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Hyperinsulinemia, hyperproinsulinemia and insulin resistance in the metabolic syndrome

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Abstract. For better comprehension of the metabolic syndrome, it is necessary to differentiate the effect of insulin on glucose metabolism on the one hand, and on other metabolic activities on the other hand. Whereas glucose utilization is affected by insulin resistance, the effect of insulin on lipid metabolism, ion and aminoacid transport does not seem to be diminished. Lipid metabolism, however, seems to play a crucial role in the induction of the vicious cycle. Increased energy and fat ingestion may be due to an increased number of galanin secreting cells in the hypothalamus. The excessive fat intake results in an increased rate of release of insulin and increased influx of triglycerides into the blood. From these triglycerides an excess of free fatty acids is released by the action of lipoprotein lipase. The increased plasma free fatty acid level then results in insulin resistance affecting glucose metabolism. Also, these free fatty acids may impair the secretion of insulin. Induction of insulin resistance results in higher glucose levels, which may cause hyperinsulinemia. Hyperinsulinemia maintains the elevation of triglycerides. When diabetes becomes overt and elevated glucose levels prevail, the hyperinsulinism acts on the metabolic pathways which are still sensitive to insulin, namely lipid metabolism, aminoacid transport and ion transport.
Key words. Insulin; proinsulin; insulin resistance; metabolic syndrome; triglycerides; free fatty acids; fat intake; galanin.

Abbreviations. HDL = high density lipoproteins; NIDDM = non-insulin dependent diabetes mellitus; oGTT = oral glucose tolerance test; oMTT = oral metabolic tolerance test; VLDL = very low density lipoproteins; WHR = waist-hip ratio.

Hyperinsulinemia versus insulin resistance – diverging explanatory models for different facets of the metabolic syndrome

Abdominal obesity, type 2 diabetes, hypertension, dyslipoproteinemia and precocious atherosclerosis are diseases of major socioeconomic impact in industrialised countries. Because of the frequent coincidence of these diseases, and on the basis of common pathophysiological features, they are combined under the term 'metabolic syndrome'.

The different facets of the metabolic syndrome are considered to be related to insulin resistance on the one hand, and to hyperinsulinism or at least hyperinsulinemia on the other hand. Generally, obesity and type 2 diabetes are associated with insulin resistance. Dyslipoproteinemia, and particularly hypertriglyceridemia and VLDL-elevation, however, are attributed to an increased insulin action, as are the increased sodium retention and the proliferation of smooth muscle cells in hypertension[2,3,20,22] (figs 1 and 2). Precocious atherosclerosis is also suggested to be related to elevated insulin levels and to an increased effect of insulin[19–23] (Table 1). Thus the different facets of one and the same syndrome are explained with two contradictory rationales: an excess of insulin action on the one hand and insulin resistance, which means a deficiency of insulin action, on the other.

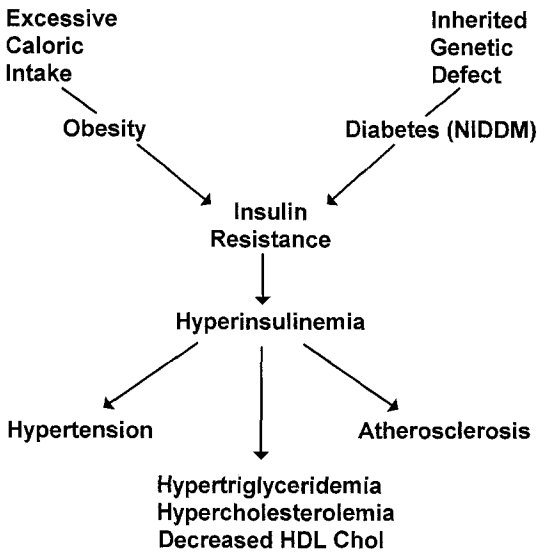

Figure 1. Scheme of the metabolic cascade of the syndrome of insulin resistance after De Fronzo and Ferrannini[3]: Leading from acquired (obesity) or inherited (NIDDM) insulin resistance to hyperinsulinemia and eventually to hypertension, abnormal plasma lipid profile and atherosclerosis.

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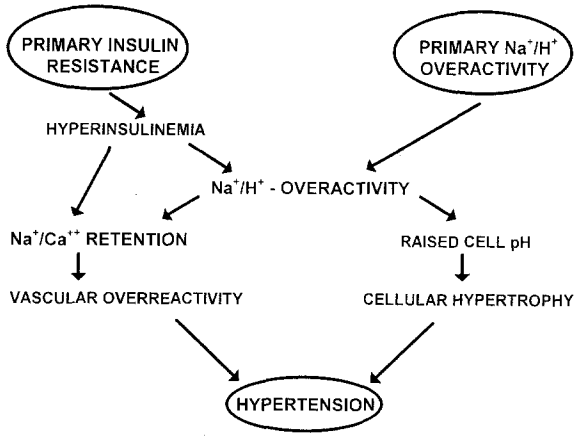

Figure 2. Scheme of the metabolic cascade resulting in arterial hypertension after De Fronzo and Ferrannini[3]: Relationship between insulin resistance, plasma insulin concentration, activity of Na^+/H^+ exchanges in arterial smooth muscles cells, and hypertension.

Table 1. Insulin effects causing the development of atherosclerosis[18–22].

- VLDL-production↑
- VLDL and chylomicron-degradation↑ by stimulation of lipoproteinlipase (LPL) activity → remnants↑
- cholesterol synthesis↑
- LDL-binding↑ of smooth muscle cells of monocytes
- proliferation↑ of smooth muscle cells
- catecholamines
- sodium retention → hypertension
- pH↑ in smooth muscle cells → hypertension

↑ = increase of; → = resulting in; VLDL = very low density lipoproteins; LDL = low density lipoproteins.

Hyperinsulinemia versus insulin deficiency in type 2 diabetes

The understanding of the syndrome is made even more complicated by findings of Hales and coworkers[7–9,24]. This group considers that in type 2 diabetes insulin secretion is deficient but secretion of proinsulin and split-proinsulin is unaltered or is higher. The workers assessed the true insulin levels (i.e. without proinsulin) and the proinsulin levels at different glucose concentrations in a clamping trial. Under these circumstances levels of insulin and proinsulin increased equally with increasing glucose level in healthy volunteers. In type 2 diabetics, however, the insulin increase was less pronounced, although the proinsulin levels reacted normally to higher glucose levels[8]. Thus, related to the glucose level, insulin deficiency is found in type 2 diabetes.

One has to take into consideration, however, that in overt diabetes glucose levels are usually elevated and, the higher insulin levels measured are related to this. If

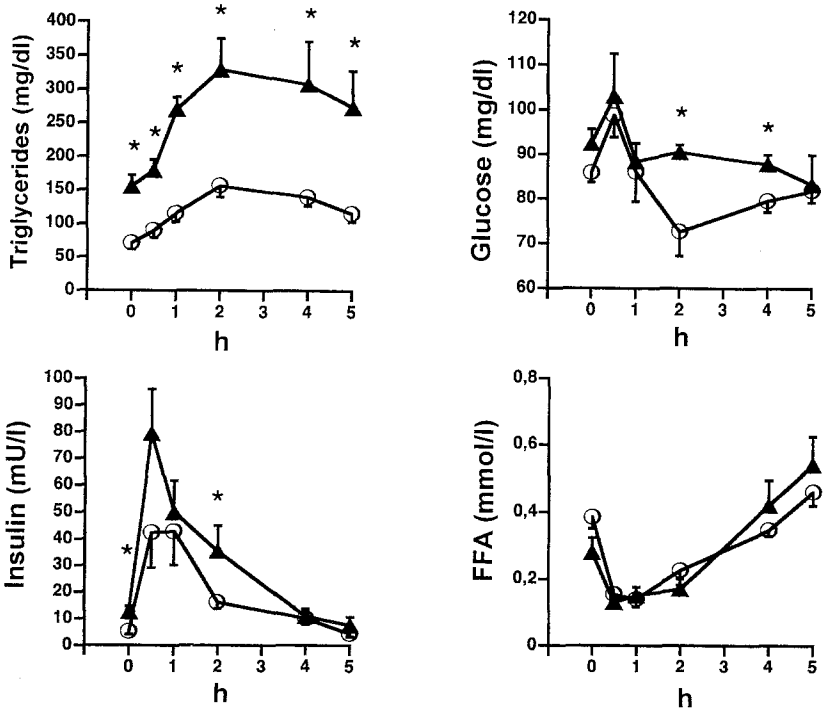

Figure 3. Serum concentrations of triglycerides, insulin, glucose and free fatty acids (FFA) in 9 so-called Normal (o) and 5 socalled High Responders (Δ, n = 12) before and after a standardized metabolic tolerance test (oMTT) containing 58 g mainly (57%) saturated fat, 75 g carbohydrates (mainly sucrose), 30 g protein and 10 g alcohol.

Table 2. Links between high triglyceride responses and the metabolic syndrome[4, 12, 15, 16].

- higher (true) insulin levels
- decreased insulin sensitivity towards glucose
- higher proinsulin/insulin ratio
- increased abdominal fat
- higher postprandial energy expenditure
- increased postprandial catecholamine release
- higher apolipoprotein E_2 prevalence
- increased atherogenic lipoprotein fractions

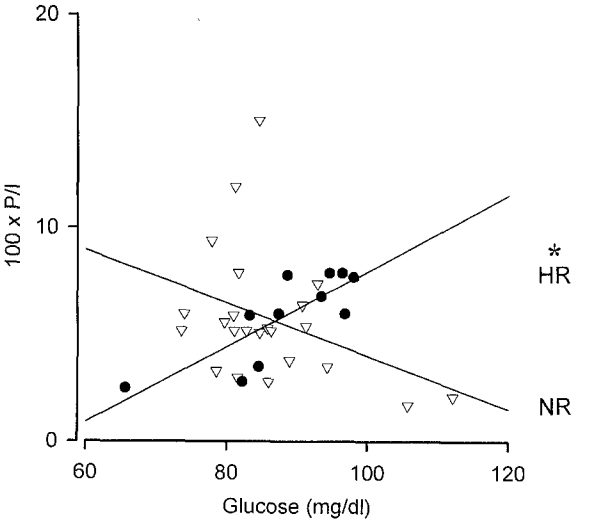

Figure 4. Ratio between proinsulin and true insulin (100 P/I) in relation to fasting glucose values, ● 11 High Responders (HR), ▽ 23 Normal Responders, according to (12); *p = 0.003, correlation coefficient r = 0.806 in HR, no significant correlation in NR.

the prevailing glucose elevation is neglected, formally hyperinsulinemia is found. In fact, there is an absolute insulin deficiency with respect to glucose levels and not only the relative insulin deficiency which is described as insulin resistance. This deficiency of insulin which becomes particularly evident at higher glucose levels, becomes even more pronounced if only the level of insulin itself ("true insulin") is considered.

The question may be raised whether the deficiency of insulin secretion is only a sign of overt diabetes, or if it already existed at an earlier stage. Therefore Reaven[11] investigated not only diabetics but also people with impaired glucose tolerance, and compared these groups with non-diabetics. He could show that the true insulin levels were in fact diminished in type 2 diabetes, but in contrast, in subjects with impaired glucose tolerance the insulin levels exceeded those in healthy controls.

In subjects with impaired glucose tolerance the glucose levels are by definition higher than normal. Therefore, the results of these investigations did not permit a decision as to whether the insulin levels were really elevated or showed a normal relationship to the higher glucose levels. Therefore we investigated a cohort who had normal glucose tolerance, but already exhibited other signs of the metabolic syndrome.

This group was defined in previous studies in healthy male volunteers at the age of 25. Fifteen percent of the subjects exhibited an excessive triglyceride response (see fig. 3) to a standardized load containing carbohydrates and fat. Based on the bimodal frequency distribution of the triglyceride maxima, we suggested that the subjects belonged to a particular cluster having the 'Phenomenon of Triglyceride High Response'[13]. This phenomenon turned out to be reproducible and was associated with the following characteristics of the metabolic syndrome: excessive triglyceride response, higher total insulin and true insulin levels (fig. 3), a reduced sensitivity of insulin in terms of reduced glucose utilization, an elevated proinsulin/insulin ratio, a

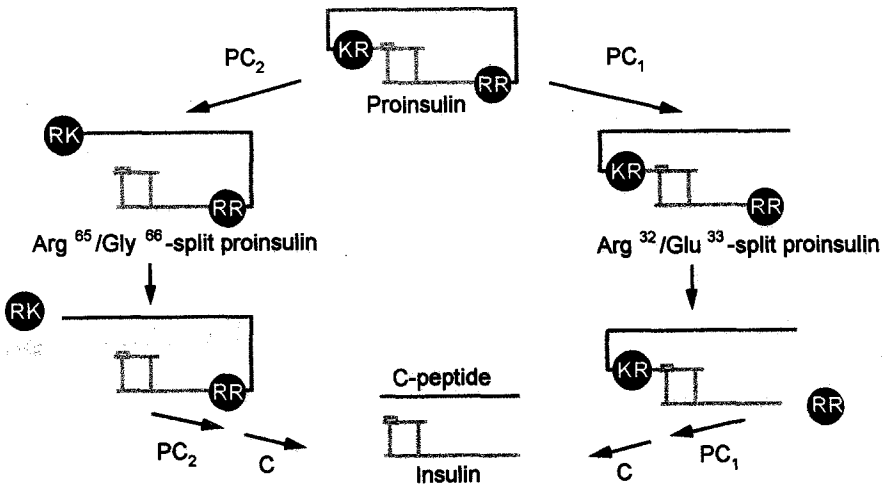

Figure 5. Enzymatic steps in proinsulin processing. Paired basic amino acids at conversion sites: lysine (K), arginine (R), carboxypeptides (C), prohormone convertase (PC_1 and PC_2).

Table 3. Differentation of insulin sensitivity with respect to its different effects in the metabolic syndrome.

- on glucose metabolism↓
- on ion transport ±
- on amino acid transport ±
- on lipid metabolism ±
- with high glucose levels →
- hyperinsulinism towards ion, aminoacid transport and lipid metabolism

↓ = reduced; ± = unaltered insulin sensitivity; → = resulting in.

higher intra-abdominal adipose tissue mass in spite of a normal body mass-index, increased dietary-induced thermogenesis, increased postprandial catecholamine release, and an elevated apolipoprotein E2 prevalence which corresponds to the prevalence seen in type 2 diabetics[4,12,14–16] (table 2).

In this group of triglyceride high responders, the ratio between proinsulin and insulin increased with increasing fasting and postprandial glucose levels, whereas this ratio remained constant, independently of the blood glucose level, in normal triglyceride responders. Thus, there is not only a quantitative but also a qualitative difference between high and normal responders. In high responders the impairment of proinsulin processing becomes evident with increasing load, whereas in normal responders an increasing load does not result in altered processing (fig. 4).

From these findings it is unlikely that the increased proinsulin secretion is caused by an increased rate of secretion at higher glucose levels. It could be due to a defect, possibly a basic one, occurring, very early. Based on the fact that 32, 33 split-proinsulin (see fig. 5) was also increased, we suggest that in this defect the prohormone convertase 2 (PC 2) or the carboxypeptidase (fig. 5) is also affected. Alternatively, an impairment of the transport processes of the secretory granula may be present.

The higher ratio of proinsulin and split proinsulin secretion may have an impact on the development of late complications in diabetes and in atherosclerosis, respectively. The risk factors which are associated with the metabolic syndrome, such as low HDL, high triglyceride levels, high arterial blood pressure, increased waist-hip ratio (WHR) and plasminogen activator inhibitor levels seem to be better correlated with proinsulin and split proinsulin levels than with the level of insulin itself[9,7]. Plasma concentrations of plasminogen activator inhibitor may even be decreased during insulin treatment, which inhibits the endogenous secretion and thus the proinsulin and split proinsulin secretion[7]. Thus in the early stage of the metabolic syndrome, where oral glucose tolerance is still normal, hyperinsulinemia is found. Already at this stage, however, an impairment of proinsulin processing is evident, resulting in higher proinsulin and split proinsulin levels. At the stage of

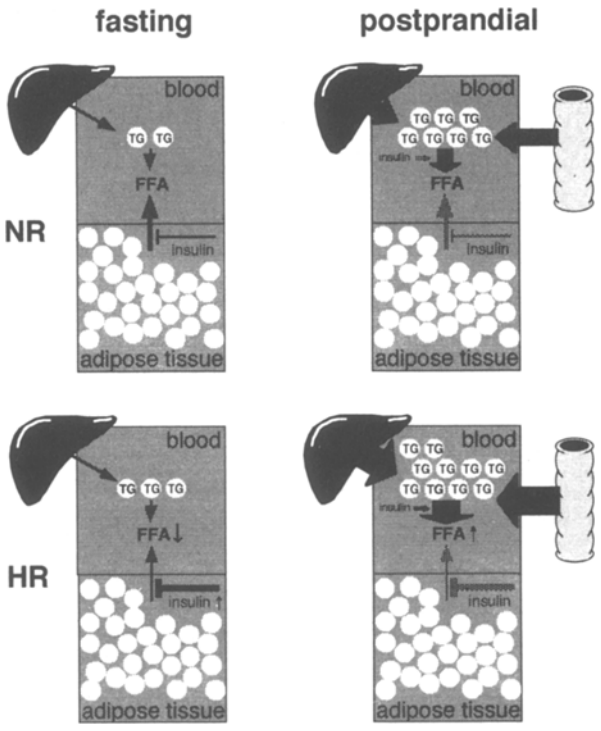

Figure 6. Insulin decreases free fatty acids (FFA) in the fasting state and increases FFA in the postprandial state: In the fasting state insulin has an antilipolytic action on the adipose tissue. In Triglyceride High Responders (HR) FFA are lower than in Normal Responders (NR). In the postprandial state insulin levels are elevated, the release of FFA from adipose tissue is inhibited. In this state FFA are released from another compartment, the affluent triglyceride-rich lipoproteins (TG). In HR higher insulin levels increase lipoprotein lipase activity and thereby release excessive FFA from increased TG.

type 2 diabetes, higher glucose and higher insulin levels and comparatively even higher proinsulin levels are found. The higher insulin levels exert their effects on the branches of insulin action other than glucose metabolism (lipid metabolism, amino acid metabolism and ion transport) to the full extent (table 3). Related to glucose levels, however, a deficiency in insulin secretion exists, but this is accompanied by undiminished secretion of proinsulin and split proinsulin.

Hyperinsulinemia versus insulin resistance

During hyperglycemia in type 2 diabetes insufficient insulin is secreted. However, the fact that higher insulin dosages have to be administered to attain a certain glucose level shows that not only an absolute but also a relative insulin deficiency, in the sense of insulin resistance, exists in type 2 diabetes. As mentioned above, this seems to be contradictory to the reflections on the pathogenesis of hypertension and dyslipoproteinemia. However, it has to be noted that insulin resistance is only defined in relation to glucose utilization. The resistance of glucose metabolism towards insulin is found mainly in subjects with excessive postprandial trigylce-

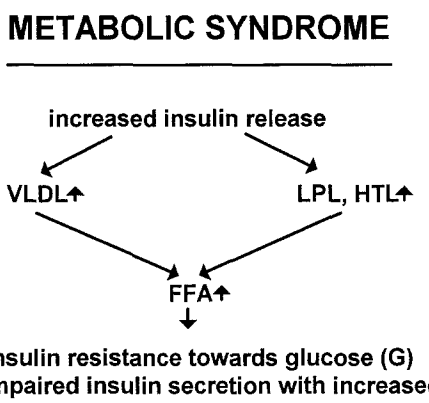

Figure 7. Hyperinsulinemia in the metabolic syndrome results in VLDL elevation (↑) and lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTL) activation leading to elevated plasma free fatty acids (FFA). These FFA levels explain insulin resistance towards glucose and impaired insulin secretion.

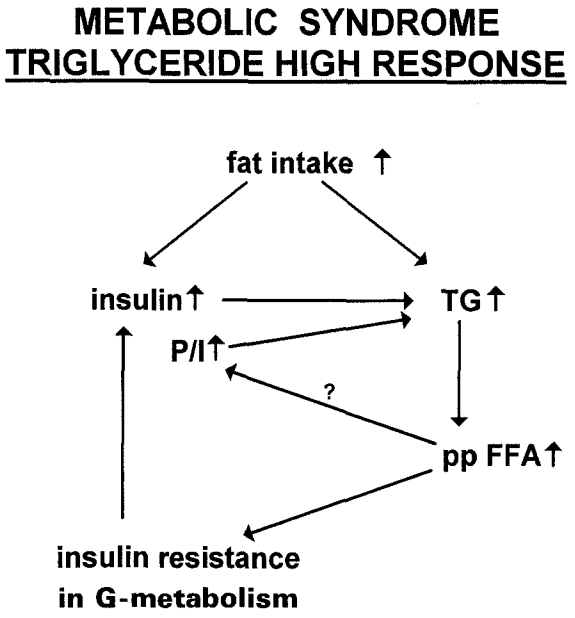

Figure 8. The vicious cycle in the syndrome, driven by increased (↑) fat intake resulting in hyperinsulinism on the one hand and insulin resistance in glucose (G) metabolism on the other hand. Resistance and eventually the impairment of insulin secretion are mediated by postprandial (pp) elevation of free fatty acids (FFA).

ride responses who seem to reflect an early stage of the metabolic syndrome ('premetabolic syndrome'?). These subjects already show higher glucose levels (although still in the normal range) after a fat, ethanol and carbohydrate containing meal than do normal triglyceride responders. These higher glucose levels are accompanied by higher insulin levels in the fasting and particularly in the postprandial state (fig. 3). This means that, in this early stage, a lowered response of glucose metabolism towards insulin exists[14].

However, in contrast to the glucose levels, the plasma concentrations of free fatty acids are lower in triglyceride high responders compared with normal responders (fig. 3), which suggests an adequate insulin effect at higher insulin levels[14].

Postprandially, the levels of free fatty acids, however, are higher in high responders than in normal responders. This again suggests a greater response to insulin, or an average response but at higher insulin levels. It must be noted that metabolic regulation in the fasting and in the postprandial state differs (see fig. 6). In the fasting state free fatty acids are derived from the adipose tissue and insulin acts antilipolytically according to its anabolic effect. Postprandially the free fatty acids are derived from another compartment, namely the lipoprotein fraction of the plasma. By definition, the influx of these lipids is increased in HR; moreover, insulin causes an increased release of free fatty acids from these lipoproteins by activation of lipoprotein lipase (fig. 7). This again corresponds to the anabolic principle of insulin, since postprandially the lipids are directed towards the tissues in which deposition of lipids occurs. Thus, in subjects with normal glucose tolerance, but already other signs of the metabolic syndrome, higher glucose levels are found at higher insulin levels, indicating that glucose utilization is showing resistance to insulin. At the same time, however, an excess of insulin action on other pathways is found in the presence of increased insulin levels, corresponding to an adequate insulin action on lipid metabolism at higher insulin levels. In conclusion, there is a dissociation of the insulin sensitivity of glucose metabolism on the one hand and of lipid metabolism on the other hand[14] (table 3).

This is in accordance with findings in hypertensive patients[18]. In these patients free fatty acids were increased during a normal day, which included several meals. Since the metabolism of the lipids from a meal lasts more than 9 h, postprandial conditions prevailed all day long, with the exception of the last two hours before blood withdrawal in the morning. Therefore the findings must be interpreted as showing adequate insulin action at increased insulin levels, and not as a result of insulin resistance in lipid metabolism. The insulin resistance only exists in the glucose branch of insulin action. Induced by insulin excess, free fatty acids are released from VLDL (figs 6 and 7) and these fatty acids induce insulin resistance in the glucose pathway[1,5,6]. In addition, particularly at higher glucose levels, the free fatty acids can result in impaired insulin secretion, as shown in in-vitro experiments of Zhou and Grill[26].

Consequently, it is considered that the free fatty acids have major impact on the pathogenesis of the metabolic syndrome. This may explain why a standardized meal containing fat, ethanol and carbohydrates unveils a metabolic impairment which is not detected by an oral glucose tolerance test[10]. This standardized metabolic test not only results in high triyglceride levels in high responders, as expected by definition, but also in higher glucose levels. In contrast to this, the glucose as well as

the insulin values after administration of glucose alone (oGTT), showed no difference compared to the controls. Only if fat was added, which caused the release of free fatty acids from the plasma lipoproteins, did insulin resistance become apparent (by an elevation of the plasma levels of glucose and insulin).

Conclusion

In conclusion, the effects of insulin on glucose metabolism and on other metabolic areas need to be differentiated. Even when there is insulin resistance in connection with glucose utilization, the effect of insulin on lipid metabolism does not seem to be diminished. The same holds true for ion and amino acid transport[3]. Fat metabolism does, however, seem to play a crucial role in causing a vicious cycle. Increased intake of fat may have particular significance since this may be due to an increased preference for fat in subjects with type 2 diabetes[25]. As histological investigations of our group showed, an increased concentration of galanin-positive cells in the nucleus arcuatus hypothalami may be responsible[17].

The increased ingestion of animal fat may result in an increased release of insulin and an increased influx of trigylcerides into the blood (fig. 8). From the increased postprandial triglycerides, an excess of free fatty acids is released by the action of excessively secreted insulin. These free fatty acids then result in insulin resistance in the glucose metabolic pathway. Insulin secretion may also be impaired by these free fatty acids. Whether the impaired processing is also induced by free fatty acids has to be shown in further investigations. Induction of insulin resistance results in higher glucose levels, which again enhance hyperinsulinemia. Hyperinsulinemia maintains the elevation of triglycerides. When diabetes becomes overt, and elevated glucose levels are prevailing, the hyperinsulinism acts particularly on those aspects of metabolism in which insulin action is not restricted, namely lipid metabolism, amino acid transport and ion transport.

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