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Review article

Melatonin and glucose metabolism.

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Abstract

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone secreted from the pineal gland during the night and is known as a synchronizer of the circadian rhythm. It is a hormone that has been present not only in vertebrates but all kinds of living organisms. Recently, several reports showed that the hormone plays very important roles such as energy metabolism and glucose metabolism, in particular. It has been reported that in animal models of type 2 diabetes, melatonin ameliorates glucose homeostasis by improving insulin action in muscle and adipose tissues. We demonstrated that melatonin treatment increased glucose uptake in a dose-dependent manner in a primary culture of goldfish brain cells using insulin-free medium. These findings suggest that nocturnal melatonin increases glucose uptake in the brain via insulin independent action. To the best of our knowledge, this study is the first to demonstrate that nocturnal melatonin directly regulates glucose uptake in place of insulin in a vertebrate species. In this paper, we introduce new findings concerning glucose metabolism by melatonin on mammals, and consider a role of melatonin in aspect of the evolution of glucose metabolism.

***KEY WORDS*:** melatonin, glucose metabolism, insulin, type 2 diabetes mellitus, diurnal rhythm

1. Melatonin Existing in Various Species of Organism and Its Main Actions

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone, belonging to amine, and is secreted mainly from the pineal gland during the night. It is also known that it is produced in other tissues (such as retina and skin) in vertebrates, and is presented in various organisms such as invertebrates [1], plants [2] and cyanobacteria [3].

The secretion of melatonin is controlled by suprachiasmatic nucleus (SCN), which is known as the existence site of the circadian clock and it shows circadian rhythm synchronized with light and dark cycle. The melatonin secreted at night time is the signal of the start of activities of nocturnal animals, and it induces the rest (sleep) of diurnal animals. The daily pattern of melatonin is recognized not only in blood but also in cerebral spinal fluid, saliva and follicle liquid. This indicates that the signal from the circadian clock communicates with the cells all over the body through the changes of concentration of melatonin.

So far, the existence of melatonin receptors in many species including vertebrates and invertebrates has been reported. For example, in the case of mammals, melatonin receptors are expressed in almost all organs and cells throughout the whole body such as SCN, cerebrum, retina, spinal cord, spleen, thymus gland, pituitary gland, adrenal gland, kidney, liver, pancreas, small intestine, heart, skin, lung, testis, ovary, blood vessel, lymphocytes and osteoblasts (***Fig. 1***). In the case of mammals, G-protein coupled membrane MT1 and MT2 receptors exist, and RORα and RZR, which are nuclear receptors, also are considered as candidates for melatonin receptors. Furthermore, melatonin has various action mechanisms such as binding with proteins of calmodulin and quinone reductase and melatonin itself being a free radical scavenger. It is considered that it's probably because melatonin is a very old substance [4] in evolutionary terms.

As the main action of melatonin, a synchronizing effect of circadian rhythm is mentioned. Recently, in addition, its various effects have been clarified, such as its strong

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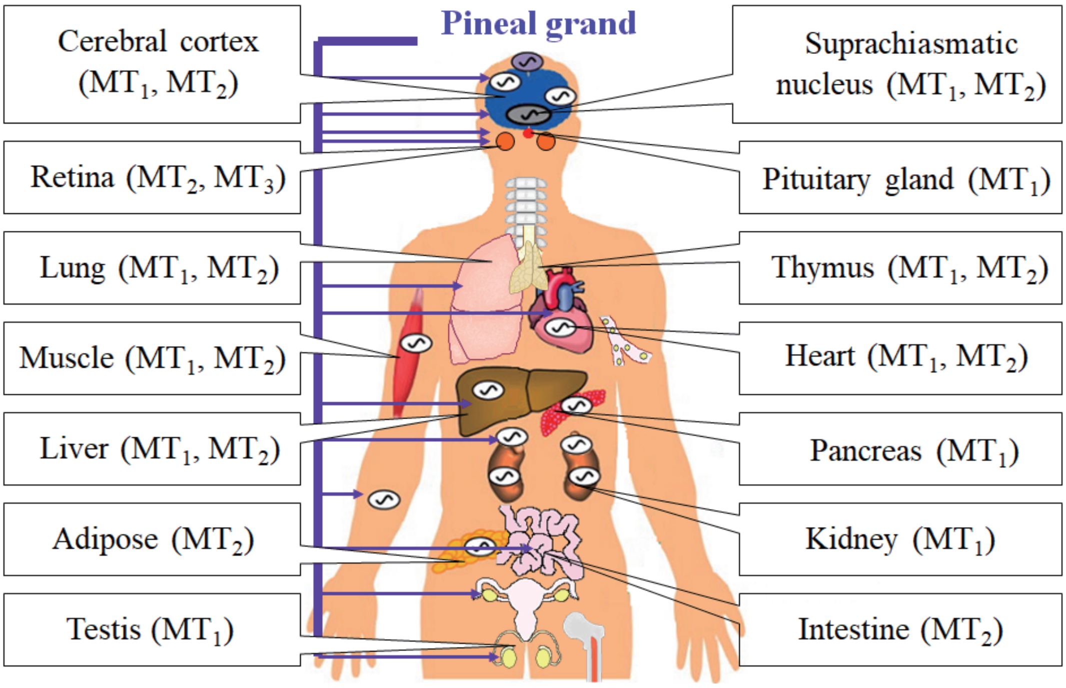

Fig. 1. **Distribution of membrane receptors (MT1/MT2) in body of mammals including humans.**
Membrane receptors for melatonin exist in the tissues of almost whole body.

antioxidant action[5], promotion of bone formation[6], inhibition of bone absorption[7] and activation of the immune system[8]. Furthermore, it is reported that melatonin controls the circadian rhythm of body temperature[9] and plays important roles in energy metabolism.

2. Melatonin's Effect on Glucose Metabolism in Mammals

Recent reports suggested that melatonin ameliorates energy metabolism, especially glucose metabolism. Actually, since a long time ago, the relationship between melatonin and glucose metabolism in rodents has been suggested. For example, research in the 1960s showed that abnormal glucose tolerance and glycogen synthesis inhibition were caused by pinealectomy[10], and also recently, glucose intolerance and the inhibition of insulin signaling in peripheral tissues (liver, adipose tissue and muscle) in pinealectomized animals are reported[11]. Meanwhile, it is reported that melatonin improved glucose metabolism and insulin resistance in animal models of type 2 diabetes mellitus (T2DM)[12], and it has been suggested that melatonin contributes to the improvement of the condition of diabetic patient. In the physiological and pathological states related to reduced melatonin levels due to aging, shift work, and exposure to light during the night, glucose intolerance, insulin resistance, and other alterations associated with metabolic disorder can be seen[13]. It is reported that lower melatonin secretor was associated with a higher developing T2DM[14] and several variants in MT2 associated with increased risk of type 2 diabetes[15]. As stated above, it is suggested that melatonin is possibly involved in the diabetes of humans.

Recent studies showed that the insulin resistance and glucose intolerance induced by pinealectomy are caused by the inhibition of intracellular transmission systems induced by insulin. The expression of mRNA of glucose transporter 4 (GLUT4) in the insulin-sensitive tissues (fat and muscle) on animals with lower melatonin by pinealectomy was significantly decreased, compared with control group, which can be improved by treatment of melatonin[16]. Meanwhile, concerning the abnormity (lowering) of insulin signals in diabetic animal models, insulin signaling is activated through a transient increase of tyrosine phosphorylation activities of the insulin receptor caused by treatment of melatonin, followed by tyrosine phosphorylation of IRS-1, and the combination of PI3 kinase and SHP-2[17]. This series of reactions are inhibited by the antagonist or blocking agent of the melatonin receptor. Furthermore, intracellular transport of glucose via GLUT4 can be increased, through Akt phosphorylation caused by tyrosine phosphorylation of IRS-1 and activation of PI3 kinase in adipose tissue by treatment of melatonin[18]. It suggests that inhibiting FOXO1 and PGC1 located downstream of PDK-1 and Akt affects deactivation of gene expression of gluconeogenesis. From the above, it is suggested that melatonin promotes uptake of glucose in diabetic animal models by increasing insulin signals (*Fig. 2*).

3. Physiological Significance Concerning Glucose Metabolism by Melatonin at Night

Melatonin is secreted from the pineal gland at night. What is its physiological significance in glucose metabolism?

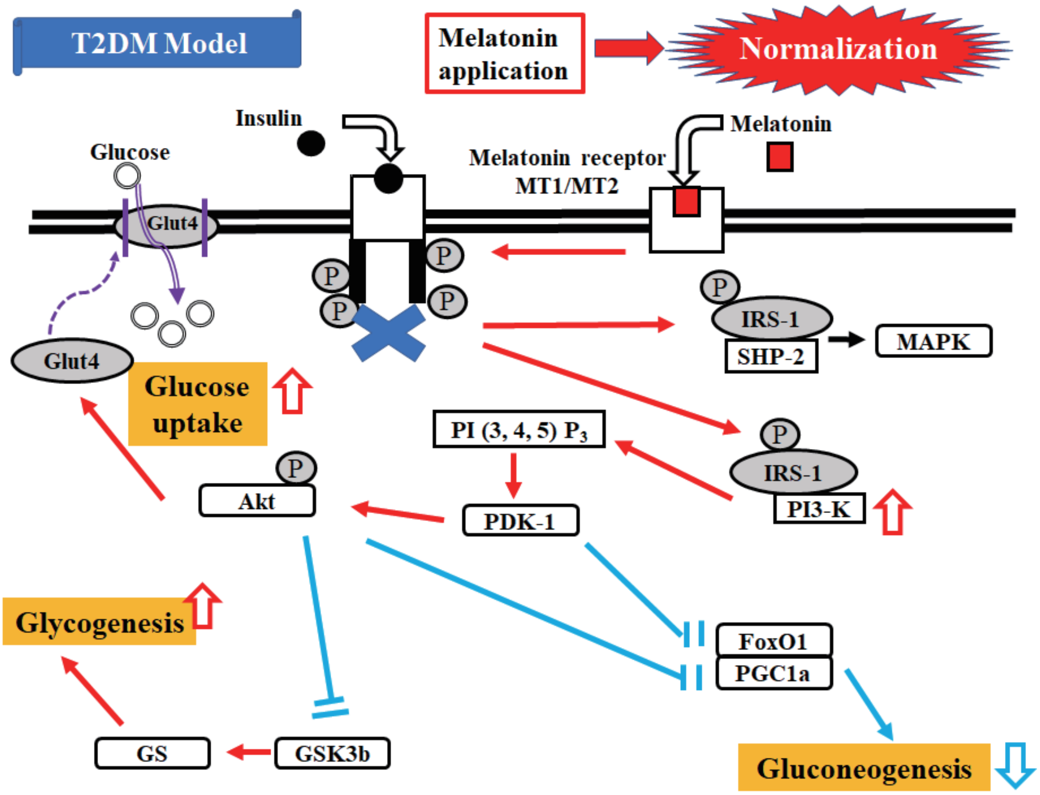

Fig. 2. **Abnormity of insulin signal in type 2 diabetic animal models and melatonin improving it.**
Signaling by melatonin is cross talking with insulin signal. "Red" shows the pathways promoted by melatonin and "blue" shows those inhibited by melatonin. (But some pathways are speculated mechanisms by the authors based on recent reports.)

In the reports on rodents and humans so far, it was clarified that insulin levels in blood are lower at night when a larger amount of melatonin is secreted [19, 20]. Several reports show that insulin secretion from the pancreas is inhibited by melatonin treatment [21]. Plasma insulin levels in MT2 deficient mice increased compared with the control group. As the physiological significance of this, it is possible that melatonin secreted at night inhibits the secretion of insulin from β-cells and restricts glucose uptake to peripheral tissues including muscle and fat at night.

So far, no orthologs of mammalian GLUT4 (typical insulin-dependent glucose transporter) have been found in zebrafish. Recently, we obtained the following results by using goldfish, genetically close to zebrafish. Using an insulin-free medium, we demonstrated that melatonin treatment increased glucose (actually 2-deoxyglucose) uptake in a primary culture of goldfish brain cells. 2-deoxyglucose is not metabolized by the glycolysis system after being incorporated by cells, so that it is often used in glucose uptake experiments. GLUT2 (insulin-independent glucose transporter) is expressed in the brain of goldfish, so the possibility shows that there exists an insulin-independent glucose uptake mechanism via GLUT2 (*Fig. 3*). Melatonin secreted at night inhibits the secretion of insulin, it increases the uptake of glucose into the brain through a mechanism that is not dependent with insulin, and is involved in the maintenance of brain function at night (for example memory formation). This is considered to be a new finding concerning melatonin involvement in glucose metabolism.

4. *Melatonin's Involvement in Energy Metabolism in Lower Organisms*

The authors consider the relationship of melatonin to energy metabolism in living organisms from an evolutionary perspective. Some cyanobacteria (*Synechocystis* sp. PCC 6803) live by taking glucose as nourishment and the structure of the membrane protein (GlcP) of its glucose transporter is greatly similar to GLUT in mammals [22], and it is also known that it shares high homology with XylE expressed in *Escherichia coli* [23]. It is also known that FGT-1 (mammalian GLUT2-like facilitative glucose transporter), mainly glucose transporter protein expressed in nematode also shares high homology with GLUT [24]. Thus, the existence of glucose transporter is widely confirmed in animal species before vertebrates appeared. In examining molecular evolution of glucose transporters, they have been highly preserved in organisms from bacteria to mammals (*Fig. 4*). Meanwhile, melatonin is a hormone (substance) that has existed for a long time in evolutionary terms. It is very interesting if melatonin is involved in glucose metabolism in lower organisms.

There is glucose as an energy source for vertebrates. In order to maintain a living organism stably, a constant energy supply is required. Highly concentrated trehalose is dissolved in insect body fluid and mainly sucrose is delivered through vascular bundles in plants. However, they do not always exist as energy sources. The problem that aquatic animals first faced when they ventured onto land was preventing themselves from drying out. It is considered that trehalose

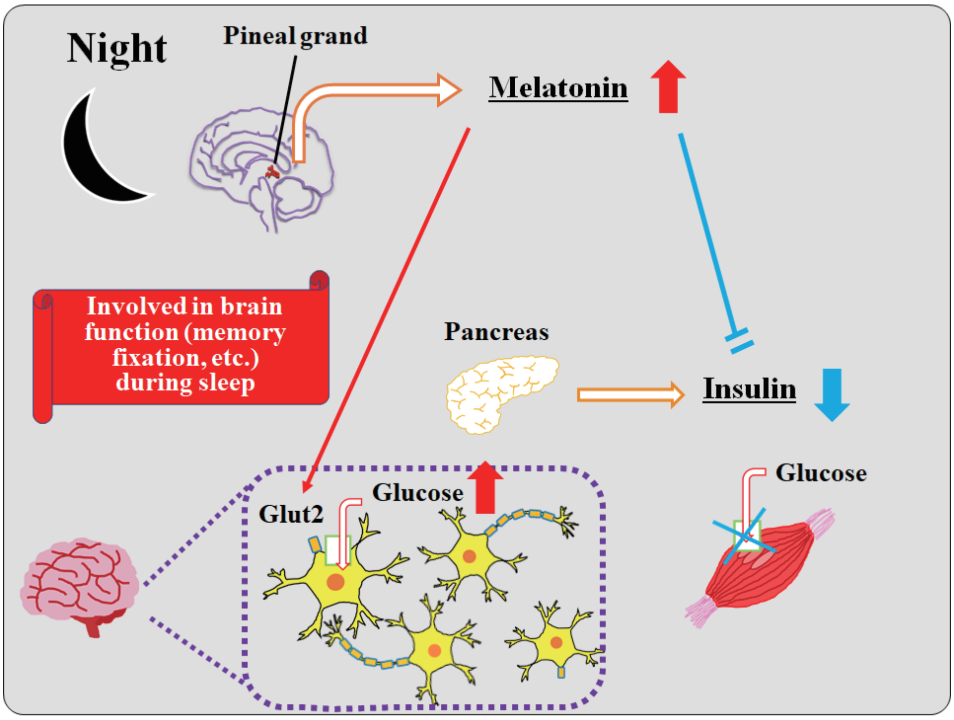

Fig. 3. **Physiological significance of glucose metabolism by melatonin at night.**

It is reported that melatonin inhibits the secretion of insulin from β-cells of the pancreas. Meanwhile, it is also reported that the uptake of glucose in the brain significantly increases at night when the level of melatonin is high compared with that in daytime. Melatonin treatment significantly increased glucose uptake in the primary culture of brain cells in insulin-free culture medium, so that it is considered that melatonin at night inhibits the uptake of glucose to peripheral tissues (muscle and liver) and that increases the uptake of glucose into the brain via insulin independent action.

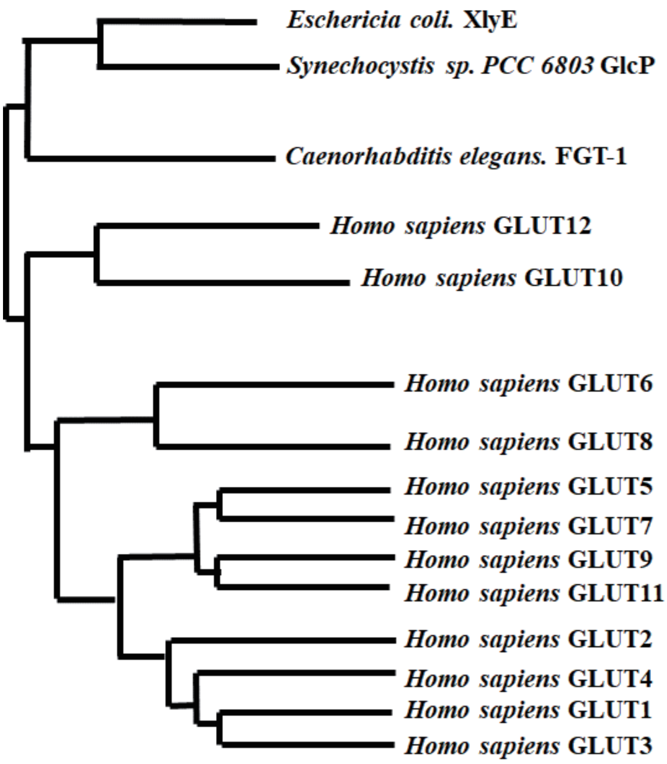

Fig. 4. **Molecular evolution of glucose transporter.**

Glucose transporter has been highly preserved from prokaryote and it exists in bacteria (*Escherichia coli*) and cyanobacteria (*Synechocystis sp. PCC 6803*). Glut2 diverged at an early stage among typical four kinds of glucose transports (1-4) in humans.

and sucrose, in particular, performed functions against drying out and freezing. It is known that trehalose and sucrose are converted to glucose and, in the part of insects and plants, they are used as energy sources[25].

5. Conclusion

Melatonin is a very interesting hormone having various functions. It is expected that melatonin's involvement in glucose metabolism and diabetes will be clarified in greater detail in the future.

Conflict of interest

The authors claim no conflict of interest in this study.

Acknowledgments

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