TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 6
Number 1 *Fall 2012*

1-1-2012

Melatonin and Its Effect on Learning and Memory

Nechama Leah Bauman (Cahn)
Touro College

MELATONIN AND ITS EFFECT ON LEARNING AND MEMORY

Nechama Leah Bauman (Cahn)

ABSTRACT

Melatonin is a neurohormone produced by the pineal gland and secreted into the body in a circadian rhythm. Melatonin is known to be involved in many vital body functions, including sleep, reproduction, and immune response. Exogenous melatonin, sold as over the counter natural supplements in drugstores, is commonly taken by many people to help cure various ailments. Melatonin also plays a role in the hippocampus. This paper investigates the effects of melatonin on long-term potentiation in the hippocampus. Long-term potentiation, described as a long-lasting strengthening of synapses between nerve cells, is thought to be responsible for long-term memory retention. It is found that melatonin has a negative effect on long-term potentiation, inhibiting its magnitude. As long-term potentiation is related to some forms of learning and memory, melatonin inhibits learning and memory too. The practice of taking melatonin supplements causes one's long-term potentiation to be inhibited to a greater degree than it would be under normal conditions and can significantly impact one's learning and memory. In conclusion, although more studies need to be conducted, one should be wary and display caution before using melatonin supplements with any regularity.

INTRODUCTION

Melatonin, N-acetyl-5-methoxytryptamine, is a neurohormone synthesized mainly by the pineal gland. It is synthesized in a series of steps, starting with the conversion of tryptophan to serotonin. Serotonin is then converted to melatonin (Cardinali and Pevet 1998) (Figure1). Melatonin is metabolized mainly in the liver. The major metabolite of melatonin is 6-sulfatoxymelatonin (Macchi and Bruce 2004).

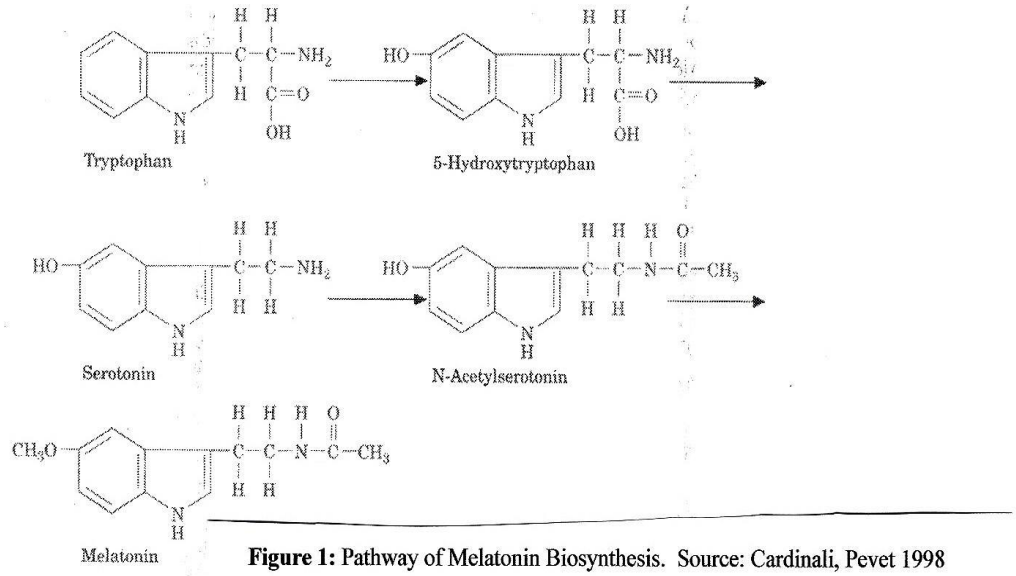

Figure 1: Pathway of Melatonin Biosynthesis. Source: Cardinali, Pevet 1998

The suprachiasmatic nucleus controls melatonin levels in the body, which follows a circadian rhythm of high melatonin levels by night and low melatonin levels by day.

This pattern is controlled by an endogenous, independently run pacemaker in the suprachiasmatic nucleus. Light and darkness do not cause the circadian rhythm of melatonin but do have the ability to change its timing. Light inhibits melatonin production, while darkness stimulates it. Photic information from the retina is sent to the suprachiasmatic nucleous and from there to the pineal gland in the form of norepinephrine. When norepinephrine enters the pineal gland, melatonin is synthesized. When light hits the retina, the retinal photoreceptor cells become hyperpolarized, inhibiting norepinephrine release, thereby inhibiting melatonin production. When it is dark outside, the retinal photoreceptors do release norepinephrine, thereby stimulating melatonin production. (Brzezinski 1997).

Melatonin is circulated to the rest of the body by passive diffusion into the bloodstream. It acts by binding to receptor sites. The receptors are part of the guanosine triphosphate-binding proteins and are G-protein coupled receptors (Brzezinski 1997). There are two subtypes of melatonin receptors: MT1 and MT2. Both subtypes are found in many areas of the body, including the cerebellum, retinal rods, ganglion cells, lymphocytes, and blood platelets. Since melatonin is very easily diffused, it has a systemic effect even without receptors at the basic cellular level, altering cytoskeletal and mitotic functions by binding to calmodulin, and acting as a free-radical scavenger (Macchi and Bruce 2004).

Endogenous melatonin is involved in many of the processes of the body, including sleep, reproduction, and the immune system. Exogenous melatonin, sold as over-the-counter tablets in drugstores and health food stores, is used by many people to cure various disorders.

Melatonin plays a major role in sleep. The circadian rhythm by which melatonin is synthesized is connected to sleep, and melatonin is also secreted in higher amounts at night, when people typically sleep (Brzezinski 1997). The effect of melatonin on sleep may also be related to changes in body temperature at night, with the nighttime decrease in body temperature, which is connected to the onset of sleep, increasing the evening secretion of endogenous melatonin. In fact, the highest point of melatonin production at night corresponds with the lowest point of body temperature (Macchi and Bruce 2004). Exogenous melatonin is often taken to correct sleeping problems. Flying over different time zones (jet lag) and working the night shift can disturb one's circadian rhythm, and many people take melatonin supplements to try and cure this. Also, people with insomnia, who have trouble falling asleep or staying asleep, often take melatonin supplements (Brzezinski 1997).

Melatonin also plays a role in the reproductive system. In animals that are seasonal breeders, the seasonal cycle, which is controlled by melatonin, regulates reproductive activity (Macchi and Bruce 2004). In humans, too, melatonin is involved in reproduction. Melatonin inhibits the reproductive process (Brzezinski 1997). Accordingly, melatonin supplements are sometimes taken by men and women to try and influence their reproductive systems. Additionally, there may be a relationship between endogenous melatonin levels and puberty (Macchi and Bruce 2004).

Melatonin also plays a role in the immune system, increasing the immune response. This is thought to happen by high levels of melatonin stimulating T-helper cells and other parts of the immune system (Macchi and Bruce 2004). Melatonin is also a strong antioxidant. It is a free-radical scavenger, scavenging against toxic hydroxyl

radicals as well as other oxygen-centered radicals. This protects the macromolecules of the body, especially DNA (Brzezinski 1997). Melatonin is also thought to have oncostatic properties, slowing down the development of tumors, and is taken by some as a treatment for cancer (Macchi and Bruce 2004).

Melatonin may also have an influence on the cardiovascular system. It may also have a connection to some psychiatric and neurological disorders (Macchi and Bruce 2004). Some people take melatonin to prevent or to reduce the effects of coronary disease, Alzheimer's disease, and Parkinson's disease (El-Sherif et al. 2002).

Melatonin is also thought to play a role in the processes of the brain. Melatonin receptors are present in the hippocampus, indicating that melatonin plays some role in that area (Wang et al. 2005). This research paper will look at the role of melatonin in the hippocampus and, specifically, at its effect on the process of long-term potentiation. It will also focus on the question of whether taking melatonin supplements, which inundate one's body with greater levels of melatonin than are naturally synthesized, has a harmful effect on the long-term potentiation in the hippocampus.

METHODS

The information in this paper was obtained by critical analysis of scientific research articles. The articles used have to do with studies conducted on the topics of melatonin, long-term potentiation, and the connection between the two. The articles were found in the Touro College library databases. ScienceDirect was the database most frequently used.

DISCUSSION

The hippocampus is an essential part of the brain, located in the medial temporal lobe of the brain. The hippocampus is made up of several structures: the hippocampus proper, the dentate gyrus, and the subiculum. There are three main excitatory pathways in the hippocampus: the perforant pathway, the mossy fiber pathway, and the Schaeffer collaterals. The hippocampus is part of the limbic system and is involved in the formation of long-term memory (Rison and Stanton 1995).

Learning and memory are stored in the brain as changes in the synapses between neurons (Medina and Izquierdo 1995). If two cells are active at the same time, the synapse between these cells is strengthened (Bliss and Collingridge 1993). In 1973, long-term potentiation (LTP), a method in which learning and memory are stored in the hippocampus, was discovered by Tim Bliss and Terje Lomo. They found that short bursts of high-frequency stimulation to excitatory pathways in the hippocampus caused an increase in synaptic excitability that was long lasting, lasting even months long (Rison and Stanton 1995). Later on, it was discovered that LTP also causes a change in the ionic current, causing the ionic current to be different than that in regular synaptic transmission (Morris 2003).

Long-term potentiation is induced by a specific mechanism. First, a high-frequency tetanus is given to the neurons. This causes the postsynaptic membrane to become strongly depolarized by AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) receptors located on the dendritic spine. The depolarization removes the magnesium (Mg) barrier of the NMDA (N-methyl-D-aspartate) receptors, also located on the dendritic spine. This allows sodium (Na), potassium (K), and calcium (Ca) to flow through (See Figure 2). Calcium concentrations rise in the dendritic spine, triggering calcium dependent processes necessary in order for LTP to occur. The calcium dependent

processes cause changes in the synapse that increase synaptic strength, achieving long-term potentiation (Rison and Stanton 1995).

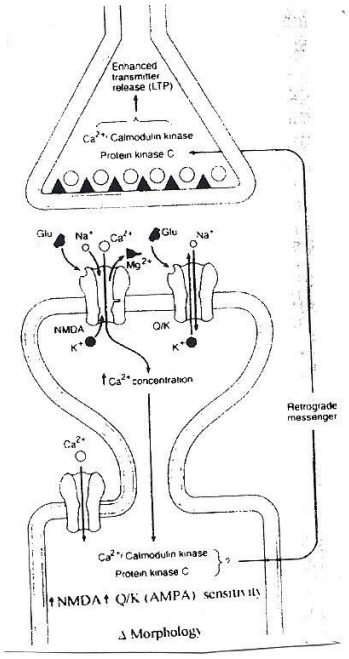

Figure 2: Model for the induction of LTP. Source: Rison, Stanton 1995

In order for the synapses to be strengthened in LTP, there must be correlated activity, meaning that the presynaptic and postsynaptic neurons must be active simultaneously. NMDA receptors make this happen by opening their channels only when stimulated by both neurons. Only after receiving glutamate from the presynaptic neuron as well as the removal of the magnesium block by depolarization of the postsynaptic neuron do NMDA receptors open their channels and enable the rest of the LTP pathway to occur (Tsien et al. 1996).

Long-term potentiation is connected to memory and learning. Synaptic plasticity, meaning change in synaptic strength, is caused by LTP and seems to be the way in which learning and memory are stored in the brain. Studies show that synaptic weights changed after learning, showing that learning is connected to LTP. Also, when the mechanisms involved in synaptic plasticity were changed, the rate of learning was also changed. Even after the learning was completed, changing of the synaptic weights affected the experimental animals' ability to remember what they learned. Interfering with LTP is seen to also interfere with learning and memory, showing that LTP is very involved with these tasks (Morris 2003).

In order to experiment with long-term potentiation, it must be easily stimulated and measured. During experimentation, long-term potentiation is usually induced by giving a tetanus, a stimulus, to a hippocampal slice. The tetanus must be sufficiently strong, usually at least 100 Hz, in order to invoke LTP (Bliss and Collingridge 1993). LTP is measured by recording the field excitatory postsynaptic potential (fEPSP) in the hippocampal slice after the tetanus. Experimenting with changes in the strength of synaptic connection allows one to learn about what causes these changes and how it might be linked to learning and memory (Wang et al. 2005).

Many studies have been performed investigating the effect of melatonin in the hippocampus. Their results showed that melatonin affects LTP by changing the synaptic transmission between neurons (Wang et al. 2005).

One such study, performed by Louisa M. Wang, proved that melatonin inhibits LTP in neurons. Wang proved this in an experiment using hippocampal slices of mice. First, LTP was induced with high-frequency stimulation, and the results were recorded for 60 minutes. Melatonin was then applied to the hippocampal slices, and LTP was induced again. This time, the field excitatory postsynaptic potential (fEPSP) slopes were much lower, showing that the melatonin had reduced the magnitude of LTP (Wang et al. 2005) (See Figure 3).

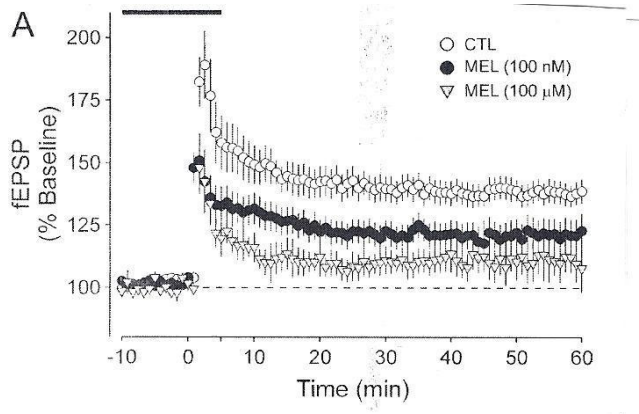

Figure 3: Inhibition of LTP by application of melatonin to hippocampal slices.
Shown is a comparison of the melatonin slices vs. the control slices. The melatonin slices have lower fEPSP, indicating an inhibition of LTP.
Soure: Wang, et. al. 2005

Yoshiyuki Takahashi also experimented with melatonin, investigating its role in LTP. Using hippocampal slices from rat brains, he tested the effect of melatonin on LTP in the CA1 region of the hippocampus. Compared to the control group, melatonin considerably lowered the expression of LTP (Takahashi and Okada 2011).

These two studies illustrate that one role of melatonin in the hippocampus is to inhibit LTP. In both experiments, after the addition of melatonin, LTP was significantly lower than the control groups.

After learning that melatonin inhibits long-term potentiation, the next step is to figure out how it is accomplished. What mechanism is in place that connects melatonin an indoleamine neurohormone, to LTP, a process of memory?

Of the two known melatonin receptor subtypes, MT1 and MT2, the inhibitory effect of melatonin seems to occur through the MT2 receptor. Wang illustrates this with his receptor-specific experiments. Luzindole, a nonselective melatonin receptor antagonist, blocked melatonin's inhibitory effect on LTP. This was expected, for if melatonin is not able to bind to receptors then it cannot act. However, 4-P-PDOT, a MT2-selective antagonist, also blocked melatonin's inhibitory effect on LTP. Here, melatonin was able to attach only to the MT1 receptors and not the MT2 receptors, and it did not act on LTP. This shows that melatonin inhibits LTP through the MT2 receptors (Wang et al. 2005).

Wang additionally proved this idea through experiments on genetically modified mice. In mice deficient in both MT1 and MT2 receptors, melatonin exhibited no inhibitory effects because it had no receptors on which to attach. In mice deficient only in

MT2 receptors, again melatonin had no effect. However, in mice deficient only in MT1 receptors, melatonin did inhibit LTP. Thus, it is the MT2 receptors which allow melatonin's effect on LTP, and as long as the MT2 receptors are present, melatonin works its effect in the hippocampus (Wang et al. 2005).

Dawn R. Collins suggested that perhaps the mechanism for melatonin's inhibition of LTP is based on N-methyl-D-aspartate (NMDA) receptors. Melatonin is similar in structure to some NMDA receptor antagonists, and if melatonin blocks NMDA receptors, then LTP would be inhibited. However, in experimentation, melatonin was found to have no effect on NMDA receptor-mediated responses, thus not inhibiting LTP through a mechanism involving the blockade on NMDA receptors (Collins and Davies 1997).

Wang hypothesized that the mechanism for LTP inhibition by melatonin involves the inhibition of the Adenylyl cyclase- protein kinase A pathway (AC- PKA pathway), which is involved in LTP. As MT2 receptors are negatively coupled to AC and PKA activity, and melatonin is mediated through MT2 receptors, it seems possible that melatonin's mechanism of action is through the AC-PKA pathway. If it is true that melatonin inhibits LTP through the inhibition of the AC-PKA pathway, then PKA inhibitors should likewise inhibit LTP the same way that melatonin does. Therefore, Wang tested H89, a PKA inhibitor, in its ability to inhibit the induction of LTP. H89 did inhibit LTP, to the same extent as melatonin did. This experiment, as well as further experiments testing the hypothesis, shows that melatonin works to block LTP induction by a mechanism involving the inhibition of the AC-PKA pathway (Wang et al. 2005).

However, the mechanism for melatonin action in the hippocampus is not straightforward. Takahashi demonstrated that melatonin blocked the induction of LTP with a mechanism involving the inhibition of the nitric oxide (NO) signaling pathway. The nitric oxide cascade is a precursor to LTP. In order for LTP to occur, a high-frequency stimulation must be given, leading to postsynaptic calcium concentrations. The calcium activates the production of nitric oxide. Nitric oxide leads to cGMP synthesis, protein kinase G activation, and finally to LTP induction. Thus, by melatonin inhibiting the nitric oxide signaling pathway, it leads to inhibition of LTP. One method Takahashi used to prove this experimentally was the application of L-NAME, a nitric oxide synthase inhibitor, to hippocampal slices. L-NAME inhibited LTP, just as melatonin did. Because melatonin inhibits LTP by inhibiting nitric oxide pathway, both melatonin and nitric oxide inhibitor should have the same end result of LTP inhibition. Each of them should achieve the same LTP inhibition, and putting both melatonin and nitric oxide inhibitor should not increase the level of LTP inhibition, because they both act on the same nitric oxide pathway. Takahashi tried this and got the hypothesized results, supporting the idea that melatonin inhibits LTP by inhibiting the nitric oxide cascade (Takahashi and Okada 2011).

Both the AC-PKA pathway and the nitric oxide pathway are mechanisms involved in melatonin inhibition of LTP in the hippocampus. There is thought to be an interaction between the two pathways (Takahashi and Okada 2011).

As previously mentioned, long-term potentiation is involved in learning and memory. Everything discussed above about melatonin inhibiting LTP means that in some way, melatonin is inhibiting the brain's ability to learn and store memory. With the endogenous melatonin produced naturally by the pineal gland, this inhibition is part of the body's natural cycle. Just as melatonin is produced in a circadian rhythm, LTP is also

found to have a circadian rhythm. The magnitude of LTP in the hippocampus is larger during the day, when less melatonin is produced, and smaller in the night when melatonin production rises (Takahashi and Okada 2011). Studies conducted by Arun V. Raghavan confirm the change in LTP strength between day and night. Raghavan found that hippocampal slices taken from hamsters during daytime showed a much greater measure of LTP than in those taken from hamsters during the nighttime (Raghavan et al. 1999). Since LTP is involved with learning and memory, learning and memory also must show a circadian rhythm (Takahashi and Okada 2011).

However, melatonin's effect on LTP is concentration dependent. Higher concentrations of melatonin have been found to inhibit LTP to a greater extent than lower concentrations (Wang, et. al. 2005). This information is crucial when considering the effects of melatonin on learning and memory. The circadian rhythm of learning and memory, from the circadian rhythm of endogenous melatonin, is a normal part of our body functioning. However, the intake of exogenous melatonin supplements places higher doses of melatonin into our body then usual, which causes LTP to be inhibited to a greater degree then normal. It is possible that melatonin supplements can seriously inhibit LTP, negatively affecting one's learning and memory to a significant degree. In fact, Xiu-Jing Cao conducted studies on the long-term effect of low dose melatonin on long-term potentiation and its subsequent effects on learning and memory, focusing especially on spatial learning. Spatial learning is awareness about one's surroundings and orientation in space. The study concluded that exogenous melatonin causes lasting harm to learning and memory (Cao et al. 2009).

Cao experimented with rats. The rats were given melatonin for sixty days and were then tested to evaluate their ability for spatial learning and to measure their LTP levels. Spatial learning was tested using the Morris Water Maze test. In this test, the rats were placed in a pool of water. In order to escape the water, the rats had to find the platform hidden in the water. The rats' spatial memory was tested by their ability to remember the platform's position by using spatial cues. When using more spatial memory, the platform was found faster. In this experiment, both the control group and the melatonin group showed decreasing reaction time, finding the platform faster as the experiment progressed. However, the group with melatonin still took significantly longer in the maze than the group without melatonin. The exogenous melatonin weakened the rats' spatial memory (Cao et al. 2009).

The long-term potentiation of the rats' hippocampi was then tested. As expected, the results showed that LTP had been inhibited in the melatonin-exposed rats, when compared to the control group. The fEPSP slope of the melatonin group was significantly less than that of the control group (Cao et al. 2009) (See Figure 3 above).

This study shows that melatonin inhibits LTP, impairing spatial memory and learning, because this type of learning and memory is related to LTP (Cao et al. 2009).

The melatonin in this study was given to the rats in low doses of 3 mg/kg for a relatively long period of 60 days. This is the same way that many people take melatonin supplements. Countless people take a low dose melatonin pill daily. However, the Cao study shows proof that this daily melatonin supplement can be harmful. It actually lowers LTP and affects spatial learning and memory. As Cao concluded, "melatonin should not be used as… [a] dietary supplement," for it harms learning and memory (Cao et al. 2009).

An experiment conducted by Ruben Soto-Moyano found that melatonin's inhibition of long-term potentiation damages visuo-spatial memory. Visuo-spatial skills involve one's visual perception of spatial relationships. Soto-Moyano tested visuo-spatial memory using the 8-arm radial Olton maze. This maze consists of a central point with eight arms extending out from it. The rat is required to run up and down the arms to find the food placed at the end of one of the arms. This maze tests visuo-spatial working memory (Soto-Moyano et al. 2005). The experiment included rats treated with melatonin and a control group of rats not treated with melatonin. In the maze, the rats treated with melatonin made more errors and took more time to solve the task than the control group. This shows that melatonin weakened the visuo-spatial working memory of rats. The control group performed better as time went on, meaning that they used long-term memory to help remember the maze. The rats with melatonin had their long-term memory damaged by the melatonin, proven by the higher number of errors even over many days of testing (Soto-Moyano et al. 2005).

This experiment by Soto-Moyano demonstrates that the LTP inhibition caused by exogenous melatonin harms visuo-spatial memory. Taking melatonin supplements may inhibit one's visuo-spatial learning and memory. Tasks that involve visuo-spatial processing, such as estimating distance and depth, may be damaged by melatonin supplements.

CONCLUSION

As seen in the above studies, melatonin inhibits long-term potentiation, consequently inhibiting learning and memory, especially spatial memory and visuo-spatial skills. With the ingestion of melatonin supplements, melatonin enters the body in amounts greater than usual. These higher levels of melatonin cause a greater inhibition of LTP and significant inhibition of learning and memory.

Additional studies must be conducted to learn more about melatonin's effect on the hippocampus. None of the findings discussed above are fully conclusive, and more research is needed on order to clarify the guidelines for the safe use of melatonin. However, it can be concluded from the studies discussed above that there is a definite relationship between melatonin, LTP inhibition, reduced spatial memory, and learning.

Melatonin is sold over the counter in the form of natural supplements in drugstores throughout the United States. These melatonin pills are often intended to help with various ailments, including jet lag, insomnia, and reproduction. However, people should be advised that taking melatonin pills long term or on a regular basis could possibly have negative side effects, impairing one's learning and memory capability. Melatonin supplements, although unregulated and promoted as natural, should not be taken unless medically advised, and even then, only with extreme caution.

REFERENCES

Bliss TVP, Collingridge GL. 1993. A synaptic model of memory: Long-term potentiation in the hippocampus. Nature 361:31-39.

Brzezinski A. 1997. Melatonin in humans. The New England Journal of Medicine 336:186-195.

Cao XJ, Wang M, Chen WH, Zhu DM, She JQ, Ruan DY. 2009. Effects of chronic administration of melatonin on spatial learning ability and long-term potentiation in lead-exposed and control rats. Biomedical and Environmental Sciences 22:70-75.

Cardinali DP, Pevet P. 1998. Basic aspects of melatonin action. Sleep Medicine Reviews 2(3):175-190.

Collins DR, Davies SN. 1997. Melatonin blocks the induction of long-term potentiation in an N-methyl-d-aspartate independent manner. Brain Research 767:162-165.

El-Sherif Y, Hogan MV, Tesoriero J, Wieraszko A. 2002. Factors regulating the influence of melatonin on hippocampal evoked potentials: Comparative studies on different strains of mice. Brain Research 945(2): 191-201.

Macchi MM, Bruce JN. 2004. Human pineal physiology and functional significance of melatonin. Frontiers in Neuroendocrinology 25:177-195.

Medina JH, Izquierdo I. 1995. Retrograde messengers, long-term potentiation and memory. Brain Research Reviews 21(2):185-194.

Morris RGM. 2003. Long-term potentiation and memory. Philosophical Transactions of the Royal Society B: Biological Sciences 358:643-647.

Raghavan AV, Horowitz JM, Fuller CA. 1999. Diurnal modulation of long-term potentiation in the hamster hippocampal slice. Brain Research 833:311-314.

Rison RA, Stanton PK. 1995. Long-term potentiation and N-methyl-D-aspartate receptors: Foundations of memory and neurologic disease? Neuroscience and Behavioral Reviews 19(4): 533-552.

Soto-Moyano R, Burgos H, Flores F, Valladares L, Sierralta W, Fernandez V, Perez H, Hernandez P, Hernandez A. 2006. Melatonin administration impairs visuo-spatial performance and inhibits neocortical long-term potentiation in rats. Pharmacology Biochemistry and Behavior 85(2):408-414.

Takahashi Y, Okada T. 2011. Involvement of the nitric oxide cascade in melatonin-induced inhibition of long-term potentiation at hippocampal CA1 synapses. Neuroscience Research 69:1-7.

Tsien JZ, Huerta PT, Tonegawa S. 1996. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87(7):1327-1338.

Wang LM, Suthana NA, Chaudhury D, Weaver DR, Colwell CS. 2005. Melatonin inhibits hippocampal long-term potentiation. European Journal of Neuroscience 22:2231-2237.