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Antihypertensive Treatment and Cardiovascular Risk Management in Patients with the Metabolic Syndrome – Focus on SNS and Insulin Resistance

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Essential hypertension is very frequently associated with an over-activity of the sympathetic nervous system (SNS) and a decrease in insulin sensitivity of skeletal muscle glucose uptake, even when glycaemic control is (still) normal. In hypertensive patients, two major functions of insulin are impaired: there is insulin resistance of peripheral glucose uptake (primarily skeletal muscle) and insulin resistance of insulin-stimulated vasodilation. This insulin resistance is very often associated with dyslipidaemia, obesity, hypertension and impaired glucose tolerance, a cluster termed the “metabolic syndrome or the insulin resistance syndrome”.

Meta-analyses of antihypertensive intervention studies indicate a less than expected reduction of coronary events (“the coronary paradox”), although blood pressure had been lowered. These findings suggest, that lowering blood pressure is not enough. Furthermore, retrospective and very recent prospective data showed a higher incidence of type 2 diabetes in subjects treated with beta-blocking agents. Thus, the metabolic side effects of the antihypertensive treatment need to receive more attention.

In the metabolic syndrome, a reduction of SNS drive would seem to be specifically effective. However, many groups have shown that antihypertensive treatment with beta-blockers, decreases insulin sensitivity by various mechanisms. In contrast the centrally acting agent moxonidine, an imidazoline II-receptor agonist, may be of interest in this context. It inhibits sympathetic outflow and causes vasodilation.

Moxonidine treatment improved insulin sensitivity specifically in insulin-resistant, obese patients with mild hypertension. Animal studies indicate an improvement of insulin-stimulated glucose uptake into the skeletal muscle and an improvement of glucose tolerance. Therefore, the beneficial characteristics of these newer class of antihypertensive agents suggest, that moxonidine could be advantageous for hypertensive patients with insulin resistance or type 2 diabetes. However, long-term studies are needed to confirm these benefits.

In the cardiovascular risk management, lowering blood pressure is just one cornerstone. Due to the known metabolic “side effects” the selection of the antihypertensive agent might be relevant for the long-term outcome. J Clin Basic Cardiol 2001; 4: 193–195.

**Key words:** hypertension, insulin resistance, antihypertensive treatment, risk factor management

Cardiovascular disease remains the leading cause of death in the industrialized world and hypertension is one important cardiovascular risk factor.

Essential hypertension is very frequently associated with an overactivity of the Sympathetic Nervous System (SNS) [1] and a decrease in insulin sensitivity of peripheral glucose disposal, primarily in skeletal muscle while glycaemic control can still be normal [2–4].

Insulin resistance per se, however, is very often associated with additional atherogenic risk factors such as obesity, dyslipidaemia, a condition referred to variously as “syndrome X” [5] or the “insulin resistance syndrome” [3]. The link among these disorders has been attributed to hyperinsulinaemia, as a consequence of the insulin resistance [6–8].

Meta-analysis of antihypertensive intervention studies indicates a less than expected reduction of coronary events (“the coronary paradox”), although blood pressure had been lowered [9]. These findings suggest that lowering blood pressure is not enough, concomitant metabolic risk factors should receive more attention.

**Effects of Antihypertensive Treatment on Cardiovascular Risk Factors**

There are numerous pharmaceutical interventions for the treatment of hypertension, including thiazide diuretics, adrenergic receptor modulators, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and sympathetic agents. The specific type of antihypertensive intervention can have important consequences on the degree of insulin sensitivity in these hypertensive subjects. Previous studies have revealed an increased prevalence of type 2 diabetes in hypertensive subjects who had been treated with diuretics and non-selective β-adrenergeneceptor antagonists [10–13].

In the last years, the influence of these different antihypertensive agents on insulin sensitivity has been examined with the aid of the hyperinsulinaemic, euglycaemic glucose clamp technique [14], which is considered a gold standard to quantify insulin sensitivity. These clamp studies have shown that many of the widely used antihypertensive agents modify insulin sensitivity in parallel with alterations in the atherogenic lipid profile [11, 15]. For example, α1-adrenergic receptor blockers, vasodilating β-adrenergic blockers, and ACE inhibitors slightly enhance peripheral insulin action, while calcium channel blockers and Angiotensin II receptor antagonists are essentially metabolically neutral. In contrast, thiazide diuretics and non-selective β-adrenergic antagonists decrease insulin sensitivity and worsen dyslipidaemia [15].

**SNS – a Key Role in the Metabolic Syndrome**

An increase in SNS activity decreases insulin sensitivity [1], as the increase in total peripheral resistance will reduce peripheral blood flow and thus substrate and hormone supply to the skeletal muscle. Furthermore, lipolysis is stimulated with an increased availability of FFA (see Figure 1 and below).
Betal-Selective Beta-Blockade and Insulin Sensitivity

At first glance it therefore would seem logical to use a beta-blocking agent in order to modify the increased sympathetic drive. This would then normalise the haemodynamic and metabolic situation, especially the negative impact of SNS on insulin sensitivity [1].

However, this is not the case, considering the increased incidence of type 2 diabetes in patients who had been treated with a beta-blocking agent [10, 12, 13, 16]. In the latter study, there was about 30 % higher incidence of type 2 diabetes within 6 years.

One of the mechanisms involved is a 15–30 % decrease of insulin sensitivity by non-selective and β1-selective beta-blockers, a metabolic effect which is equivalent to a weight gain of more than 10 kilograms [17].

Another mechanism is a beta-blocker induced decrease in clearance of triglycerides and also an increase in total peripheral resistance, thus reducing peripheral blood flow mainly to skeletal muscle [15]. Vasodilating beta-blockers were shown to do better in this regard: they do not decrease insulin sensitivity, in contrast some studies even describe an increase in insulin action [18].

Clinical Observations – Metabolic Effects of Antihypertensive Agents are Relevant

Two large intervention trials have provided evidence that long-term ACE inhibitor treatment can have a positive impact on the incidence of type 2 diabetes in individuals at variable risks for cardiovascular disease. The Captopril Prevention Project (CAPP), a prospective, randomised and open study, enrolled almost 11,000 subjects in Sweden and Finland. These subjects had only hypertension as a cardiovascular risk factor. A greater incidence of type 2 diabetes was observed in the hypertensives taking a beta-blocker (atenolol) or a diuretic, whereas a lesser incidence of type 2 diabetes was seen in these subjects taking the ACE inhibitor captopril [19]. More recently, the Heart Outcomes Prevention Evaluation (HOPE) study evaluated the effects of the ACE inhibitor ramipril on cardiovascular disease in subjects with high cardiovascular risk reported a significantly lower incidence of type 2 diabetes (~34 %) in those on the ACE inhibitor compared with the placebo group [20].

In the UKPDS study the comparison between the ACE inhibitor captopril with the beta-selective beta-blocker atenolol seemed to show no relevant impact of their metabolic effects, as the endpoints were very similarly reduced. However, one has to realize that those individuals treated with atenolol had a significantly higher need for antihyperglycaemic agents in order to maintain glycaemic control [21].

Hypertensive subjects per se (ie without any pharmacological intervention) have a much higher risk for type 2 diabetes [16]; however, when they are treated with a beta-blocking agent the incidence is even higher (+30 % in a time period of 6 years).

Central Modification of SNS – a Better Approach?

As an increase in SNS plays an important role in cardiovascular disease, another promising approach could be the modification of central SNS drive. This could be achieved for example via moxonidine, which is a centrally acting, selective imidazoline I1-receptor modulator. It reduces sympathetic outflow and thereby lowers blood pressure [22].

Experimental Data Show Benefit for Moxonidine in Insulin Resistance

Several research groups independently found an improvement of insulin sensitivity in various animal models of insulin resistance such as the fatty Zucker rat, a non-diabetic model of the metabolic syndrome, the fructose fed rat, the Koletsky rat and in the diabetic fatty Zucker rat [23–26].

Our group found an increase of whole body insulin sensitivity as determined during an oGTT with marked decreases of glucose and insulin levels. This was paralleled by a dose-dependent increase in insulin-stimulated glucose uptake in the isolated skeletal muscle [27]. This suggests direct effects of moxonidine on skeletal muscle glucose transport.

Another mechanism in the development of insulin resistance is the competition between free fatty acids and glucose [28]. An increased oxidation of FFA instead of glucose reduces glucose utilisation. In insulin resistant subjects as well as in patients with type 2 diabetes, suppression of lipolysis (= systemic FFA) is reduced [29].

Chronic treatment of the insulin-resistant, hyperinsulinaemic and dyslipidaemic obese, non-diabetic Zucker rats with moxonidine lowered plasma levels of FFA [28]. This mechanism could therefore contribute to the beneficial effects of moxonidine on glucose metabolism.

Clinical Studies with Moxonidine in Insulin-Resistant Subjects

To see whether these benefits observed in animal models can also be documented in humans, Lithell’s group investigated obese hypertensive patients in a (placebo-controlled) study [29]. Before and after a 9 week treatment period it was quantified by the euglycaemic hyperinsulinaemic glucose clamp. After treatment insulin sensitivity had increased significantly in all subjects (by 11 %). However, when those with the most pronounced impairment of insulin sensitivity were taken as a subgroup, insulin sensitivity had increased even more (by 21 %; [29]). This effect is similar to those seen with ACE antagonists [15].

There are several observations from safety studies which also report an improvement of glycaemia in patients with type 2 diabetes mellitus (Lilly, data on file).

Conclusion

Patients with hypertension frequently show several atherogenic risk factors, a cluster described as the metabolic (or insulin resistance) syndrome, in which insulin resistance plays...
a central role. Augmented sympathetic nervous system activity is involved in aggravating the metabolic and haemodynamic alterations.

In the past it has been shown that many of the currently widely used antihypertensive agents modify insulin sensitivity. Some of them, such as high dose diuretics and beta-blockers (non-selective and β1-selective), have a negative impact on metabolism as they decrease insulin sensitivity, while others, the ACE inhibitors, alpha-blockers, vasodilating beta-blockers and moxonidine have beneficial effects on insulin sensitivity.

Considering that lifelong treatment of hypertension is necessary, these metabolic side effects can have very important impacts on the atherosclerotic risk. Thus, the choice of an antihypertensive agent should not only focus on lowering blood pressure, but should also respect these metabolic issues. If you want to lower cardiovascular risk, it is not enough to only lower blood pressure.

References
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