

# Renin-angiotensin system inhibition prevents type 2 diabetes mellitus

## Part 2. Overview of physiological and biochemical mechanisms

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### SUMMARY

The inhibition of the renin-angiotensin system (RAS) with either angiotensin converting enzyme inhibitors (ACEIs) or AT1 angiotensin receptor blockers (ARBs) consistently and significantly reduces the incidence of type 2 diabetes in patients with hypertension or congestive heart failure. The mechanisms underlying this protective effect appear to be complex and may involve an improvement of both insulin sensitivity and insulin secretion. These two effects may result, at least in part, from the well known effects of these pharmacological agents on the vascular system on the one hand, on the ionic balance on the other hand. Indeed, the vasodilation induced by ACEIs or ARBs could improve the blood circulation in skeletal muscles, thus favouring peripheral insulin action, but also in the pancreas, thus promoting insulin secretion. Preserving cellular potassium and magnesium pools by blocking the aldosterone effects could also improve both cellular insulin action and insulin secretion. However, besides these classical effects, new mechanisms have been recently suggested. A direct effect of the inhibition of angiotensin and/or of the enhancement of bradykinin on various steps of the insulin cascade signalling has been described as well an increase in GLUT4 glucose transporters after RAS inhibition. Furthermore, it has been demonstrated that angiotensin II inhibits adipogenic differentiation of human adipocytes *via* A1 receptors and, therefore, it has been hypothesised that RAS blockade may prevent diabetes by promoting the recruitment and differentiation of adipocytes. Finally, some lipophilic ARBs appear to induce PPAR-gamma activity in the adipose tissue. Hence, the protection against type 2 diabetes observed after RAS inhibition may be partially linked to a thiazolidinedione-like effect. In conclusion, numerous physiological and biochemical mechanisms could explain the protective effect of RAS inhibition against the development of type 2 diabetes in individuals with arterial hypertension or congestive heart failure. What might be the main mechanism in the overall protection effect of ACEIs or ARBs remains an open question.

**Key-words:** ACE inhibitors · Adipose tissue · Angiotensin · AT1 receptors blockers · Insulin resistance · Insulin secretion · Type 2 diabetes mellitus.

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### RÉSUMÉ

#### L'inhibition du système rénine angiotensine prévient le diabète de type 2. Partie 2. Analyse des mécanismes physiologiques et biochimiques

Le blocage du système rénine-angiotensine (RAS) avec un inhibiteur de l'enzyme de conversion de l'angiotensine (IEC) ou avec un antagoniste des récepteurs AT1 de l'angiotensine (ARA) réduit, de façon consistante et significative, l'incidence de diabète de type 2 chez les patients avec hypertension artérielle ou avec insuffisance cardiaque. Les mécanismes sous-tendant cet effet protecteur apparaissent complexes et peuvent impliquer une amélioration à la fois de la sensibilité à l'insuline et de l'insulinosécrétion. Ces deux effets peuvent s'expliquer, au moins en partie, par les actions connues de ces agents pharmacologiques, d'une part, sur le système vasculaire, d'autre part, sur la balance ionique. En effet, l'action vasodilatatrice des IECs et des ARAs peut améliorer la circulation sanguine dans les muscles squelettiques, amenant à une meilleure action périphérique de l'insuline, mais aussi dans le pancréas, contribuant à favoriser l'insulinosécrétion. Préserver les pools cellulaires de potassium et de magnésium en bloquant les effets de l'aldostérone pourrait aussi contribuer à améliorer l'action et la sécrétion de l'insuline. Cependant, à côté de ces effets classiques, de nouveaux mécanismes ont été suggérés récemment. Un effet direct de l'inhibition de l'angiotensine II et/ou de l'augmentation de la bradykinine sur différentes étapes de la cascade de signalisation insulinoïque a été rapporté ainsi qu'une augmentation des transporteurs du glucose GLUT4 après inhibition du RAS. De plus, il a été démontré que l'angiotensine II inhibe la différenciation des adipocytes humains via les récepteurs AT1 et il a été proposé que le blocage du RAS puisse prévenir le diabète en favorisant le recrutement et la différenciation adipocytaire. Enfin, certains ARAs lipophiles apparaissent exercer une induction de l'activité PPAR-gamma dans le tissu adipeux. Dès lors, la protection contre le diabète de type 2 exercée par l'inhibition du RAS pourrait résulter, au moins partiellement, d'un effet apparenté à celui décrit pour les thiazolidinediones. En conclusion, de nombreux mécanismes physiologiques et biochimiques peuvent expliquer le mécanisme de protection procuré par l'inhibition du RAS vis-à-vis du développement d'un diabète de type 2 chez les individus à risque présentant une hypertension artérielle ou une insuffisance cardiaque. La question reste ouverte quant à savoir quel est, parmi les divers mécanismes possibles, celui qui joue le rôle principal dans la protection contre le diabète observée avec les IECs ou les ARAs.

**Mots-clés:** Angiotensine · Antagonistes des récepteurs AT1 · Diabète de type 2 · Inhibiteurs de l'enzyme de conversion · Insulinorésistance · Insulinosécrétion · Tissu adipeux.

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Several randomised clinical trials (RCTs) suggested that the inhibition of the renin-angiotensin system (RAS) reduces the risk of new type 2 diabetes mellitus (T2DM) in patients with arterial hypertension [1, 2] or with congestive heart failure [2]. A recent meta-analysis of 10 RCTs including a total of 69950 non-diabetic subjects with arterial hypertension and a total of 5727 non-diabetic patients with congestive heart failure demonstrated a 22% relative risk reduction after a mean follow up of 4-5 years when using an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor AT1 blocker (ARB) as compared to placebo or various reference drugs (beta-blockers or diuretics or amlodipine) [3]. The beneficial effect was similar with ACEIs and with ARBs as well as in patients with hypertension and in those with heart failure, and was also present whatever the comparator. Considering the pandemic of T2DM, such pharmacological approach deserves further attention among the strategies aiming at preventing the disease. This preventive effect of RAS inhibition on the development of T2DM should involve the intimate mechanisms of the complex pathophysiology of T2DM [4, 5].

While it is clear that hyperglycaemia of type 2 diabetes is associated with both insulin resistance and beta-cell dysfunction, there has been much debate over the past few decades regarding the relative importance of these two abnormalities and which of them precedes the other in the natural history of the disease [6, 7]. What so ever, from a theoretical point of view, preventing type 2 diabetes by RAS inhibition may result from an improvement of beta-cell function and/or an enhancement of insulin sensitivity thereby decreasing the need for pancreatic insulin secretion [8]. Targeting RAS may lead to alterations in microcirculation and changes in ionic status that potentially could affect both cellular insulin action and islet insulin secretion [9]. However, unexpected mechanisms might also play a role in such a protective effect of RAS inhibition as newly recognised components of the RAS seem to modulate cardiovascular and renal regulation [10], and angiotensin appears to exert direct cellular effects [11], including in the adipose tissue [12].

The purpose of this review is to describe the possible mechanisms involved in the prevention of T2DM with the inhibition of RAS, especially the possible effects on insulin action and/or insulin secretion, the two main players in the vicious circle leading to the development of T2DM [4-7].

## Effects of RAS inhibition on insulin action

Some improvement in insulin sensitivity has been reported after ACEI or ARB treatment [2]. However, considerations into the influence of RAS inhibition on insulin sensitivity has yielded conflicting results. These controversial observations might result from the heterogeneity in the

material and methods used, especially the various populations investigated (healthy volunteers, hypertensive subjects, patients with type 2 diabetes), the various methods to assess insulin sensitivity (glucose clamp, insulin suppression test, intravenous glucose tolerance test with minimal model method, homeostasis model assessment,...), the different compounds tested (different ACEIs or ARBs), the various dosages and durations of the pharmacological treatment (from a few days to several months), the presence of potentially confounding comedications, the number of subjects (risk of type I error, i.e. risk of false positive, in trials including small groups) [9]. Among 20 available studies investigating the effects of ACEIs on insulin action using the gold standard method, i.e. the euglycaemic hyperinsulinaemic clamp, in non-diabetic patients with mild to moderate hypertension, 9 reported significant increase of insulin sensitivity index (between +11 and +61%), while 9 failed to detect any significant improvement, and only 2 trials reported a significant mild deterioration (respectively -11% and -6%) (review in 2). Similarly, among nine clinical trials investigating the effects of ARBs on insulin action using the same methodology in hypertensive non-diabetic patients, only four studies reported significant increase of the clamp-derived insulin sensitivity index, whereas all others were not able to demonstrate any significant beneficial or deleterious effect of ARBs [2]. Only a few studies provided direct comparison between ACEI and ARB regarding their effects on insulin action, with again conflicting results [2]. Possible differences between the effects of ACEIs and ARBs on insulin sensitivity might be explained by various mechanisms, especially the role of angiotensin II (ATII) and bradykinin on muscular blood flow and on insulin signalling [13].

Although the evidence is far from consistent, there are reasonable grounds for accepting that ACEIs are associated with a modest increase in insulin-mediated glucose uptake, especially in insulin-resistant hypertensive patients with type 2 diabetes [16, 17]. The mechanisms by which RAS inhibition improves insulin sensitivity are not completely clear and might be partially independent of the vascular effect of the compounds. The effects of ATII on insulin action appear rather complex. Indeed, recent clinical studies have made the intriguing observation that both pressor and subpressor doses of ATII increase insulin-mediated glucose uptake in healthy subjects as well as in patients with type 2 diabetes [14]. Under hyperinsulinaemic euglycaemic conditions, infusion of ATII has opposing effects on regional arterial blood flow, i.e. an increase in skeletal muscle blood flow, but vasoconstriction of renal vasculature [15]. Both effects are antagonised by blockade of subtype 1 ATII receptors with irbesartan. The full significance of these observations has yet to be demonstrated. Nevertheless, a promoting effect of RAS inhibition on insulin action has been confirmed in various animal models [18]: as an example, in the fructose-fed Wistar rat with insulin resist-

ance, an ACEI or an ARB showed similar improvement of insulin sensitivity and hypoglycaemic actions as compared to troglitazone, a well-known insulin sensitiser of the thiazolidinedione family [19]. This effect may result from an improvement in blood flow to skeletal muscle tissue and/or an enhancement of insulin signalling at cellular level, independently of any effect on microcirculation [18] (*Tab I*).

### Improved muscle blood flow

An inverse relationship was observed between the blood pressure-lowering effect of captopril and the improvement in insulin-mediated whole-body glucose disposal [20]. The notion that increased muscular blood flow is associated with increased glucose utilisation has considerable bearing on the proposed haemodynamic theory of insulin resistance [21-23]. Several reviews provide evidence that haemodynamic factors influence insulin sensitivity in subjects with essential hypertension [24] or with diabetes [23]. Consequently, vasodilatation or a specific increase in blood flow to skeletal muscles would lead to increases in glucose and insulin delivery to insulin-sensitive tissues and cause an increase in glucose utilisation [25]. It has been shown that the ACEI quinapril may significantly improve vascular sensitivity to insulin via global enhancement of endothelial function [26], and endothelial dysfunction is associated with obesity, insulin resistance, hypertension and type 2 diabetes [27, 28]. This haemodynamic hypothesis is further supported by the demonstration that ATII has no direct metabolic effect on skeletal muscle glucose metabolism [29], thereby implicating haemodynamic factors as causative of the changes in glucose utilisation and insulin sensitivity observed after ATII inhibition [30]. However, it has been

shown that ATII induces insulin resistance independent of changes in interstitial insulin [31], a finding that may suggest that other effects independent of vascular changes could also play a role.

ACEIs enhance blood flow through the microcirculation of skeletal muscles although the respective roles of ATII inhibition and bradykinin enhancement remain controversial [32, 33]. Bradykinin seems to play a significant role in arterial blood pressure regulation after RAS inhibition as bradykinin receptor blockade could partially reverse the blood pressure lowering effect of ACEI in normotensive and hypertensive subjects [34]. Infusion of exogenous bradykinin was shown to improve glucose utilisation by forearm muscles and enhance insulin sensitivity in humans [35]. It is now apparent that bradykinin functions as a circulating hormone with a short half-life of a few seconds and as an autocrine-paracrine factor generated and acting locally within various tissues [33]. It is generally accepted that almost all physiologically significant actions of bradykinin are mediated by bradykinin type 2 receptors [32, 33, 36]. The increased insulin-mediated glucose uptake by skeletal muscle in response to an ACEI appears to be due to increased bradykinin-mediated nitric oxide production and not to reductions in ATII production or action [37, 38], a finding that may explain the lower effects of ARBs as compared to ACEIs on insulin sensitivity in hypertensive patients observed in some trials [39, 40]. It is noteworthy that, in addition to their effects on microcirculation, both ATII and bradykinin may also exert direct effects on insulin signalling cascade (see below).

### Decreased sympathetic activity

Overactivity of the sympathetic nervous system may contribute to blood pressure elevation and insulin resistance in subgroups of hypertensive patients [41]. ACE inhibition characteristically does not lead to cardioacceleration, indicating attenuation of the sympathetic response to vasodilatation. In normotensive subjects with type 2 diabetes, captopril treatment significantly increased insulin-mediated total glucose uptake and reduced plasma norepinephrine and epinephrine levels [42]. In this study, percentage changes in the ratio of total body glucose uptake to circulating insulin levels and corresponding decrements of baseline plasma epinephrine levels after captopril therapy were negatively correlated. Thus, the reduction in circulating catecholamines could contribute, at least in part, to the captopril-related improvement in insulin sensitivity. Similar results were obtained with losartan in hypertensive non-diabetic patients: glucose disposal rate during a euglycaemic hyperinsulinaemic clamp increased by 30% while plasma norepinephrine decreased by 40% during treatment with losartan, suggesting that losartan may improve insulin sensitivity in essential hypertension, possibly by a sympatholytic effect [43].

**Table I**

Summary of the potential mechanisms involved in the protection against Type 2 diabetes with the inhibition of the renin-angiotensin system.

#### 1) Effects on insulin sensitivity

- Improved muscle blood flow
- Decreased sympathetic activity
- Favourable ionic changes ( $K^{++}$  and  $Mg^{+}$ )
- Enhanced insulin signalling (tyrosine kinase, IRS-1, PI3-kinase, GLUT4)
- Effects on adipose tissue (FFA, adiponectin, adipogenesis)
- Partial PPAR-gamma activity (thiazolidinedione-like effect of some ARBs)
- Effects on muscular fibre composition

#### 2) Effects on insulin secretion

- Improved ionic balance ( $K^{+}$  and  $Mg^{++}$ )
- Improved islet blood flow

## Ionic changes

Potassium appears to play a greater role in insulin secretion than in insulin action [9]. Pollare *et al.* [20] observed no significant correlation between changes in insulin sensitivity and serum potassium levels during treatment with either hydrochlorothiazide or captopril (in which study only captopril improved the insulin sensitivity). Combination of bendrofluazide with captopril resulted in deleterious effects on insulin action compared to captopril alone, independently of significant alterations in serum sodium/potassium status [44]. However, it may be that the change in insulin sensitivity would be derived from a change in the muscle potassium level, which is not necessarily reflected by plasma potassium.

In a pooled analysis of four double-blind studies with four different ACEIs (captopril, enalapril, fosinopril and lisinopril) in a total of 96 patients with essential hypertension, changes in insulin sensitivity index were directly correlated to alterations in serum magnesium, and inversely correlated to changes in serum calcium and in the ratio between serum calcium and magnesium concentrations [45]. Magnesium status has been shown to play a key-role in glucose metabolism [46], and improved insulin response and action by chronic magnesium administration in aged patients with type 2 diabetes have been reported [47]. However, the question as to whether the change in mineral status represents a cause or an effect, or both, of improved insulin sensitivity after ACEI therapy still remains [45].

## Enhanced insulin signalling

It has been shown that ATII utilises the insulin-receptor substrate (IRS)-1 to relay signals towards their intracellular destination, an observation that provides the biochemical explanation of how insulin and ATII may interact [48]. There is a direct cross-talk between insulin and ATII signalling pathways at the level of both tyrosine phosphorylation and phosphatidylinositol 3 (PI3)-kinase activation [49]. ATII negatively modulates insulin signalling by stimulating multiple serine phosphorylation events in the early components of the insulin signalling cascade [50]. However, other results in rats strongly suggest that ATII-induced insulin resistance cannot be attributed to impairment of early insulin-signalling steps and that oxidative stress, possibly through impaired insulin signalling located downstream from PI 3-kinase activation, is involved in ATII-induced insulin resistance [51].

Initial reports demonstrated that inhibition of AT1 receptors prevents decline of glucose transporter-4 (GLUT-4) in diabetic rat heart [52], and further studies reported that chronic administration of ACEIs or AT1 antagonists to insulin-resistant rodents can increase protein expression of GLUT-4 in skeletal muscle and myocardium [11]. ACEIs increase GLUT-4 concentration/translocation and activate hexokinase, one of the major enzymes of glucose pathway

[53]. These changes are probably secondary to activation of the PI3-kinase signalling pathway by enhancing tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and improvement of PI3-kinase-IRS-1 complexing [11, 54]. Accumulated bradykinin following ACEI increased both basal and insulin-stimulated rate of glucose uptake in skeletal muscle in insulin-resistant obese Zucker rats [38]. It has been shown that this metabolic effect occurred independently of vasodilatation by improving insulin signalling and glucose transport [38]. The bradykinin-mediated facilitation of insulin-dependent glucose transport and utilisation seems to be a direct action of the bradykinin type 2 receptor, which enhances insulin receptor phosphorylation and insulin-stimulated translocation of the glucose transporter GLUT4 from cytosol to plasma membrane [33]. Following treatment with captopril, there was improvement in insulin sensitivity, accompanied by an increase in insulin-induced insulin receptor and IRS-1 phosphorylation as well as in IRS-1/PI 3-kinase association in the liver and muscle of aging rats [53]. In contrast, the ARB losartan had no significant effect on insulin-stimulated IRS-1 phosphorylation in both tissues. These increases were simulated by the administration of bradykinin, an observation that may help to explain the mechanism by which ACEIs improve insulin sensitivity more markedly than ARB [53]. Potential mechanisms of a cross-talk between bradykinin and insulin receptor have also been described [54].

## Effects on free fatty acids and adipose tissue

ACEIs reduced free fatty acid (FFA) levels, ameliorating FFA-induced inhibition of glucose consumption, in insulin-resistant animal models [55]. It has been reported that resistance to the antilipolytic action of insulin is a characteristic feature in hypertensive subjects with abdominal obesity and may be linked to the elevated blood pressure and a more active RAS in these individuals, a condition reversed by enalapril [56]. This may be important because increased circulating FFA concentrations may lead to decreased cellular insulin signalling and increased hepatic glucose production [57].

A recent Japanese study suggested that hypoadiponectinaemia is related to insulin resistance in essential hypertension [58], as it is in obesity and type 2 diabetes [59]. Interestingly, it also showed that treatment with an ACEI (temocapril) or an ARB (candesartan) significantly decreases blood pressure and increased insulin-mediated glucose disposal and plasma adiponectin concentrations. These observations suggest that RAS blockade may improve insulin sensitivity by increasing adiponectin, a new adipocytokine known to enhance insulin action [59]. Owing to the considerable interest raised by adiponectin in the metabolic field [59], these original observations require further confirmation.

All components of the RAS are expressed in human adipose tissue [12] and RAS genes are differentially regulated in human obesity and hypertension [60]. These data warrant further studies to explore the role of the adipose-tissue RAS in the development of obesity-hypertension or related metabolic abnormalities such as T2DM. Recent observations showed that ATII markedly inhibits adipogenic differentiation of human adipocytes via AT1 and that expression of ATII-forming enzymes in adipose tissue is inversely correlated with insulin sensitivity [61, 62]. Therefore, it has been hypothesised that RAS blockade may prevent diabetes by promoting the recruitment and differentiation of adipocytes [57], a mechanism that has been well described with the insulin sensitiser thiazolidinediones [63]. Increased formation of adipocytes would counteract the ectopic deposition of lipids in other tissues (muscle, liver, pancreas), thereby improving insulin sensitivity and preventing the development of type 2 diabetes [64].

### Partial PPAR- $\gamma$ activity of some ARBs

The nuclear hormone receptor peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) plays an important role in the regulation of insulin sensitivity, especially in the adipose tissue and subsequently in skeletal muscles and is considered as the main target of thiazolidinediones [63]. A recent study demonstrates that a subset of ARBs induces PPAR- $\gamma$  activity by interaction with the PPAR- $\gamma$  ligand binding domain, thereby promoting PPAR- $\gamma$  dependent differentiation in mouse 3T3-L1 adipocytes [65]. ARBs with PPAR- $\gamma$  activating properties at low (telmisartan), medium (irbesartan), and very high concentrations (losartan) as well as a nonactivating ARB (eprosartan) have been identified. Significant differences among the PPAR- $\gamma$ -activating ARBs are likely caused by their physicochemical properties. High lipophilicity is required to obtain sufficiently high penetration rates to bind to intracellular PPAR- $\gamma$ . Interestingly, activation of PPAR- $\gamma$  by these ARBs was also observed in the absence of AT1 receptors, demonstrating that the activation is independent of blocking the AT1 receptors. Thus, these observations of induction of PPAR- $\gamma$  activity demonstrate new pleiotropic actions of certain ARBs, providing a potential mechanism for their insulin-sensitizing/antidiabetic effects.

Another group also showed that telmisartan, a structurally unique ARB, can function as a partial agonist of PPAR- $\gamma$ , influence the expression of PPAR- $\gamma$  target genes involved in carbohydrate and lipid metabolism, and reduce glucose, insulin, and triglyceride levels in rats fed a high-fat, high-carbohydrate diet [66]. None of the other commercially available ARBs appeared to activate PPAR- $\gamma$  when tested at concentrations typically achieved in plasma with conventional oral dosing. The authors concluded that molecules that can simultaneously block the ATII receptor and activate PPAR- $\gamma$ , such as telmisartan, have the poten-

tial to treat both haemodynamic and biochemical features of the metabolic syndrome and could provide unique opportunities for the prevention and treatment of diabetes and cardiovascular disease in high-risk populations [67]

The large ongoing ONTARGET (“Telmisartan Alone and in combination with Ramipril Global Endpoint trial”), which compared telmisartan, ramipril, and telmisartan plus ramipril, will investigate new hypotheses on the physiological consequences of ATII, especially the development of diabetes [68]. Interestingly, the design of the study will allow the exploration of consequences of ACEI alone, of ARB alone (specifically telmisartan that has been shown to have PPAR- $\gamma$  activity), and of the combination of both strategies, thus providing a more complete RAS inhibition. Patients who cannot tolerate ACEIs will be enrolled in a parallel study, TRANSCEND (“Telmisartan Randomized Assessment Study in Angiotensin Inhibitor-Intolerant Patients with Cardiovascular Disease”), which will compare telmisartan treatment with placebo. These trials would demonstrate whether telmisartan indeed exerts a greater protection against type 2 diabetes than that already observed with other ACEIs or ARBs [3].

### Effects on muscular fibre composition

Animal studies suggested that fibre composition of skeletal muscle is linked to insulin resistance, and that ACEI may modulate muscle fibre composition through its vasodilative effect in hypertension. Indeed, in fructose-fed rats as an insulin-resistant hypertensive model, ACEI decreased blood pressure and improved insulin sensitivity. Furthermore, the composite ratio of type 1 fibre of soleus muscle was decreased significantly in fructose-fed rats compared to controls and the administration of an ACEI produced a recovery of the composite ratio of type I fibre to the same level as control [69]. As type 1 fibres are those which have the greatest oxidative metabolism, such an effect of ACEI on muscular fibre composition may contribute to improve glucose uptake by the skeletal muscles and thus increase insulin sensitivity. Whether this type of effect is also present in humans is still unknown.

### Effects of RAS inhibition on insulin secretion

Defective insulin secretion plays a major role in the development of T2DM although this has been largely underestimated for many years, probably because of the overwhelming role recognized to insulin resistance in the metabolic syndrome and related cardiovascular diseases [6, 7]. RAS inhibition may positively influence insulin secretion by improving ionic balance (potassium and magnesium) and/or by enhancing microcirculation in the islets of Langerhans in the pancreas.

## Improved ionic balance

The effects of insulin on plasma potassium levels and whole-body potassium content and the effect of potassium on glucose-induced insulin release identify a physiological glucose-potassium cycle [9]. The impaired glucose tolerance classically seen in primary hyperaldosteronism first described by Conn is generally thought to be secondary to potassium depletion [70]. It is well known that the RAS plays a key role in potassium homeostasis [9]. Among almost 900 newly diagnosed patients with type 2 diabetes screened in the UKPDS, the hypertensive patients had significantly lower plasma potassium levels than the normotensive ones even when they were untreated for their high blood pressure [71]. Whether body potassium depletion and hypokalaemia may constitute an independent risk factor for the development or maintenance of hypertension and/or diabetes remains an open question [9].

There is abundant evidence that thiazide diuretics impair carbohydrate metabolism through the potassium depletion associated with their prolonged use, a metabolic effect mainly due to an interference with the insulin secretory response to glucose [72]. Conversely, when potassium is given, thiazide-induced glucose intolerance and insulin hyposecretion are fully prevented [73]. Thus, hypokalaemia substantially impairs the insulin secretory response to glucose, an effect that may be favourably affected by ACEIs or ARBs. These compounds indeed lower aldosterone secretion and renal potassium wasting, which could preserve beta-cell responsiveness [9]. As an example, in contrast to bendrofluazide, lisinopril treatment that increased serum potassium concentration significantly potentiated the initial insulin response to glucose and thereby improved glucose tolerance [74].

Besides a possible reduced cellular insulin action associated to magnesium deficiency [46], insulin secretion may also be impaired when hypomagnesaemia is present [75] and oral supplementation in patients with T2DM and mildly decreased plasma magnesium levels has been shown to improve both insulin sensitivity and secretion [47]. Thus, positive magnesium balance resulting from RAS inhibition and aldosterone blockade might favour insulin secretion and thus contribute to delay T2DM in hypertensive patients.

## Improved islet blood flow

Animal studies demonstrated that ATII has a marked vasoconstrictive effect on the vasculature of endocrine pancreas [76, 77]. In view of the close correlation between islet blood flow and insulin release, a decreased islet blood flow, e.g. due to hyperactivity of the angiotensin system in the islet vasculature, might be of importance for impairments of insulin release. Interestingly, the most prominent effect of ATII in the perfusion experiments was a delay of the first phase of glucose-stimulated insulin release [76, 77], a

well-known abnormality of insulin secretion in patients with T2DM or even in individuals at risk to develop the disease [78]. Whether overactivity of the endothelium-dependent vasoconstriction in the islet microvasculature may contribute to the defective early insulin response in T2DM remains to be shown. Conversely, ACEIs may increase islet blood flow and pancreatic beta-cell perfusion by reducing ATII-mediated vasoconstriction in the pancreas [73, 74]. These effects may potentially slow or reverse the decline in beta-cell function.

Similar observations were made in humans. In healthy volunteers, subpressor and pressor doses of ATII affects both basal and glucose-stimulated insulin secretions [79]. After an oral glucose load, the insulinaemic response was significantly lower and plasma glucose concentrations were significantly higher with infusion of ATII compared with placebo [79]. Conversely, several studies in hypertensive patients with ACEIs have described an increased early insulin peak in response to intravenous [20] or oral [80] glucose administration. These observations may be of relevance with respect to the involvement of the RAS in the genesis of disturbances in glucose metabolism in human disease and the prevention of diabetes after its inhibition [79].

## Conclusion

Besides life-style modifications and classical pharmacological strategies using various antidiabetic agents, drugs that inhibit RAS activity might be considered as a valuable alternative to prevent T2DM, especially in patients with arterial hypertension who are well recognized at risk to develop the disease. Since overactivity of the RAS seems to interfere with the microcirculation to key-organs for insulin secretion (endocrine pancreas) and insulin sensitivity (skeletal muscles) as well as to impair intracellular response to insulin signalling, cardiovascular drugs that modulate RAS have attracted particular interest. The intimate relationship between RAS and adipose tissue may play a role in the pathophysiology of both hypertension and T2DM, especially in overweight and obese individuals. Finally, recent animal data suggesting a PPAR- $\gamma$  activity of some ARBs are particularly enticing, even if they require further confirmation in humans.

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