inhibit both Ang II signaling (Li et al., 2005) and aldosterone production (Romero et al., 2006) . Although the precise mechanism for the up regulation of *Rgs2* is not fully understood, recent findings have implicated a role for PLA2 (phospholipase A2) in this process. Together, these results suggest a reciprocal relationship between RGS2 and Ang II, which is supported by *in vivo* studies showing that the *Rgs2*-null animals are more sensitive to Ang II-induced hypertension than wild-type controls (Hercule et al., 2007).

4.3.3 Clinical hypertension and RGS2 deficiency

The importance of RGS2 in the regulation of blood pressure homoeostasis is evident also in human studies. Recent studies have identified human genetic polymorphisms within the *RGS2* locus that are associated with hypertension in different ethnic populations (Riddle et al., 2006; Freson et al., 2007). The *RGS2* gene consists of five exons that show minimal genetic variation between subjects. No coding polymorphisms have been yet identified in Caucasian subjects; however, one single nucleotide polymorphism (SNP) was found in Black Americans (Riddle et al., 2006), and nine different SNPs in Japanese subjects (of which five are non-synonymous) (Yang et al., 2005). In the case of the Japanese population, hypomorphic *RGS2* allele function could partially explain the development of hypertension in subjects carrying missense mutations at Q2L,Q2R and R44H. For example, Q2L and Q2R variant proteins were shown to be less stable compared with normal RGS2 and, as a result, these subjects are thought to express lower steady-state levels of RGS2. By contrast, another study showed that the R44H variant of RGS2, although not compromising stability, disrupt the amphipathic *a*-helix that is crucial for proper plasma-membrane targeting and function (Gu et al., 2008a). Notably, another mutation at the Arg44 position, R44G, has also been shown to be associated with hypertension and higher than normal BMI (body mass index), suggesting a further role of RGS2 in causing obesity and metabolic syndrome. In addition, to those changes identified in the coding regions, the promoter region, introns and untranslated regions of *RGS2* also contain several SNPs and I/D (insertion/deletion) polymorphisms, of which one has been shown to result in enhanced calcium mobilization in fibroblasts in response to Ang II (Semplicini et al., 2006), and one has been linked to an increase in risk of the metabolic syndrome in white Caucasian Europeans (Freson et al., 2007). Remarkably, their allelic frequency differs markedly between ethnicity, and some are exclusively found in one ethnic group. Taken together, these studies of both non-synonymous mutations and extra-exonic polymorphisms suggest the possibility that *RGS2* variation contributes to some of the variability of blood pressure observed between different ethnic groups.

Noteworthy, too much RGS2 may also provide a pathophysiological stimulus within the cardiovascular tissues. It has been reported that the RGS2 protein is overexpressed in patients with Bartter's syndrome (B/S) and Gitelman's syndromes (G/S), and that this

abnormally high expression inhibits Ang II-mediated intracellular calcium release (Calo' et al., 1998) and promotes altered vascular remodeling. Indeed, fibroblasts taken from patients with B/S and G/S have enhanced RGS2 expression and reduced signaling through the AT1 receptor (Calo' et al., 2004), the effects of which can be normalized by the knockdown of RGS2 expression (Calo' et al., 2008).

All these findings strongly suggest that the precise control of RGS2 protein level and function is extremely important for the normal regulation of vascular function and blood pressure control. This hypothesis received further support by our findings that 1) RGS2 expression is reduced in PBMs and in cultured fibroblasts from hypertensive patients in comparison with normotensive individuals (Semplicini et al., 2006), 2) low RGS2 expression predicts a poor response to antihypertensive treatment. In fact, resistant hypertensives were characterized by higher plasma aldosterone, ARR and reduced RGS2 expression in peripheral blood mononuclear cells in comparison to responder to antihypertensive drugs. (Semplicini et al., 2010).

The association between resistant hypertension and low RGS2 expression suggests increased vascular tone of the resistance vessels due to unopposed Ang II-mediated vasoconstriction, while the association with high plasma aldosterone and high ARR is an indicator of disproportionate aldosterone response to Ang II in the adrenals.

In the vasculature, chronic upregulation of Ang II activity, due to low RGS2 expression, was suggested not only by the finding of increased BP, but also of increased plasma BUN and urate levels, an indicator of increased renal efferent artery resistance, reduction of renal blood flow and increased hydraulic pressure in the glomerular capillary, with consequent increased glomerular filtration rate, and urate and sodium reabsorption along the early proximal tubule. (Perlstein et al., 2004; Johnson et al., 2005).

In the adrenals, the association between low RGS2 and high plasma aldosterone and high ARR is an indicator of disproportionate aldosterone response to Ang II (Semplicini et al., 2010).

5. Disproportionate aldosterone secretion and reduced RGS2 expression: a proposed link in resistant hypertension deserving further investigations

Identification and treatment of uncontrolled and resistant hypertension is a task of paramount importance in cardiovascular preventive medicine. In fact, poor blood pressure control carries unacceptably high risk of cardiovascular complications and premature death. Improving blood pressure control at individual and population level may reduce cardiovascular morbidity and mortality but this major goal can not be achieved with such a high prevalence of uncontrolled and resistant hypertension.

The data summarized so far suggest which pathways should be investigated to unravel the pathophysiology of resistant hypertension and how to improve its drug treatment. The research results of our and others' laboratories indicate that aldosterone plays a key role in the pathogenesis of resistant hypertension and suggest that aldosterone antagonists should be tested in selected patients with resistant hypertension.

Calhoun et al. (2008) and Gallay et al. (2001) reported that PA is present in 20% of individuals with resistant hypertension. High-normal levels of circulating aldosterone

increase the risk of poor blood pressure control. High aldosterone with high ARR and low PRA may reflect either primary aldosterone overproduction or, more likely, increased adrenal response to Ang II.

Our working hypothesis is that the exaggerated aldosterone production in resistant hypertensives is due to low RGS2 expression. This hypothesis originates from our recent findings (Semplicini et al., 2010) showing in a cohort of resistant hypertensives that:

1. there is an inverse correlation between RGS2 expression and baseline BP,
2. low RGS2 expression is associated with resistant hypertension,
3. resistant hypertension with low RGS2 expression is associated with high plasma BUN and acid uric, indicating increased sodium and water reabsorption in the renal proximal tubules,
4. resistant hypertension with low RGS2 is associated with high plasma aldosterone and ARR,
5. the accuracy of RGS2 and ARR in predicting response to antihypertensive treatment is similar and not additive.

Aldosterone stimulates RGS2 expression, and upregulation of RGS2 by Ang II functions as a negative feedback of aldosterone production. The fact that we showed in resistant hypertensives high aldosterone with low RGS2 expression provides strong support to our hypothesis that abnormal regulation of RGS2 expression increases the duration of action of the intracellular signaling cascade, leading to persistently increased secretion of aldosterone in resistant hypertensives.

RGS2 is one of the genes involved in human essential hypertension, because it regulates the cell responses to Ang II and other vasoconstrictive agents and it controls peripheral vasoconstriction and blood pressure. Our data provide robust indication that reduced expression of RGS2 acts also as a promoter of aldosterone excess in resistant and uncontrolled hypertension.

Dysregulation of RGS2 plays a crucial role in the pathogenesis of cardiovascular diseases, making RGS2 as a potential therapeutic target or biomarker of hypertension or hypertensive heart disease. There is no firm evidence of the cause of reduced RGS2 expression in resistant hypertension, but it could be associated to a susceptible genetic polymorphism, and it is still unknown how to control the activity of its gene to up-regulate its expression.

On clinical grounds, according to our hypothesis, we propose a short course of aldosterone antagonists in resistant hypertensives. If it provides a good blood pressure response, long term treatment with aldosterone antagonists is recommended. This therapeutic approach has to be tested in long term controlled studies. In the meanwhile, further in depth studies of these mechanisms are recommended to allow a wider comprehension of resistant hypertension and to provide further support to its therapeutic approach with aldosterone antagonists.

6. References

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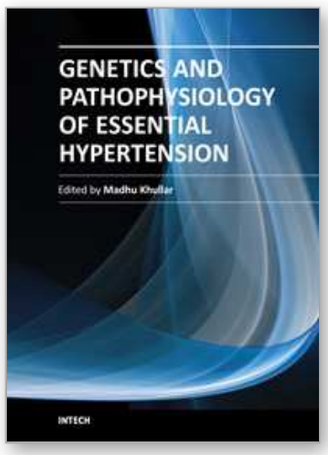

Genetics and Pathophysiology of Essential Hypertension

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This book, authored by renowned researchers in the field of Hypertension Research, details the state of the art knowledge in genetics, genomics and pathophysiology of Essential hypertension, specifically the genetic determinants of hypertension and role of gene variants in response to anti-hypertensive therapy. Two chapters describe mitochondrial mutations in Essential hypertension and in hypertension associated Left ventricular hypertrophy, one chapter reviews in detail the global gene expression in hypertension, and an up to date treatise on pathophysiology of resistant hypertension is detailed in another chapter. Other topics included in the book are end organ damage, baroreceptor sensitivity and role of music therapy in essential hypertension.

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