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GENETICS (T FRAYLING, SECTION EDITOR)

Tired of Diabetes Genetics? Circadian Rhythms and Diabetes: The *MTNR1B* Story?

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Abstract Circadian rhythms are ubiquitous in biological systems and regulate metabolic processes throughout the body. Misalliance of these circadian rhythms and the systems they regulate has a profound impact on hormone levels and increases risk of developing metabolic diseases. Melatonin, a hormone secreted by the pineal gland, is one of the major signaling molecules used by the master circadian oscillator to entrain downstream circadian rhythms. Several recent genetic studies have pointed out that a common variant in the gene that encodes the melatonin receptor 2 (*MTNR1B*) is associated with impaired glucose homeostasis, reduced insulin secretion, and an increased risk of developing type 2 diabetes. Here, we try to review the role of this receptor and its signaling pathways in respect to glucose homeostasis and development of the disease.

Keywords SNP rs10830963 · *MTNR1B* · MT2 · Insulin secretion · Glucose homeostasis · Type 2 diabetes · Genetics · Circadian rhythms

Introduction

Biological rhythms are ubiquitous in all cellular structures and circulating levels in many of the body's signaling molecules, such as hormones, are known to display rhythmicity, mostly over a 24 hour period. Rhythms can have different length and amplitude, with the most studied rhythm being the circadian oscillation ("*circa*", around; "*dies*", day) that ranges over a 24 hour period. This rhythm is manifested by a structure in the brain, the suprachiasmatic nucleus (SCN), which for mammals constitutes the "master clock". In the last decade, many studies in several species have focused on circadian clocks outside of the SCN in peripheral tissues, such as liver and heart, as well as different cell types [1]. These peripheral clocks are believed to influence and be under the influence of the "master clock" in the SCN. They are sometimes termed "slave clocks". Indeed, there is now also evidence for the existence of a circadian clock in pancreatic β-cells [2, 3].

The maintenance of the circadian rhythm is endogenously generated, but can be altered by external parameters. One major signaling molecule for entrainment and upkeep of circadian clocks is melatonin. Deficiency in melatonin signaling in rodents has been shown to lower amplitude and misalign transcription of several genes involved in circadian rhythm [4]. A disparity in clock input and output signals, especially those involved in metabolism, has been associated with several metabolic diseases [5]. Certainly, the metabolic syndrome is more prevalent in humans who have an altered circadian rhythm, for example in shift workers. Also, the misalliance of circadian rhythms has a profound impact on metabolic hormone levels, such as those of leptin and insulin [6].

In this review, we discuss a latest view of a chronobiotic factor melatonin in glucose homeostasis and risk for type 2 diabetes.

Melatonin Biosynthesis and Physiological Functions

Melatonin, also known as the hormone of darkness, is an indoleamine with the chemical name N-acetyl-5-methoxytryptamine. Circulating plasma concentrations are produced by the

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pineal gland. In mammals, the circulating levels display a diurnal rhythm, with high plasma levels during night (80–100 pg/ml) and low levels during the day (10–20 pg/ml) [7]. Several biological functions are characterized by rhythmicity and melatonin is one important signaling molecule in the entrainment of biological rhythms in the body, a "zeitgeber" (German: "time giver"). The hormone exerts its effects both through activation of its receptors [8], but also via its capacity to act as an antioxidant [9]. These effects can either be through the circulating levels of the hormone or in a more autocrine/paracrine fashion near target tissues [10, 11]. In humans, there are 2 functional receptors described so far, the MT1 and the MT2 receptor encoded by the genes *MTNR1A* and *MTNR1B*, respectively [12]. Here, the gene for *MTNR1B* is located on chromosome 11q21-q22, whereas the gene for *MTNR1A* is located on chromosome 4.

Melatonin is widely known to affect the central nervous system (CNS), where it alters hormone release and phase shifts neuronal firing both in the 24 hour rhythm and seasonal changes [12, 13]. The latter is evident in seasonal reproducing animals, but still debated in humans [14]. The phase-advancing effects of melatonin are taken advantage of in the treatment of insomnia or limiting jet lag when traveling across time zones [15–17].

In the periphery, melatonin promotes vasoconstriction through the MT1 and vasodilation through the MT2 receptors [18]. In the adrenal cortex, it lowers cortisol secretion [19], an action shared with insulin [11]. Interestingly, human adipocytes, a major target tissue for insulin, express MT2 and have been shown to reduce expression of the insulin-dependent glucose transporter, Glut4, after melatonin stimulation [20]. In muscle cells, melatonin stimulates glucose uptake by phosphorylation of insulin receptor substrate-1 (IRS-1) through suggested MT2 signaling [21]. MT2 expression has also been shown in hepatocytes and melatonin injections elevated glucose release from the liver in mice [22].

Melatonin and Glucose Homeostasis

It is known that plasma insulin levels exhibit a circadian rhythm and that disturbance in the rhythmicity affects plasma glucose and hormone levels [6]. Furthermore, there is evidence that the diurnal secretion of melatonin is reduced in patients and rodent models of type 2 diabetes and that melatonin receptor expression is increased [23]. In addition, the pineal gland may express insulin receptors, but this needs further confirmation by other groups [23]. Also, exogenously administered melatonin has been shown to inhibit insulin secretion in rodents [24]. In human islets, melatonin stimulates glucagon release and most probably, as a consequence, also increases insulin secretion [25]. Melatonin receptors are widely expressed in the gut and could thus have an effect on incretin hormones like glucagon-like peptide 1 (GLP-1) [26]. Moreover, INS-1 β-cells have been proposed to sensitize cAMP signaling after long term exposure to melatonin (mimicking elevated melatonin levels during the night), resulting in an upregulation of the GLP-1 receptor. In this study long-term exposure of melatonin augments GLP-1 stimulated insulin secretion, through cAMP dependent mechanisms in INS-1 β-cells [27]. This suggests that there might be a link between incretin hormones and melatonin signaling. While the literature is confusing and studies exist from different eras, overall, it proposes the existence of cross-talk between these 2 hormones, insulin and melatonin, and their receptors, where melatonin in general appears to exert a negative effect on insulin.

Melatonin Receptors

Melatonin receptors belong to a family of receptors called G-protein coupled receptors (GPCR) [28]. In humans, there are 2 melatonin receptor subtypes, melatonin receptor 1 (MT1; *MTNR1A*) and melatonin receptor 2 (MT2; *MTNR1B*), although a third putative melatonin receptor has been identified, belonging to the family of quinone reductases [12]. The affinity for melatonin is different for MT1 and MT2, where MT1 binds melatonin at a much lower K_d (K_d=20–40 pM) than MT2 (K_d=160 pM). Consequently, MT1 is active at a much lower melatonin concentration [12].

Melatonin receptors are widely distributed throughout the body. The detection of the MT1 and MT2 receptors has mainly been achieved on the mRNA level by RT-PCR or in situ hybridization. In humans, MT1 has been detected in the brain, more specifically in the SCN, cortex, hippocampus, thalamus, cerebellum [29–31], and the retina [14]. The mammalian MT1 receptor is expressed in the majority of the peripheral tissues that have been studied, eg, ovary, testis, mammary gland, retina, coronary blood vessels and aorta, liver, kidney, gallbladder, skin, the immune system, and α-cells of the pancreas [32, 33, 34•]. MT2 is also expressed in the human brain: so far it has been detected in whole brain and the hippocampus, although the levels are lower than those reported for MT1. In addition, MT2 is found in the retina [35, 36]. In peripheral tissues, MT2 has been detected in lung, cardiac, aortic and coronary tissue, myometrium and granulose cells, immune cells, duodenum, adipocytes, liver, and pancreatic β-cells [32, 34•, 37]. Thus, several tissues express both MT1 and MT2.

Melatonin Signaling in Pancreatic Islets

Melatonin receptors signal through several different G-proteins and thus also influence a variety of downstream signaling pathways. MT1 and MT2 signal through some

common and some separate pathways in islets. In β-cells, MT1 and MT2 have been shown to signal through inhibitory G-proteins lowering cAMP in the cell and thus decrease the protein kinase A (PKA) dependent and/or independent pathways, resulting in decreased insulin secretion [27, 38]. Both receptors are also implicated to activate phospholipase C (PLC) stimulating the release of Ca^{2+} from intracellular stores as well as protein kinase C (PKC) and thus stimulating insulin release [39, 40]. In contrast, only the MT2 receptor inhibits the formation of cyclic guanosine monophosphate (cGMP) and its downstream targets via the soluble guanylate cyclase pathway and inhibits insulin secretion similarly to the cAMP mediated pathway [41, 42].

Biological Effects of *MTNR1B* in Humans

Effects of Variants in *MTNR1B* on Glucose Levels and Risk for Type 2 Diabetes

Genome wide association studies (GWAS) for glucose and insulin traits reveal that variants in the melatonin receptor 2 gene (*MTNR1B*) are associated with decreased insulin and elevated glucose concentrations [43••, 44•, 45]. Furthermore, we [43••] and others [44•, 45] demonstrate that rise in glucose levels in carriers of the risk genotypes of *MTNR1B* is translated into increased risk of future type 2 diabetes in 2 large prospective studies with an odds ratio (OR) of 1.12 [43••]. The risk for type 2 diabetes conferred by the G-allele of this SNP rs10830963 is also confirmed by the latest Diabetes Genetics Replication And Meta-analysis Consortium (DIAGRAM) meta-analyses for type 2 diabetes [46]. A very recent study, however, has demonstrated that the effect of the risk genotypes of the *MTNR1B* SNP rs10830963 is observed to be significantly greater on transition from normal glucose tolerance (NGT) to impaired fasting glucose (IFG) than on transition from IFG to type 2 diabetes [47]. These findings support earlier observations in children and adolescents suggesting that *MTNR1B* variants influence glucose levels from childhood onwards [48].

In a large scale exon re-sequencing study of the *MTNR1B* gene in 7,632 Europeans, including 2,186 individuals with type 2 diabetes, Bonnefond et al. have identified 40 non-synonymous variants and tested their functional consequences and risk for type 2 diabetes [49••]. Elegantly, researchers identify 4 rare, not previously reported in public SNP databases, variants (MAF <0.1 %) with partial- or total-loss-of-function that in combination yield an OR of 3.9 for association with type 2 diabetes in 11,854 individuals, including 5,967 with type 2 diabetes [49••]. The question remains to be addressed whether these rare variants are independent signals of originally discovered variant rs10830963 and thus contribute to a part of the "missing heritability" of type 2 diabetes.

Variants in the *MTNR1B* Gene and Risk of Gestational Diabetes Mellitus (GDM)

The association between the *MTNR1B* locus and impaired glucose homeostasis is also found in non-European populations. Thus, a recent GWAS in a Korean population consisting of 468 women with (GDM) and 1,242 non-diabetic control women reports that a variant near *MTNR1B*, SNP rs10830962 in linkage disequilibrium (LD) with the European SNP rs10830963 (D′=0.885, r2=0.547), is associated with GDM at a genome-wide significant level [50]. In a smaller study from Greece, SNP rs10830963 also confers association with GDM [51], while in 1 study of Chinese pregnant women the same variant rs10830963, but also several other variants, in moderate or strong LD with the former (rs1387153, rs2166706, and rs1447352) are associated with elevated glucose concentrations [52]. Moreover, an independent Chinese study demonstrates that carriers of SNP rs10830963 have reduced β-cell function as measured with HOMA-B index [53]. Notably, it has also been demonstrated that the *MTNR1B* gene is strongly conserved between species and shows evidence of positive adaptive selection in humans [54].

Insulin Secretion and Action

In our Diabetes Genetics Initiative (DGI) GWAS for insulin secretion [43••], we show that the *MTNR1B* risk genotype is associated with impaired early insulin release to both oral (insulinogenic and disposition index) and intravenous (first-phase insulin response) glucose load. In addition insulin secretion deteriorates over time in the risk allele carriers [43••]. Furthermore, we demonstrate that *MTNR1B* mRNA is expressed in human islets, and immunocytochemistry confirmed that MT2 primarily localizes to β-cells in islets. In a collaborative effort we show that the expression of the *MTNR1B* gene is increased in pancreatic islets from donors with type 2 compared with non-diabetic donors. Non-diabetic individuals carrying the risk allele show increased expression of the receptor in islets when compared with non-risk allele carriers. Also, insulin release from clonal β-cells in response to glucose is inhibited in the presence of melatonin [43••]. In an INS-1 β-cell line expressing recombinant human MT2 receptors (cDNA for human MT2), the formation of cAMP and cGMP are more strongly inhibited than in control cells, resulting in a more pronounced suppression of insulin secretion in these cells [55]. Also, the MT2 knock out mouse displays increased insulin secretion in vitro after melatonin stimulation, indicating a loss of inhibition of insulin secretion via MT2 in islets [37].

In line with previous findings that variants in the *MTNR1B* gene are also associated with hepatic insulin resistance [56, 57], we have preliminary observations that the risk carriers of the *MTNR1B* SNP exhibit an insulin resistant phenotype for

the given impairment in insulin secretion (Jonsson et al. unpublished data).

Clinical and Pharmacological Implications

Data on melatonin administration and glycaemia in healthy individuals and/or patients with type 2 diabetes are sparse. In one randomized, double-blind study of 36 patients with type 2 diabetes and insomnia, the short-term use of melatonin did not have an effect on glucose metabolism, however long-term administration had a beneficial effect on HbA1c [58]. Another study of 42 patients with nonalcoholic fatty liver disease demonstrates that 3-months melatonin treatment improves plasma liver enzymes, but has no effect on glucose levels [46]. Nevertheless, given that most observations available today support a direct inhibitory effect of melatonin on insulin secretion, selective blocking of the melatonin ligand-receptor system in pancreatic islets could be an attractive potential pharmacological target for the treatment of type 2 diabetes. An individual who carries the risk allele may thus be more sensitive to the inhibitory melatonin effect, than an individual without the risk allele, with a normal level of *MTNR1B* expression in islets. Such a restraining effect of melatonin fits with the impairment of early phase insulin secretion that we observed in risk carriers [43••]. Thus, assessment of an effect of melatonin administration on glucose levels and insulin response during an oral glucose tolerance test and/or during different time points of the day in risk and non-risk genotype carriers of the *MTNR1B* gene deserve future studies to support or reject this notion. Finally, recent data have suggested catecholamines to play a causal role in the melatonin-insulin antagonism reinforcing the protective role of elevated melatonin concentrations in pancreatic β-cells to counteract glucose-induced oxidative stress [59].

Conclusions

The proposed mechanism by which altering melatonin signaling could predispose to progression to type 2 diabetes involves altering expression of *MTNR1B* in pancreatic β-cells leading to decreasing cAMP/cGMP concentrations via G proteins and, thereby, impaired insulin secretion. This, in turn, would lead to increased glucose concentrations and eventually overt type 2 diabetes (Fig. 1). Particularly interesting in the future is to elucidate the role of melatonin in the cross-talk between β- and α-cells in pancreatic islets,

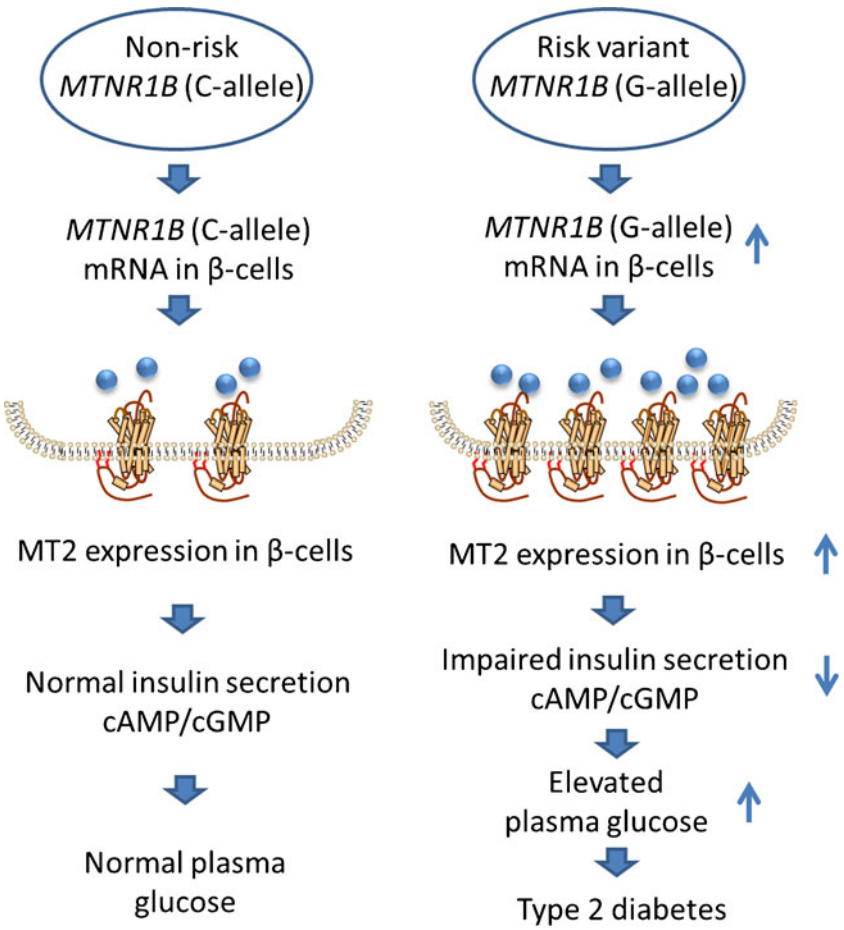

Fig. 1 Proposed pathogenetic mechanism. On the *left panel*, we illustrate the mechanisms at work in non-risk (C-allele) carriers. Here, the *MTNR1B* mRNA levels are unaltered resulting in unchanged expression levels of the protein in β-cells. As a consequence cAMP/cGMP levels and insulin secretion are not altered and plasma glucose is within normal range. On the *right panel*, we describe the gain-of-function mutation in the *MTNR1B* risk variant. In these carriers, *MTNR1B* mRNA expression is increased and thus receptor expression is likely to be increased in β-cells. This results in a decrease in cAMP and cGMP levels in the β-cell followed by impaired insulin release. Elevated plasma glucose values and type 2 diabetes are possible consequences of these changes

especially in respect to the circadian rhythm. Finally, it would be important to see an OR for type 2 diabetes of a composite risk score in *MTNR1B* locus consisting of disease-associated rare functional variants, common variants in the gene, consistently associated with increased risk (rs10830963) and circulating metabolites or key enzymes in the melatonin pathway such as tryptophan and phenylalanine ratio, which is shown to be affected by SNP rs10830963 in the *MTNR1B* gene [60].

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