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# Mitochondrial diabetes mellitus: a review

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**Abstract**

We review the relationship between various types of mitochondrial DNA mutations and the prevalence as well as the pathobiochemical and clinical features of mitochondrial diabetes mellitus. An A to G transversion mutation in the $tRNA^{Leu(UUR)}$ gene is associated with diabetes in about 1.5% of the diabetic population in different countries and races. Phenotypically this type of mitochondrial diabetes is combined with deafness in more than 60% and is clinically distinguishable with respect to several characteristics from the two idiopathic forms of diabetes. The underlying pathomechanism is probably a delayed insulin secretion due to an impaired mitochondrial ATP production in consequence of the mtDNA defect.

*Keywords:* Mitochondrial DNA; DNA; Diabetes mellitus; Wolfram syndrome

While glucose intolerance is a symptom of various diseases, the term diabetes mellitus represents a genetically heterogenous group of disorders. Currently, diabetes is subdivided into two idiopathic forms, type 1 and type 2 diabetes or IDDM and NIDDM on one side and a group of about 60 genetic syndromes on the other side, in which diabetes is only one symptom [1]. This combination with quite different genetic syndromes demonstrates that glucose intolerance can be a result of mutations at many different nuclear loci. Furthermore, it also illustrates that quite different pathogenetic mechanisms are associated with the symptom diabetes. Genetic factors contribute to the development of diabetes not only in several genetic syndromes but also in both idiopathic forms of diabetes mellitus (Table 1). Concordance rates in identical twins of near 100% and less than 40% for type 2 and type 1 diabetes, respectively, clearly demonstrate a different genetic background for both forms. Furthermore, IDDM but not NIDDM shows an association to the HLA system. About 95% of diabetic Caucasians have HLA-DR 3 and/or 4 indicating heterogeneity within the IDDM class. As about 50% of subjects in the nondiabetic Caucasian population also carry these HLA alleles HLA-DR 3 or DR 4 are not pathognomonic of IDDM. Several other, non-HLA genes are supposed to contribute to the genetic predisposition to IDDM. However, by comparing the risks of HLA-identical siblings to that of monozygotic twins one can estimate that HLA provides approximately 60–70% of the overall genetic susceptibility to IDDM [1]. The association with the HLA-system is accompanied with specific immunologic phenomena in IDDM but not in NIDDM.

## 1. Different types of mtDNA mutations are associated with diabetes

Hints for the contribution of mtDNA to the development of diabetes [2–4] came from two different observations: first, from epidemiological studies revealing a predominantly maternal transmission of NIDDM [5–7]; secondly, from observations that diabetes is frequently associated with mitochondrial diseases [2,8,9]. The presence of diabetes has been noted in single patients with chronic progressive external ophthalmoplegia and the complete Kearns–Sayre syndrome carrying large mtDNA deletions and duplications [8–11]; in patients with Pearson's bone marrow pancreas syndrome [12]; with renal tubular dysfunction [13,15] and in maternally inherited syndromes such as the MELAS syndrome (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) [14,19], rarely in those with the MERRF syndrome (myoclonus epilepsy with ragged red fibers) [16,17].

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Table 1
Differences between IDDM, NIDDM and mitochondrial diabetes (MDM)

| | IDDM | NIDDM | MDM |
|---|---|---|---|
| Clinical characteristics | thin | obese | lean |
| | ketosis prone | ketosis resistant | no ketosis |
| | insulin dependent | diet + drugs | mostly insulin |
| Onset | childhood, adulthood | mostly after 40 | mostly before 40 |
| Insulin response to glucose | no or small response | variable response | delayed response |
| Peripheral insulin effect | yes | resistant | yes |
| Glucagon secretion | normal | normal | impaired |
| Genetic defect | not known | not known, mutations of glucokinase MODY | mutations in mtDNA |
| Monozygotic twin studies | concordance < 40% | concordance > 90% | ? |
| HLA association | yes | no | no |
| Antibodies against: insulin | yes | no | ? |
| GAD | yes | no | no |
| islet cells | yes | no | no |

GAD = glutamic acid decarboxylase; MODY = maturity onset diabetes of the young.

In 1992 two large pedigrees have been identified with diabetes and deafness, one harboring a unique 10.4 kb mtDNA deletion flanked by a 10 bp direct repeat at nucleotide positions (nps) 4389 and 14812 [3], and the other carrying the 'MELAS-associated' $tRNA^{Leu(UUR)}$ mutation at np 3243 [4]. This latter observation has been

Table 2
$tRNA^{Leu(UUR)}$-3243 mutation and diabetes (update June 1994)

| Subjects | Number of families ($n$) | Number of mutations, $n$ (%) | Reference |
|---|---|---|---|
| Familial IDDM | 55 | 3 (5.5) | Kadowaki et al. [24] |
| | 17 | 1 (5.9) | Jaksch et al. [27] |
| | 90 | 0 | Vionnet et al. [23] |
| | 6 | 0 | Katagiri et al. [25] |
| | 200 | 0 | Hattersley et al. [52] |
| IDDM without | 25 | 0 | Odowara et al. [31] |
| familial history | 85 | 0 | Kadowaki et al. [24] |
| All IDDM | 481 | 4 (0.8%) | references above |
| Slowly progressive IDDM | 27 | 3 (11%) | Oka [53] |
| | 50 | 2 (4%) | Bain [54] |
| Familial NIDDM | 267 | 5 (1.9%) | Vionnet et al. [23] |
| | 30 | 1 (3.3%) | Awata et al. [22] |
| | 100 | 2 (2%) | Kadowaki et al. [24] |
| | 68 | 1 (1.5%) | Alcolado et al. [26] |
| | 215 | 6 (2.8%) | Hashiramoto [28] |
| | 294 | 4 (1.4%) | Katagiri et al. [25] |
| | 210 | 5 (2.4%) | Otabe et al. [32] |
| Maternal NIDDM | 65 | 2 (3.1%) | Van den Ouweland et al. [29] |
| | 28 | 3 (10.7) | 't Hart et al. [30] |
| | 12 | 1 (8.3%) | Walker et al. [55] |
| NIDDM and deafness | 5 | 3 (60%) | Kadowaki et al. [24] |
| NIDDM without | 35 | 0 | Van den Ouweland et al. [4] |
| familial history | 150 | 0 | Alcolado et al. [26] |
| | 80 | 0 | Van den Ouweland et al . [29] |
| | 473 | 2 (0.5%) | 't Hart et al. [30] |
| | 550 | 5 (0.9%) | Kadowaki et al. [32] |
| | 89 | 3 (3.4%) | Odowara et al. [31] |
| | 300 | 0 | Saker et al. [56] |
| All NIDDM | 2971 | 43 (1.4%) | references above |
| All IDDM and NIDDM | 3529 | 52 (1.5%) | all references |

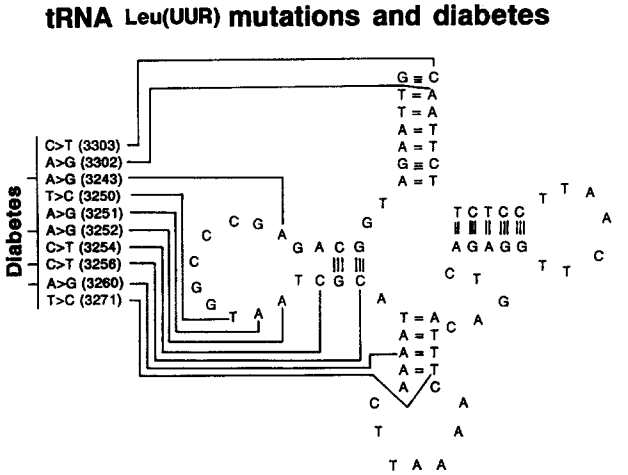


Fig. 1. $tRNA^{Leu(UUR)}$ mutations and diabetes.

confirmed by many other reports even in pedigrees with different racial background [18–32]. The mitochondrial $tRNA^{Leu(UUR)}$ gene appears to be an etiological hot spot for mtDNA mutations. Ten disease-related mutations have been described, so far, in this gene which comprises about 60% of all mitochondrial tRNA gene mutations [35] (Fig. 1). Four of them have been described in single cases as being associated with diabetes and various other symptoms. An A/G transition at np 3252 was found in a patient with mitochondrial encephalomyopathy, pigmentary retinopathy, dementia and hypothyroidism [33], an A/G mutation at np 3260 in single patients from a large pedigree with maternally inherited myopathy and cardiomyopathy [34] and a C/T exchange at np 3256 in a patient with a MERFF-like syndrome [35].

## 2. Prevalence of the $tRNA^{Leu(UUR)}$-3243 mutation among diabetics

The overall prevalence of diabetes in the western European countries lies between 3 and 6%. The contribution of the $tRNA^{Leu(UUR)}$ mutation at np 3243 has recently been investigated in the Netherlands, France, U.K., Germany and Japan (Table 2) [18–32]. The prevalence of mitochondrial diabetes (MDM) seems not to be quite different between the different countries and races and is about 1.5% among both idiopathic diabetes forms and about 2–5 fold higher in cases with familial history of diabetes. Thus, the $tRNA^{Leu(UUR)}$-3243 mutation seems not to be a major cause of diabetes but contributes substantially to its overall incidence. The prevalence of MDM is therefore about 0.06% in the general population, and this accounts, for example, for about 200000 diabetic patients in the European community carrying this mutation. The occurrence may, in fact, even be higher since the amount of mutated mtDNA molecules is low in blood cells of some patients and hardly detectable when compared to fibroblasts, skeletal muscles or epithelial cell from a mouthwash. Thus, screening for the heteroplasmic 3243 mutation as well as for duplication/deletion mutations on mtDNA extracted from blood may lead to an underestimation and should, therefore, be preferentially performed on other cells. With the exception of the 3243 exchange mutations at other positions within the $tRNA^{Leu(UUR)}$ gene have, so far, not been investigated systematically in large diabetic collectives. Only the 3271 mutation has been tested in a group of 215 NIDDM with familial history but no respective case has been found [28]. A search for large duplication/deletion mutations has been performed by Alcolado et al. [26]

Table 3
Clinical symptoms in affected members from 45 families with diabetes and a mitochondrial $tRNA^{Leu(UUR)}$ mutation at np 3243

| Reference | Number of families ($n$) | Number of affected members ($n$) | Clinical symptom | | | | |
|---|---|---|---|---|---|---|---|
| | | | DM | D | DM + D | DM + D + N or DM + M | D + N |
| Van den Ouweland [4] | 1 | 18 | 1 | 6 | 11 | – | – |
| Reardon [18] | 1 | 13 | 4 | 2 | 7 | – | |
| Gerbitz [19] | 1 | 5 | – | – | 3 | 2 | – |
| Sue [20] | 2 | 34 | 1 | 12 | 8 | 7 | 6 |
| Awata [22] | 1 | 3 | 1 | – | 2 | – | – |
| Kadowaki [24] | 22 | 57 | 17 | 4 | 28 | 8 | – |
| Katagiri [25] | 4 | 19 | 9 | 1 | 9 | – | – |
| Van den Ouweland [29] | 2 | 12 | – | 5 | 5 | 2 | – |
| 't Hart [30] | 2 | 13 | 1 | 1 | 11 | – | – |
| Suzuki [44] | 7 | 17 | 3 | – | 7 | 7 | – |
| Hattersley [52] | 2 | 8 | 4 | – | 4 | – | – |
| Sum | 45 | 199 | 41 | 31 | 95 | 26 | 6 |
| Percentage | | 100 | 21 | 15 | 48 | 13 | 3 |

DM, diabetes mellitus; D, deafness; N, neurological symptoms; M, complete MELAS syndrome.

in 68 diabetic subjects with affected siblings and by Van den Ouweland et al. [29] in 45 NIDDM patients with maternal history without any positive findings. It is, thus far, not known to what degree further mtDNA point mutations contribute to the prevalence of diabetes.

## 3. Phenotypic diversity of the tRNA$^{Leu(UUR)}$ mutation in association with diabetes

The tRNA$^{Leu(UUR)}$-3243 mutation was first described in MELAS patients and subsequently in patients with maternally inherited diabetes. Of the 199 affected members from 45 families with diabetes and the tRNA$^{Leu(UUR)}$-3243 mutation so far described 48% suffered from diabetes and deafness, 13% had diabetes combined with deafness and other neurological symptoms including MELAS, 21% had only diabetes and 15% had deafness alone or combined with neurological alterations (3%) (Table 3). The high percentage of about 60% of the combination of both symptoms diabetes and deafness is striking. Due to the lack of examination for hearing abnormalities by the physicians the symptom hearing loss might be underestimated to some degree. The clinical variability of the 3243 mutation may not be restricted to these two disorders, as emphasized by the recent discovery of its presence in patients with cardiomyopathy [58] and an Alport-like syndrome (Jansen, J.J., Van den Ouweland, J.M.W., Van der Woude, F.J., Buijn, J.A., 't Hart, L.M., Maassen, J.A., Van Oost, B.A. and Lemkes, H.H.P.J., unpublished data). The degree of heteroplasmy varies in different organs and tissues which might be responsible for the phenotypic diversity caused by the mutation [14]. Another theoretical explanation is that further nuclear or mitochondrial mutations may influence the variability of the phenotype. While searching for such additional and synergistically functioning mutations we have found a transition at np 3398 in a family with the tRNA$^{Leu(UUR)}$-3243 mutation, suffering from diabetes, deafness and cardiomyopathy [19]. The 3398 mutation changes a highly conserved methionine to a threonine within the *ND1* gene and is accompanied with a severe complex I deficiency. It was neither demonstrable in 143 disease controls nor in 263 subjects with NIDDM of whom two also had the 3243 mutation, indicating that it is not diabetes-specific, but may contribute to the severity of the disease.

A similar variant of the same ND1 codon, i.e. a base exchange at 3397 causing a methionine to alanine exchange in this conserved region, was recently described by Shoffner et al. [36] in two patients with Parkinson and Alzheimer, respectively. Thus, these two mutations of the same ND1 codon and, in consequence, the respective amino acid exchanges possibly influence the phenotypic expression of quite different disorders in single patients.

In the large Dutch pedigree with diabetes and deafness carrying the 3243 mutation, 45 mutations have been identified by direct sequencing compared to the published Cambridge sequence [4]. However, besides 14 silent mutations in coding sequences and 29 known polymorphic sites, only the A to G transition at np 3243 was present in all members of the branch affected with diabetes while absent in another branch without diabetes. Furthermore, six additional mutations present in this pedigree, which could confer the phenotype of the 3243 mutation to diabetes, were absent in three other pedigrees with diabetes and deafness, showing that the 3243 mutation alone associates with this particular phenotype [29].

## 4. Is the symptom diabetes in other genetic disorders related to mtDNA?

Wolfram's syndrome (MIM 222300) is characterized by diabetes insipidus, diabetes mellitus, optic atrophy and deafness giving rise to the acronym DIDMOAD. Other less common endocrinological and neurological abnormalities are hypogonadism, atonic bladder, ataxia, insomnia, seizures and a relatively high incidence of depression and psychotic behaviour. The syndrome has long been known as an autosomal recessive disorder. As most of the clinical phenotypes characteristic of the syndrome are consistent with an ATP supply defect, Bu and Rotter have recently proposed that the syndrome represents a mitochondrially mediated disease with either a nuclear or a mitochondrial genetic origin [37]. This hypothesis was confirmed by one report on a sporadic case with a 7.6 kb deletion mutation of the mitochondrial genome [38]. We were not able to demonstrate mtDNA deletions or insertions (Van den Ouweland, J.M.W. and Maassen, J.A., unpublished observation) or any disease-related alterations in all mitochondrial tRNA genes from DIDMOAD patients [39]. Using SSCP, restriction analysis and direct sequencing of PCR

Table 4
LHON class II point mutation pattern in 7 Wolfram-syndrome suffering families

| Mutation site (np) | Gene | Nucleotide exchange | AS exchange | Conservation | Controls (%) | Families | | | | | | | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| 3394 | ND1 | T/C | Y/H | high | < 2 | − | − | − | − | − | + | − | 14 |
| 4136 | ND1 | A/G | Y/C | moderate | < 6 | − | − | − | + | − | − | − | 14 |
| 4216 | ND1 | T/C | Y/H | low | 7–13 | − | − | + | + | + | + | + | 71 |
| 4917 | ND2 | A/G | D/N | high | < 4 | − | − | + | − | + | + | + | 57 |

fragments we have extended our studies by investigating all the mitochondrially encoded respiratory chain subunits in index patients from seven families with complete and incomplete (without diabetes insipidus) Wolfram syndrome. In five of these families we have detected a mutation pattern usually found in LHON families [40,41] Table 4. Our finding is confirmed by a recent report [42] on a young man suffering from incomplete Wolfram syndrome and carrying the most common LHON mutation at np 11778.

Thus, the symptom diabetes can be associated with three different types of mtDNA mutations: (i) deletion/duplication mutations, (ii) biogenic mutations in the $tRNA^{Leu(UUR)}$ gene, and (iii) missense mutations in the ND subunit genes.

In other words, the term 'mitochondrial diabetes mellitus (MDM)' represents a heterogenous group at the mtDNA level.

## 5. Possible pathomechanisms in MDM with respect to the current concept of insulin secretion

The idiopathic forms of diabetes (IDDM and NIDDM) are characterized by quite different pathomechanisms. In IDDM the destruction of the pancreatic beta-cells leads to an absolute insulin deficiency of the whole organism. Increased glycogenolysis and gluconeogenesis as well as a decrease in hepatic and peripheral glucose uptake by insulin-sensitive tissues are the respective results. NIDDM is usually characterized by normal or even elevated blood insulin concentrations, but also by a delayed insulin secretion after glucose stimulation as well as by a peripheral insulin resistance; i.e., a diminished responsiveness to insulin by muscle and adipose tissue. The latter symptom of an impaired insulin sensitivity in the periphery seems to be the primary, i.e., the first demonstrable defect in the development of NIDDM, but the exact mechanism is unknown and subject of worldwide extensive research [43].

Table 1 compares the clinical data of the two idiopathic forms of diabetes with those found in patients with diabetes and the $tRNA^{Leu(UUR)}$-243 mutation indicating that mitochondrial diabetes is clinically as well as pathogenetically a distinct entity. Thus, the 'mitochondrial diabetics' are mostly lean (in contrast to NIDDM), have usually no ketotic episodes (in contrast to IDDM) and are often to be treated with insulin. As demonstrated below, insulin secretion after a glucose load is delayed in patients with MDM, while they do not show significant resistance to insulin by muscle and adipose tissue (in contrast to NIDDM). The development of MDM seems not be accompanied by immunological phenomena such as antibodies directed against $\beta$-cell structures or defined $\beta$-cell peptides such as glutamic acid decarboxylase (GAD). Furthermore, in contrast to IDDM MDM seems not to be associated with certain HLA-subtypes.

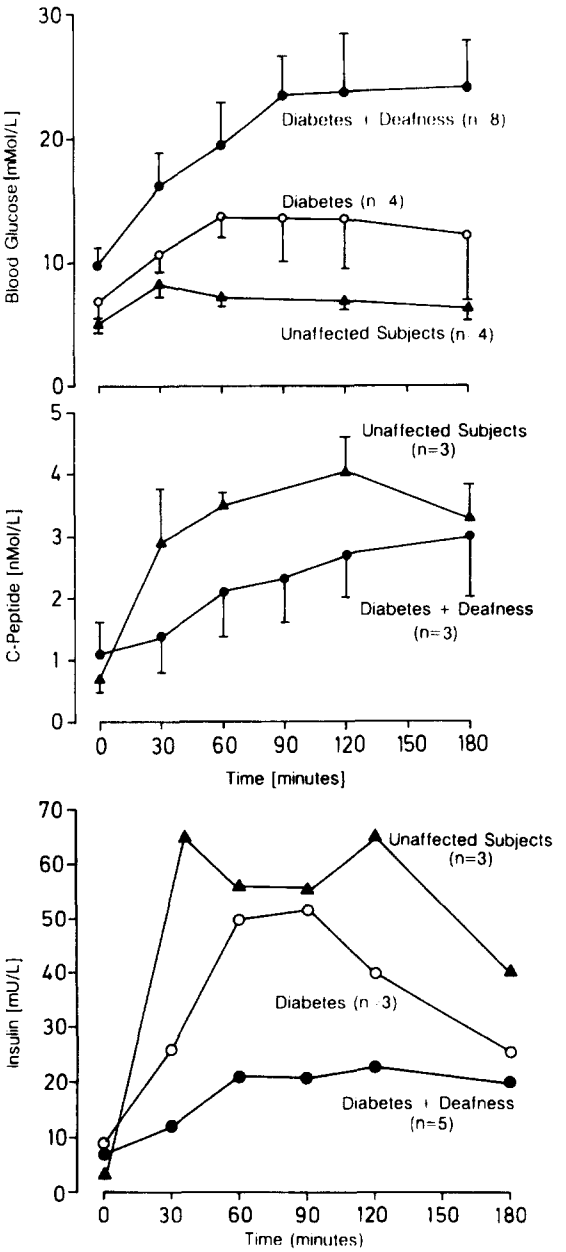


Fig. 2. Oral glucose tolerance tests (100 g) in subjects with the $tRNA^{Leu(UUR)}$ mutation at np 3243 unaffected patients are from unrelated families with MELAS carrying the 3243 mutation but without any clinical symptoms [27]; data of diabetic subjects are taken from references [25,27,28]; mean ± S.D.

The exact way in which the $tRNA^{Leu(UUR)}$ mutation affects glucose homeostasis in MDM is unknown but preliminary studies using glucose tolerance tests and various euglycemic clamp techniques [23,27,28] suggest a defect in the secretory capacity of the beta-cells. As shown in Fig. 2, which combines our own data and those from the literature [25,57,27,28], diabetics with the $tRNA^{Leu(UUR)}$ mutation demonstrate an abnormal, i.e. delayed and insufficient insulin and C-peptide response to a glucose load. Urinary C-peptide secretion is markedly decreased in these patients [24,44]. Euglycemic clamp studies [8,23,28] re-

vealed no or only moderate peripheral insulin resistance. Thus, MDM can tentatively be described as a type of diabetes which is caused by a secretory defect of the beta-cells due to a mtDNA mutation. In contrast to the impairment of secretion in NIDDM, which is restricted to the beta-cells, MDM seems to be additionally characterized by an impaired function of glucagon secreting alpha-cells, as recently demonstrated by arginine infusion tests in patients with the $tRNA^{Leu(UUR)}$ mutation [28].

We have subdivided into two groups the patients subjected to an oral glucose tolerance test- our own and those reported in the literature [23,27,28]: one group with diabetes alone and the other with diabetes combined with deafness or other neurological symptoms. Fig. 2 clearly shows that the presence of further neurological symptoms is accompanied by a more severe derangement of the glucose balance, i.e., higher blood glucose concentrations and lower secretion profiles of insulin and C-peptide when compared to the diabetic group without deafness. Thus, it seems reasonable to assume that the severity of the phenotype is dependent on the degree of heteroplasmy of the $tRNA^{Leu(UUR)}$-3243 mutation in different tissues.

The current concept of insulin secretion (Fig. 3; [45,46]) involves several steps, starting with glucose uptake into the $\beta$-cell by a glucose transporter (Glut 2), followed by phosphorylation by glucokinase. Neither steps are rate-limiting. Recent studies have demonstrated that cytosolic NADH produced along the glyceraldehyde dehydrogenase reaction mediates the glucose signal [46]. As NADH cannot enter the mitochondrium the reducing equivalents are transferred into the mitochondrium via shuttle mechanisms, the oxaloacetate-malate cycle, which works by transamination, and the dihydroxyacetone phosphate–glycerol phosphate cycle [46]. The reduction of the mitochondrial pyridine nucleotide and flavin pool is followed by stimulation of the electron transport chain and hyperpolarization of the mitochondrial membrane as well as by an increase in the ATP production rate and an increase in intracellular ATP/ADP ratio. This leads to a closure of ATP dependent potassium channels ($K_{ATP}$ channels), a depolarization of the beta-cell membrane, the opening of voltage-activated calcium channels, and an increase of the intracellular calcium concentration which promotes the secretion of insulin [45]. This partly hypothetical concept is confirmed by several observations. First, the rate of oxygen consumption parallels the increase of glucose concentration in isolated islets of Langerhans [47,48]. Secondly, agents which inhibit mitochondrial oxidative metabolism also produce marked activation of the $K_{ATP}$ channels and, vice versa, blocker of $K_{ATP}$ currents promote insulin secretion [45,46]. For example, 2-ketoisocaproic acid, a deamination product of leucine which is directly metabolized via the Krebs cycle, increases oxygen consumption in isolated $\beta$-cells, inhibits $K_{ATP}$ channel activity [49] and also acts as a potent insulin secretagogue [45]. The exact mechanism by which glucose metabolism in beta-cells is coupled to insulin secretion remains to be established. However, mitochondrial oxidative ATP turnover seems to play an important role. If so, one would expect that mutations of the mtDNA which impair the

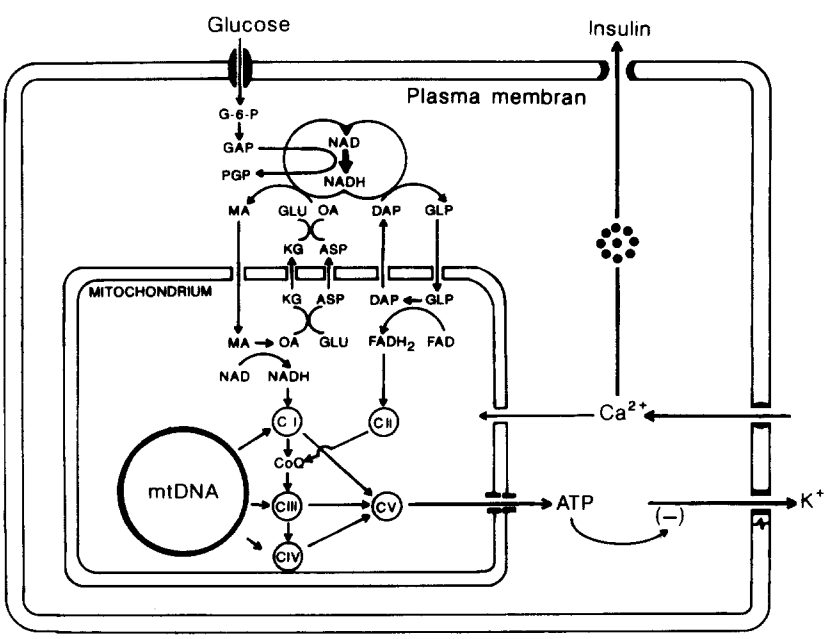


Fig. 3. Current concept of insulin secretion by pancreatic beta-cells; scheme modified according to references [45], [46] and [59]. Abbreviations: G-6-P, glucose 6-phosphate; GAP, glyceraldehyde-3-phosphate; MA, malate; PGP, 1,3-bisphosphoglycerate; GLU, glutamate; ASP, aspartate; OA, oxaloacetate; KG, $\alpha$-ketoglutarate; DAP, dihydroxyacetonephosphate; GLP, glycerol phosphate; C I, complex I (NADH-ubiquinone oxidoreductase); C II, complex II (succinate-ubiquinone oxidoreductase); C III, complex III (ubiquinol; ferricytochrome-*c* oxidoreductase); C IV, complex IV (cytochrome-*c* oxidase); C V, complex V (ATP synthase).

exact function of the oxidative phosphorylation, i.e. ATP-synthesis, will result in a derangement of the specific function of the beta-cell, i.e. insulin secretion.

## 6. mtDNA and other endocrinopathies

Several endocrine abnormalities have recently been described in 21 patients with chronic progressive external ophthalmoplegia (CPEO) [9]. As far as tested most of these patients carried a mtDNA deletion [50]. 8/21 had impaired glucose tolerance or diabetes, 5/15 investigated patients with CPEO had growth hormone deficiency, 2/19 had hypoparathyroidism, 4/17 showed follicle stimulating hormone deficiency and 6/19 had hypogonadism. In a recent review on endocrine abnormalities in KSS 20% of the patients had gonadal dysfunction and 13% diabetes mellitus with or without other endocrine symptoms [60]. Thus mitochondrial myopathies presenting with CPEO seem to be much more often associated with endocrinopathies than the general population. In about one half of the cases reported in the literature the endocrine abnormalities precede the ocular myopathy. Therefore, unclear endocrinopathies should be subjected to investigation of the mtDNA in order to elucidate the underlying pathomechanism. Recently it has been demonstrated that also the physiologically altered function of the human ovary gland during menopausis is accompanied by an accumulation of deleted mtDNA in the ovary [51].

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