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Perspective

Melatonin receptors in diabetes: A potential new therapeutical target?

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ABSTRACT

Melatonin is synthesized and secreted mainly by the pineal gland in a circadian fashion, and it thus mediates endogenous circadian rhythms and influences other physiological functions. Both the G-protein coupled receptors MT1 (encoded by MTNR1A) and MT2 (encoded by MTNR1B) in mammals mediate the actions of melatonin. Evidence from in vivo and in vitro studies proved a key role of melatonin in the regulation of glucose metabolism and the pathogenesis of diabetes, as further confirmed by the recent studies of human genetic variants of MTNR1B. Remarkably, it was also suggested that genetic variations within MTNR1B disordered β-cells function directly, i.e. insulin secretion. This indicated the functional link between MT2 and T2D risk at the protein level, and it may represent the prevailing pathomechanism for how impaired melatonin signaling causes metabolic disorders and increases the T2D risk. It is speculated that melatonin and its receptors may be a new therapeutic avenue in diabetes.

1. Introduction

Melatonin is synthesized and secreted mainly by the pineal gland of the mammalian brain in a circadian manner at night, and thus it mediates endogenous circadian rhythms and influences other physiological functions. Two membrane receptor isoforms that belong to the class of G-protein coupled receptors, MT1 (Mel_{1a}, encoded by MTNR1A) and MT2 (Mel_{1b}, encoded by MTNR1B) have been described to transmit the actions and effects of melatonin by coupling with pertussis toxin-sensitive G_i proteins, which mediate inhibition of adenylate cyclase (AC), leading to a fall in cellular cAMP levels, and, thereby, downstream targets (Peschke and Mühlbauer, 2010). In addition, another high-affinity binding site for melatonin, the subtype MT3 (Mel_{1C}) has been cloned from the zebrafish, Xenopus and chicken, but not from mammals (Sugden et al., 2004). A mammalian ortholog of MT3 is the orphan receptor GPR50 (Peschke et al., 2013), which, however, does not bind melatonin and its biological function in humans remains unknown.

2. Melatonin and glucose homeostasis

Evidence suggests a role of melatonin in glucose metabolism and pathogenesis of type 2 diabetes (T2D) both in animals and humans (Peschke and Mühlbauer, 2010). Pinealectomy, by eliminating melatonin production, induced glucose intolerance and insulin resistance, which could be restored by melatonin supplementation (Lima et al., 1998; Zanquetta et al., 2003). This proved directly that melatonin plays a prominent role in glucose homeostasis. As melatonin synthesis reduces with aging, the insulin signaling is impaired in organisms of aged rats; however, melatonin supplementation increases insulin sensitivity and prevents the age-related insulin resistance (Zanuto et al., 2013). Reduced melatonin levels were observed in Goto Kakizaki (GK) rats and humans with T2D (Peschke et al., 2006). Administration of melatonin lowered insulinemia and HOMA-IR in a T2D model of Zucker rats (Agil et al., 2012), and improved metabolic syndrome induced by diet in rats (Kitagawa et al., 2012). In neonatally streptozotocin (STZ)-induced diabetes rats, melatonin treatment improved metabolic disorders and insulin responsiveness of adipocytes, i.e. glucose utilization (de Oliveira et al., 2012). Faria et al. (2013) found that intracerebroventricular injection of melatonin activated hypothalamic Akt and suppressed hepatic gluconeogenesis in rats, indicating melatonin activated hypothalamus–liver communication. This further suggested a physiopathological relationship between the reduced melatonin found in T2D patients and circadian disruptions in metabolism.

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On the other hand, being complementary to the known fine control exerted by melatonin on glucose metabolism, Amaral et al. (2014) recently have reported the impairment of hyperglycemia on melatonin synthesis perhaps for the early-stage reduction of β-adrenergic receptor expression, which is critical for triggering the melatonin synthesis cascade. This is supposed to be further detrimental to glucose homeostasis and aggravate the diabetes.

3. Melatonin receptors and insulin secretion

Well-known as a synchronizing agent (zeitgeber), melatonin participates in the control of circadian rhythms in various parts of the body, and regulates various important functions like sleep–wake cycle, food intake, energy metabolism, and gastrointestinal tract action (Mirzaei et al., 2014; Reiter et al., 2012). Thus, it is suggested that the effects of melatonin on sleep, mediators of ingestion like ghrelin and leptin, adiposity and body weight regulation, etc. may contribute to its regulation of glucose homeostasis, metabolic syndrome and risk of T2D (Konturek et al., 2011; Mirzaei et al., 2014; Zanuto et al., 2013).

However, since insulin is the key regulator of metabolism, effects of melatonin on insulin secretion must be focused on. Using a perifusion system, Peschke et al. (1997) proved that melatonin decreased insulin secretion. This was subsequently reproduced both in vitro and in vivo (la Fleur et al., 2001; Picinato et al., 2002). Also, the inhibitory effect is also supported by that melatonin supplementation can stop the age-related increase of insulin in rats (Zanuto et al., 2013). Although a stimulation effect of melatonin on insulin secretion was once showed in human islets, it was just a consequence of glucagon release led by direct stimulation of melatonin at α-cells via MT1 (Ramracheya et al., 2008).

It has been determined that the modulations of melatonin on insulin secretion are mediated through both MT1 and MT2. Via melatonin receptors and Gi-protein signaling cascade, melatonin inhibits the AC/cAMP (MT1 and MT2) and the GC/cGMP system (MT2), and thus reduces the release of insulin (Fig. 1). On the contrary, by coupling to Gq, melatonin receptors activate phospholipase C, and thus melatonin induces insulin secretion by IP3-signaling pathway.

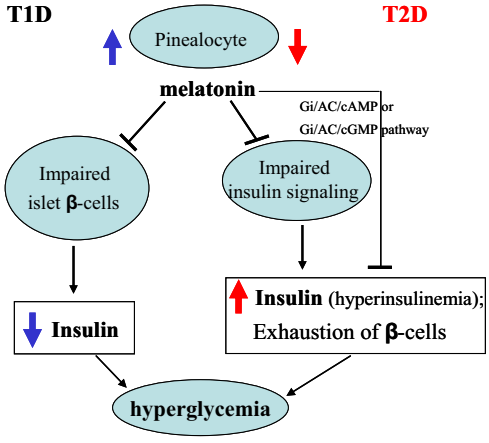

Fig. 1. Effects of melatonin on insulin and glucose homeostasis. In general, the functions are based on the melatonin receptors (MT1 and MT2) of the pancreatic β-cells. By AC/cAMP or GC/cGMP pathway, melatonin inhibits insulin secretion from β-cells. This protects β-cells against functional overstrain in T2D and attenuates hyperinsulinemia. On the other way, melatonin protects β-cell (regeneration/proliferation, prevention of apoptosis) and its function in T1D. Thus, melatonin plays a role in glucose homeostasis, and disturbed circadian rhythm of melatonin explains the changed levels of insulin and hyperglycemia. In T1D, a high level of melatonin as well as decreased plasma insulin (blue arrows) is present, in contrast, decreased melatonin and increased insulin levels are shown in T2D (red arrows).

However, negative consequences on insulin release are the predominant effects (Karamitri et al., 2013; Peschke et al., 2013).

Conflict with the report that MT1 was not expressed by human β-cells (Ramracheya et al., 2008), Lyssenko et al. (2009), by immunocytochemistry, observed expression of MT2 predominantly in β-cells in both human and rodent islets, and also less abundant MT1 in a population of peripherally located β-cells. Again, using MT1 knockdown or knockout technology, Mühlbauer et al. (2012) indicated that melatonin influenced insulin secretion primarily via MT1 receptors in rodents. This discrepancy of receptor subtype (s) localization means un-conclusive signal pathway of melatonin on β-cells. Obviously, it will be necessary to replicate the results, especially in human before drawing any conclusion.

4. Relevance of melatonin and insulin in diabetes

For the predominant inhibition by melatonin, insulin shows an opposite rhythm to melatonin (Boden et al., 1996), and this is also present in diabetes. At early stage of T2D in GK rats (Frese et al., 2009) and humans (Peschke et al., 2007), insulin secretion is increased while melatonin is decreased. Under T1D conditions, such as in STZ-treated Wistar rats and spontaneous T1D LEW.1AR1-iddm rats (Peschke et al., 2008, 2011), they are going in the opposite direction. Catecholamines are suggested to be the key to understand the reciprocal relationship in diabetes (Peschke et al., 2012). Catecholamines, especially noradrenaline (NE), not only trigger melatonin synthesis and secretion by the adrenoceptor β1-cAMP or α1-IP3 cascade, but also they can inhibit insulin secretion through α2 receptors. Supporting this, the rat models of T1D (STZ) show increased plasma catecholamines, coinciding with the T1D-associated stress, enhanced melatonin and reduced insulin (Peschke et al., 2012, 2013). In addition, α2 adrenoceptors can also inhibit NE release through the autoreceptors of the nerve terminals. In that case, the significantly more strongly expressed α2 receptors in T2D GK rats (Bach et al., 2010) imply a reduced NE release and an attenuated NE-trigged synthesis of melatonin. These may explain the diminished plasma catecholamines, the reduced melatonin and high level of insulin in T2D (Frese et al., 2009; Peschke et al., 2006).

As the exhaustion of β-cells is implicated in the genesis of T2D, it is presumed that, by inhibiting insulin secretion, melatonin protects β-cells against functional overstrain (Karamitri et al., 2013), and thus against the development of T2D. So the reduced melatonin and increased incidence of insulin resistance and T2D with aging in humans can be understood. On the other hand, in STZ rats or in isolated rat pancreatic islets, melatonin shows a positive impact on β-cell regeneration/proliferation as well as prevention of apoptosis (Kanter et al., 2006; Simsek et al., 2012). These indicate protective roles of melatonin on both β-cell and its function. So, in the case of T1D, the increased melatonin signifies a protective reaction of the organism by counteracting diabetes-induced stress, thereby attenuating the oxidative stress-induced β-cell damage (Reiter et al., 2009). Altogether, melatonin can improve β-cell function and hinder the progression of diabetes (Fig. 1).

5. Current evidence

In genome-wide association studies, single nucleotide polymorphisms (SNPs) in the MTNR1B locus were associated with impaired glucose homeostasis and increased incidence of T2D in populations of different ethnic backgrounds (McMullan et al., 2013). For example, two common variants, intron-localized rs10830963 (Langenberg et al., 2009; Lyssenko et al., 2009; Sparsø et al., 2009) and 5′ promoter region-localized rs1387153 (Bouatia-Naji et al.,