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MINI REVIEW

Genetic variants in *MTNR1B* affecting insulin secretion

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Abstract

The incidence of type 2 diabetes mellitus has markedly increased worldwide over the past decades. Pancreatic β-cell dysfunction as well as central and peripheral insulin resistance appears to be elementary features in the pathophysiology of type 2 diabetes mellitus. Major environmental conditions predisposing to the development of type 2 diabetes are excessive food intake and sedentary life-style on the background of a genetic predisposition. Recent genome-wide association studies identified several novel type 2 diabetes risk genes, with impaired pancreatic β-cell function as the underlying mechanism of increased diabetes risk in the majority of genes. Many of the novel type 2 diabetes risk genes, including *MTNR1B* which encodes one of the two known human melatonin receptors, were unexpected at first glance. However, previous animal as well as human studies already pointed to a significant impact of the melatonin system on the regulation of glucose homeostasis, in addition to its well known role in modulation of sleep and circadian rhythms.

This brief review aims to give an overview of how alterations in the melatonin system could contribute to an increased diabetes risk, paying special attention to the role of melatonin receptors in pancreatic β-cell function.

Key words: *Diabetes mellitus type 2, melatonin receptors, pancreatic beta-cell, single nucleotide polymorphism, SNP*

Introduction

The incidence of type 2 diabetes mellitus has markedly increased worldwide over the past decades, reaching epidemic proportions with major health consequences at an individual as well as a public health level (1). Although the underlying mechanisms of type 2 diabetes are not completely understood, pancreatic β-cell dysfunction as well as central and peripheral insulin resistance appears to be elementary features in the pathophysiology of type 2 diabetes mellitus (2,3). Major environmental conditions that predispose to the development of type 2 diabetes are excessive food intake and sedentary life-style on the background of a genetic predisposition (4).

Recent genome-wide association (GWA) studies identified a series of new risk loci for type 2 diabetes (5–19). Many of the novel type 2 diabetes risk genes, including *MTNR1B* which encodes one of the two known human melatonin receptors, were unexpected at first glance. However, previous animal as well as human studies already pointed to a significant impact of the melatonin system on the regulation of glucose homeostasis, in addition to its well known role in modulation of sleep and circadian rhythms (20). In humans, insulin secretion rates and serum insulin concentrations underlie circadian changes, with increasing insulin secretion during the day and decreasing during the night (21). Plasma melatonin levels, a major regulator of the circadian rhythm, behave in the opposite manner, with lowest values when insulin secretion rates peak and vice versa (21). Disturbances of sleep and circadian rhythms, typically found in shift-work and jet lag, can lead to significant changes in energy metabolism and represent, therefore, important mechanisms in the development of obesity and type 2 diabetes (22). In accordance, a

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Key messages

- *MTNR1B* was recently added to the growing list of diabetes genes.
- Similar to the majority of novel diabetes genes, variants in *MTNR1B* confer pancreatic β-cell dysfunction.
- Melatonin receptors appear to be involved in insulin secretion, though their role especially in human pancreatic β-cells is only incompletely understood, and the literature regarding this is partly controversial.

Abbreviations

cAMP	cyclic adenosine monophosphate
cGMP	cyclic guanosine monophosphate
GLP-1	glucagon-like peptide-1
GWA	genome-wide association
IP_3	inositol-1,4,5-trisphosphate
MTNR1A	melatonin receptor 1A
MTNR1B	melatonin receptor 1B
MTNR1C	melatonin receptor 1C

simulated phase shift significantly alters pancreatic β-cell responses, postprandial glucose levels, and lipid metabolism (23), and circadian misalignment results in postprandial glucose responses in the range characteristic of a prediabetic state (24).

This brief review aims to give an overview of how alterations in the melatonin system could contribute to an increased diabetes risk, paying special attention to the role of melatonin receptors in pancreatic β-cell function.

Effects of *MTNR1B* type 2 diabetes risk variants on β-cell function

Several variants within the *MTNR1B* gene locus, i.e. rs1387153, rs2166706, rs10830962, rs4753426 (all located in the 5'-flanking region), rs10830963, rs3781638 (both located in intron 1), and rs8192552 (located in exon 1, resulting in the non-synonymous mutation G24E)—localization within the locus depicted in Figure 1—were found to associate with impaired fasting glucose (16,25–35) and increased risk of type 2 diabetes (16,26–29,32,34) in both adult and child populations of different ethnicity. All studied single nucleotide polymorphisms (SNPs) confer impaired fasting glucose, whereas an increased risk of type 2 diabetes was described for rs1387153, rs2166706, and rs10830963 (Table I). Similar to other diabetes risk genes, the odds ratio for presence or later development of type 2 diabetes was moderate, ranging from 1.09 to 1.23 (16,26–29,32,34), supporting the multifactorial genesis of type 2 diabetes with complex interactions of a large quantity of susceptibility genes. The *MTNR1B* variant rs10830963 that shows considerable consistency over these studies is located within the single 11.5 kb intron of the *MTNR1B* gene (Figure 1) without interfering with consensus transcription factor binding or alternative splicing (16).

MTNR1B is one of the recently identified 13 diabetes risk genes that confer an impaired pancreatic β-cell function (16,25,26,29,30,33,36–38). *MTNR1B* variants rs10830962, rs4753426, rs10830963, and rs3781638 associated with reduced insulin secretion, whereas one SNP, i.e. rs3781638, affected insulin sensitivity (25) and one SNP, i.e. rs8192552 (G24E), associated with changes in measures of obesity (35) (Table I). In the latter study, the minor allele of rs8192552 was associated with increased body mass despite decreased fasting plasma glucose levels. The authors hypothesized that these discrepant results may be due to differential regulation of the melatonin receptor in specific target tissues (35).

Given that the described polymorphisms in *MTNR1B* affect different aspects of prediabetes and that they are only in moderate linkage disequilibrium (LD), as depicted in Figure 1, these variants probably do not reflect all the same association signal.

Though the underlying mechanisms by which common genetic variation within these loci affects β-cell function are not completely understood, risk variants may alter glucose-stimulated insulin secretion, proinsulin conversion, incretin sensitivity or incretin secretion. Impairments of the following measures of β-cell function were found to be associated with *MTNR1B* variants: homeostasis model assessment of insulin secretion (16,33), insulin release after oral and intravenous glucose challenges (25,29,36), and, in particular, the early insulin response to both oral and intravenous glucose (26,30,37,38). In carriers of *MTNR1B* risk variants, faster deterioration of glucose-stimulated insulin secretion during a 7-year follow-up period was reported (26). Furthermore, *MTNR1B* was one of eight type 2 diabetes genes, summation of which was associated with reduced first-phase glucose-stimulated insulin secretion during hyperglycaemic clamps (39). In a very recent study, the risk allele of the *MTNR1B* SNP rs10830963 associated with increased insulin responses towards glucagon-like peptide-1 (GLP-1) and arginine stimulation, despite reduced insulin secretion after an oral glucose challenge (36). This finding surprises in so far as incretins, including GLP-1, mediate, at least to some extent, the insulin secretion after oral glucose intake.

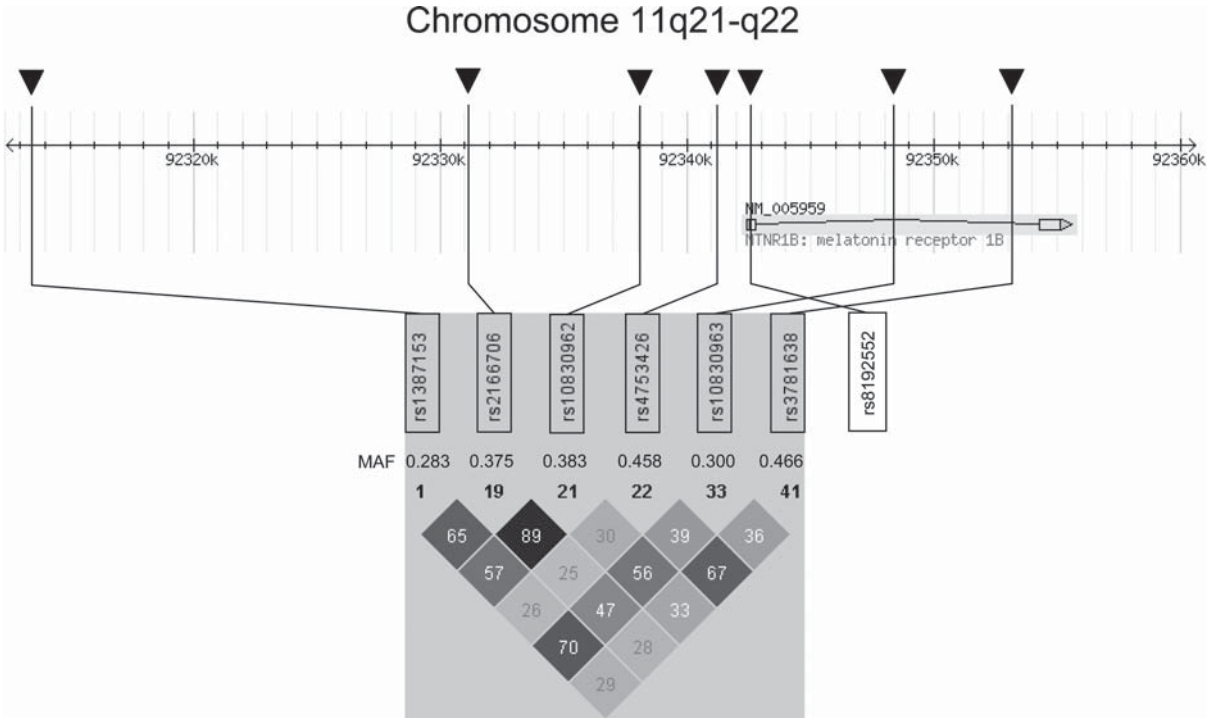

Figure 1. Genomic region of human chromosome 11 harbouring the *MTNR1B* gene locus and linkage disequilibrium (LD) data of representative single nucleotide polymorphisms (SNPs) within this region (HapMap data). The *MTNR1B* gene consists of 2 exons and spans 13,160 bases from nucleotide 92,342,437 to nucleotide 92,355,596. The locations of the genotyped representative SNPs are indicated by arrows. The HapMap minor allele frequencies (MAF) are given below the SNP numbers. The Haploview LD colour scheme '*r*-squared' was chosen to visualize LD data. Within the diamonds, the r^2 values are given. SNP rs8192552 (G24E) is not covered by the HapMap data and was added, therefore, on the right side of the diamonds. No linkage data are available for this SNP.

Expression and function of melatonin receptors in pancreatic β-cells

MTNR1B (melatonin receptor 1B; OMIM entry no. 600804) encodes one of two known human melatonin receptors, which are *MTNR1A*, also known as Mel_{1A} or MT_1, and *MTNR1B*, also known as Mel_{1B} or MT_2 (40). In amphibia and birds, with *MTNR1C*, also known as Mel_{1C} or MT_3, a third melatonin receptor subtype has been identified (41). *MTNR1B* is located on the long arm of chromosome 11, contains two coding exons that span about 10 kb, and shares about 60% nucleotide sequence homology with *MTNR1A* (40). Both receptors belong to the G protein-coupled receptor family which is characterized by seven transmembrane domains, an extracellular N-terminal domain, and an intracellular C-terminal domain. While the *MTNR1A* subtype is expressed in the pars tuberalis of the pituitary gland, the suprachiasmatic nuclei of the hypothalamus, and the paraventricular thalamus, the *MTNR1B* subtype is present in rodent suprachiasmatic nuclei and hippocampus as well as in human retina and, to a lesser extent, brain (42).

Furthermore, melatonin receptors have been detected in neonatal rat pancreas (43), in the insulin-secreting rodent insulinoma cell lines INS-1 and MIN-6 (44,45), as well as in rat and human islets and pancreatic β-cells (46,47). Early studies showed a significantly lower *MTNR1B* expression in comparison with *MTNR1A* expression in human and rat islets as well as in the murine MIN-6 cell line (46,47). Analysis of *MTNR1A* mRNA content at the single cell level showed its expression in human pancreatic α-cells, but not in β-cells (47). In a very recent study, the occurrence of *MTNR1A* and *MTNR1B* in human islets as well as in clonal β-cells was confirmed (26). However, in contrast to previous studies (46,47), both melatonin receptors were almost equally expressed in human islets (26). While *MTNR1B* was predominantly detected in β-cells in both human and rodent islets, *MTNR1A* was present only in a population of peripherally located β-cells in human, mouse, and rat islets (26).

In the vast majority of *in-vitro* studies, treatment of pancreatic β-cells with melatonin attenuated insulin secretion (43–45,48,49), though a limited number of studies in pancreatic islets did not reveal inhibitory (50) but even stimulatory effects (47) of melatonin on β-cell function. A potential explanation for the discrepant results is that the stimulatory action of melatonin on insulin release that has been observed in one study most probably resulted

Table I. Associations of single nucleotide polymorphisms within or in proximity to the *MTNR1B* gene locus with prediabetes phenotypes and risk of type 2 diabetes.

Single nucleotide polymorphism	Risk allele (frequency)	Metabolic phenotype of risk allele carriers	References
rs1387153	T (0.30)	Impaired fasting plasma glucose, increased type 2 diabetes risk (odds ratio = 1.15)	(27)
rs2166706	C (0.45)	Impaired fasting plasma glucose, increased type 2 diabetes risk (odds ratio = 1.21)	(32)
rs10830962	G (0.40)	Impaired fasting plasma glucose, reduced β-cell function	(25)
rs4753426	C (0.50)	Impaired fasting plasma glucose, reduced β-cell function	(25)
rs10830963	G (0.30)	Impaired fasting glucose, reduced β-cell function, increased type 2 diabetes risk (mean odds ratio = 1.15; range 1.09–1.23)	(16,25,26, 28–31,33, 36–39)
rs3781638	A (0.55)	Impaired fasting glucose, reduced β-cell function, diminished insulin sensitivity	(25)
rs8192552	G (0.90)	Impaired fasting glucose, decreased body mass	(35)

indirectly from melatonin-induced glucagon secretion (47). In agreement with the negative actions of melatonin on β-cell function *in vitro*, in animal studies, pinealectomy caused severe hyperinsulinaemia (51) and a significant insulin hypersecretion in isolated pancreatic islets (49,52), whereas exogenous application of melatonin decreased insulin plasma levels (53). Besides, very recently insulin secretion from isolated islets of *MTNR1A*, *MTNR1B*, or *MTNR1A* and *MTNR1B* double-knockout animals was found to be enhanced compared to wild-type islets (54). In line with these findings, over-expression of melatonin receptors has been found in islets from patients with type 2 diabetes in comparison with non-diabetic subjects (55).

The two melatonin receptors, *MTNR1A* and *MTNR1B*, on pancreatic β-cells are linked to three highly divergent signalling pathways, each with different impact on insulin secretion. The adenylyl cyclase/cyclic adenosine monophosphate (cAMP) pathway predominates regarding insulin liberation from pancreatic β-cells (56). *MTNR1A* as well as *MTNR1B* are coupled to the pertussis toxin-sensitive inhibitory $G_{i\alpha}$ protein that can inhibit cAMP-dependent signalling and subsequently insulin secretion (40,49). The importance of pertussis toxin-sensitive inhibitory G proteins as regulators of insulin secretion has been underscored by a recent mouse study showing that pancreatic β-cell-specific inactivation of the inhibitory G proteins (Gi/o) resulted in constitutive hyperinsulinaemia, increased insulin secretion in response to glucose, and resistance to diet-induced hyperglycaemia (57). This study identified several highly expressed Gi/o-coupled receptors, such as α2A-adrenoceptor, glucagon-like peptide-1 (GLP-1) receptor, and glucose-dependent insulinotropic peptide (GIP) receptor, in pancreatic β-cells, though *MTNR1B* was not among those. While acute treatment with melatonin reduced the forskolin- and GLP-1-stimulated cAMP formation and insulin secretion in pancreatic β-cells (44,45), after prolonged exposure to melatonin treatment cAMP-mediated responses to forskolin and GLP-1 were enhanced (45) due to the well known G protein-coupled receptor desensitization mechanisms in which G protein-coupled receptor kinases are involved (58). Inhibition of the guanylate cyclase/cyclic guanosine monophosphate (cGMP) pathway following activation of the *MTNR1A* (but not *MTNR1B*) is a further mechanism for inhibitory effects of melatonin on insulin secretion (59). Though less relevant than the aforementioned pathways, melatonin exerts its biological effects on the pancreatic β-cell also via *MTNR1A*-dependent, but $G_{i\alpha}$-independent activation of phospholipase C and release of its second messenger inositol-1,4,5-trisphosphate (IP_3). Binding of IP_3 to its cognate receptor results in opening of calcium channels and an increase in intracellular calcium, thereby facilitating insulin secretion from pancreatic β-cells (60). Thus, the actions of melatonin on pancreatic β-cells and on insulin release result from a complex interplay of intracellular signal transduction cascades, which comprise the cAMP-, cGMP-, and IP_3-signalling pathways. Furthermore, effects of melatonin on pancreatic β-cells appear to be species-specifically regulated, given that in one study melatonin did not alter the cAMP content in human islets, whereas melatonin treatment reduced cAMP formation and, subsequently, insulin secretion in murine MIN-6 cells (47).

In this context it is important to note that the use of nocturnal animals as model organisms is limited, in so far that in these animals melatonin levels are high during their active period, in contrast to humans where

they are highest during the non-active period. These differences could explain some of the controversial data on melatonin and glucose metabolism found in humans and in murine animal models.

Although *in-vitro* studies have clearly shown direct effects of melatonin on pancreatic β-cell function, it cannot be excluded that there are also other effects of melatonin that indirectly influence β-cell function and glucose homeostasis. This assumption is supported by the expression of the melatonin receptors in tissues with crucial functions in carbohydrate metabolism, such as adipose tissue, skeletal muscle, liver, and hypothalamus (61,62). Previous studies in human brown adipocytes pointed to an important role of melatonin in adipocyte physiology, including glucose transporter 4 expression and glucose uptake, through *MTNR1B* activation (63). The impact of melatonin through melatonin receptor activation on early events of the insulin-dependent cascade, such as the insulin receptor substrate-1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K) pathway, as well as on end-points of insulin action, including glucose transport, have been also described in murine skeletal muscle cells (64). In line with this, in a very recent mouse study, functional knock-out of *MTNR1A* significantly impaired glucose metabolization, probably due to increased insulin resistance (65). Melatonin-induced activation of insulin signalling pathways, such as the IRS-1/PI3K or the IRS-1/mitogen-activated protein kinase (MAPK) pathways, most likely via *MTNR1B*, were also found in rat hypothalamic suprachiasmatic nucleus which directly controls the circadian rhythm of plasma glucose concentration (66). As shown in hepatic HepG2 cells, melatonin modulates central mechanisms of insulin action in the liver, such as glycogen synthesis, via a protein kinase C (PKC)-ζ/Akt/glycogen synthase kinase 3β (GSK3-β) pathway (67). In agreement with these preclinical data, two recent genetic studies showed associations of *MTNR1B* variants with measures of insulin sensitivity (25) and body mass (35).

Future outlook

In light of the inhibiting actions of melatonin on insulin secretion in pancreatic β-cells (68), the increased expression of the melatonin receptor *MTNR1B* in islets of subjects with type 2 diabetes (26,69), and the association between common variants in *MTNR1B* and type 2 diabetes risk (26–29,31,32), *MTNR1B* appears to be a potential target for the development of anti-diabetic therapies. Treatment with melatonin receptor antagonists, such as the non-selective melatonin receptor antagonist luzindole (N-acetyl-2-benzyltryptamine) as well as the *MTNR1B*-specific antagonist 4P-PDOT (4-phenyl-2-propionamidotetraline), reversed the inhibiting effect of melatonin on insulin secretion in pancreatic β-cells (68). Both melatonin receptor antagonists proved effectively to ameliorate melatonin actions also in animal models (66). However, while melatonin agonists, such as agomelatine (Valdoxan™), have become mainstays in the current treatment of depression (70), preclinical studies on melatonin receptor antagonists are not yet at the point where clinical trials can be recommended.

Conclusions

MTNR1B was recently added to the growing list of diabetes genes. Variants within the *MTNR1B* gene locus were found to associate with impaired fasting glucose and increased risk of type 2 diabetes in both adult and child populations of different ethnicity. Similar to the majority of novel diabetes genes, variants in *MTNR1B* confer pancreatic β-cell dysfunction. These associations appear highly plausible, in light of substantial evidence in human and animal studies linking disturbances of circadian rhythms and sleep to metabolic disorders, such as diabetes and obesity, the significant involvement of the melatonin system in the regulation of glucose homeostasis, and the, though not completely understood, role of the melatonin receptors in pancreatic β-cell function and, in particular, insulin secretion.

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