

The Potential Role of Melatonin on Mental Disorders: Insights from Physiology and Pharmacology

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Abstract

Back Ground: Mental diseases have become common in modern society, which seriously harm the human health. The etiology of mental diseases is complex, general theories and methods of mechanism and prevention guidance of mental diseases cannot fully explain the clinical hysteresis effects of antipsychotic and antineuropathy drugs.

Methods: In this review, we summarize recent advances in melatonin research, focusing on the mental diseases with special emphasis on the alterations of melatonin secretion and the associated changes in biological rhythms of disorders.

Results: With the results from biochemical measurements in melatonin treatment of mental disorders, including anxiety, depression, schizophrenia, autism and attention deficit hyperactivity disorder, showed that melatonin treatment of mental disorders did not have serious negative consequences melatonin will likely be widely used in the treatment of mental disorders in clinical practice. At the same time, the measurements of the effects of melatonin treatments would become more standardized and effective.

Conclusion: In the future, there would be a breakthrough progress in the treatment of mental disorders field by using melatonin. The potential role of melatonin on mental disorders would be attached great importance by related disciplines.

Keywords: Melatonin; Anxiety; Depression; Schizophrenia; Autism; Attention deficit hyperactivity disorder

Introduction

Mental diseases have become common in modern society, which seriously harm the human health. There are nearly 100 million people with mental diseases worldwide currently, onset mostly in young adults, it gradually becomes chronic, with high recurrence rate and disability rate. Without active treatment, patients may suffer from mental deterioration and personality changes, and difficult to adapt to social life. The etiology of mental diseases is complex, general theories and methods of mechanism and prevention guidance of mental diseases cannot fully explain the clinical hysteresis effects of anti-psychotic and anti-neuropathic drugs. And current treatments for mental diseases are limited in their efficacy, because their therapeutic benefits can take several weeks before setting in and they are only effective in approximately one third of people. Individuals with treatment-resistant mental diseases often suffer greatly in the absence of an effective drug treatment. The current clinical application of drugs of mental diseases in play a role of treatment at the same time, also often occur as extrapyramidal side effects (EPS), increase the quality of body, electrocardiogram (ecg) changes (such as QTC extension), hyperglycemia, hyperlipidemia and other adverse reactions [1]. Various types of drugs because of different structures, its mechanism is also different. With chlorpromazine as the representative of classical anti-psychotic drug and anti-neuropathy drug central dopamine D2 receptor, can reduce the frontal area of dopamine, its curative effect, but there are serious extrapyramidal side effects (EPS); And represented by chlorine nitrogen equality of classical antipsychotic drugs and anti-neuropathy drug mainly through the antagonism of 52 serotonin (52 ht), norepinephrine (NE) receptor, and adjust the glutamate receptors play a role [2]. Recent studies have found that melatonin (MT) is related to mental diseases like anxiety disorders, depression, schizophrenia, phobias and autism, attention deficit hyperactivity disorder (ADHD) and has a quick and lasting effect, and

can play a role for which traditional antidepressant treatment is invalid [3-5]. Therefore, a systematic and comprehensive understanding of melatonin would have positive significance on the etiology, process, prevention and treatment of mental diseases.

Melatonin

Known as the pineal hormone, melatonin is a peptide hormone secreted by the pineal gland, synthesized in the retina, belonging to the indole compounds, 5-serotonin acid derivatives, and its chemical name is N-acetyl-methoxytryp-amine. In 1958, Lerner proposed a substance separated of from pineal glands of 300,000 cows, and poured it into the frog body, and then he found that the frog skin color becomes shallow, melatonin is thus named.

Melatonin and immune system

Recent study suggests that melatonin immune enhancing function is related to the existence of melatonin receptor in immune organs. The melatonin can enhance wild-type and MT₁ functional gene deletion rat spleen cells proliferation, while MT₂ receptor antagonist (2-phenyl-N-acetyl serotonin) can reduce this effect of melatonin [6]. In an experimental model of septic shock in mice, melatonin improves the

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survival of mice with septic shock via its pleiotropic functions as an immune modulator, antioxidant and anti-apoptotic mediator [7].

Melatonin and reproductive system

On the one hand, melatonin can be combined with the ovaries, testes and adrenal receptors, directly regulating their physiological function, thereby controlling the reproductive organs mature. On the other hand, melatonin can affect the reproductive system function by inhibiting the hypothalamic-pituitary-gonadal axis function [8]. By the G-protein coupling specificity of high affinity receptor, melatonin inhibits the increase of gonadotrophin-releasing hormone-induced cyclic adenosine monophosphate and Ca²⁺, thus inhibiting the release of some sex hormones to regulate the reproductive system [9].

Melatonin and digestive system

Cabeza reported that melatonin acted directly on cholinergic nicotinic channels in the small intestine submucosal plexus, inhibiting calcium channel activity of muscle cell membrane and calcium-activated potassium channel activity, thereby inhibiting the gastrointestinal movement [10]. In addition, melatonin inhibits gastric acid secretion, increases gastric mucosal blood flow, improves mucosa microcirculation, and protects the gastric mucosa [11,12].

Antioxidant effects of melatonin

Melatonin has strong antioxidant effects, mainly through two ways: one is to directly combine with the free radical, organizing a series of chain reaction of free radical oxidation; the other way is to reduce the production of free radicals [13].

Melatonin and Mental diseases

Melatonin and anxiety

According to studies, the high doses of melatonin could increase exploratory behavior of anxiety rats or change the conflict behavior pattern [14-16]. According to research of the effect of melatonin on sleep, it induces relaxation and maintains quiet wakefulness [17-19]. Evidences have demonstrated that melatonin alleviated lipopolysaccharide-induced anxiety which suggests that melatonin may be used as adjuvant anti-anxiety treatment [20]. Another animal study showed that the combination of melatonin with agomelatine can enhance the effect of anti-anxiety drugs in the treatment of anxiety [21]. In clinic, Hansen and others have successfully applied melatonin to ease the anxiety in patients with insomnia [22]. In addition, Bustamante and Lira used melatonin to reduce anxiety scores of patients [23].

Melatonin and depression

Recently, researchers have found that depression is closely related to melatonin. Melatonin biosynthesis and secretion are mainly regulated by norepinephrine; the level of Melatonin reflects the norepinephrine activity in brain. And Melatonin secretion is an index of norepinephrine activity in depressed patients [24]. Several studies have supported this finding. Higher serum melatonin levels were found in patients suffering from major

depressive disorder which decreased after pharmacological treatment [25]. Others noted that in both men and women who were diagnosed as having major depressive disorder, nocturnal melatonin secretion increased significantly above the average seen in normal subjects [26].

Although there is an ongoing debate regarding the efficacy and safety of this novel antidepressant agent, nevertheless, its unique mechanism of action on major depressive disorder may represent the particular characteristics for patients. Further studies are needed to test [27]. The function of melatonin treatment of depression was also demonstrated by animal study. The study found that intrauterine melatonin deprivation might be linked to the depressive-like behavior in adult male offspring. Female Wistar rats were exposed to continuous light (500 lux) during the second half of the pregnancy (day 12 to 21), while control rats were kept under a 12:12 light-dark cycle. Male offspring have been behaviorally assessed for depression after postnatal day 60 using Forced Swim Test and Tail Suspension Test (TST) to examine the level of depression. The results showed that animals from the

Melatonin-deprived pregnancies have developed an abnormal response in the Tail Suspension Test [28]. In another study, melatonin has been shown to significantly reduce the risk of depression within three months after surgery. Women with breast cancer, who were found no depressive tendencies before surgery, after surgery, those women took oral melatonin 6mg a day would report less anxiety, pain and sleep disorders than those without melatonin treatment [29].

Currently, consistent evidences showed that melatonin secretion would decrease during the onset of depression, but rise again after remission. Therefore, melatonin level might be used as an effective indicator of the diagnosis for depression [26]. However, melatonin is not effective for the treatment of all forms of depression [30]. Above all, the relationship between melatonin and depression is complex. Study on the role of melatonin in the pathogenesis and in treatment of depression will still be one of the important subjects for future depression research.

Melatonin and schizophrenia

Using melatonin in treatment of schizophrenia can be traced back to 1920, when using the method of extraction of the pineal body in the treatment of a group of "dementia praecox" patients [31]. Since then there has been an increased interest in research on relationships between melatonin and psychiatry [32,33]. McIsaac attempted to link melatonin with schizophrenia in 1961 as he proposed that hallucinations and delusion are core positive symptoms of schizophrenia and the chemical structure of melatonin was very similar to the structure of the hallucinogenic harmala alkaloids, harmine and harmaline [34].

Another study found that melatonin could be used for treatment of sleep disorders in schizophrenic patients [35,36]. Melatonin can reduce waking up at night in paranoid schizophrenic patients who have sleep disorders [37] (Table 1). There were two areas of research clearly delimited in psychiatry with respect to melatonin. The first area is related to the use of melatonin as a biological marker of psychiatric

Anxiety	Depression	Schizophrenia
Melatonin could increase exploratory behavior of anxiety rats.	Melatonin secretion is an index of norepinephrine activity in depressed patients.	Melatonin could be used for treatment of sleep disorders in schizophrenic patients.
Melatonin can enhance the effect of anti-anxiety drugs.	Melatonin can reduce the risk of depression within three months after surgery.	Melatonin as a possible psychiatric therapeutic agent.
Melatonin to ease the anxiety in patients with insomnia.	Melatonin level might be used as an effective indicator of the diagnosis for depression.	Melatonin levels have also been used to differentiate clinical subtypes of schizophrenia.

Table 1: Melatonin and psychosis.

pathology. The second area is related to the clinical uses of melatonin as a possible psychiatric therapeutic agent [32,33].

Melatonin levels have also been used to differentiate clinical subtypes of schizophrenia. The paranoid subtype has been reported to have lower melatonin levels than healthy subjects, as well as similar levels to healthy controls [34] melatonin concentration is lower in paranoid subtype of schizophrenia patients [38].

Melatonin and autism

Supplemental melatonin has been used to treat sleep onset insomnia in children with autism spectrum disorders (ASD). Have researcher assessed endogenous and supplemental melatonin profiles in relation to sleep in nine children with autism spectrum disorders and found that melatonin parameters were comparable to those previously published for typically developing children. This finding supports that children with autism spectrum disorders and insomnia responsive to low dose Melatonin treatment have relatively normal profiles of endogenous and supplemental Melatonin [39].

Another study found that elevated whole-blood serotonin and decreased plasma melatonin (a circadian synchronizer hormone that derives from serotonin have been reported independently in patients with autism spectrum disorders [40]. The altered melatonin rhythm is also considered to underlie the impairment in sleep onset and maintenance in autism spectrum disorders. The study reports three cases of autistic disorder in whom has severe insomnia and behavior problems improved in two cases with 2mg melatonin and in the third case with 8 mg melatonin. This findings demonstrate that melatonin is effective not only for insomnia, but for behavioral problems as well, in patients with autistic disorder [41].

Furthermore, there are relatively few side effects such as headaches, vomiting, upset stomach, dizziness, diarrhea, daytime sleepiness which are promising in children with autism spectrum disorders treated with melatonin. Considering the relatively low rates of side effects and the consistent findings regarding sleep onset latency, melatonin treatment for children with autism spectrum disorders who struggled with sleep onset is supported by the literature [3].

Melatonin and attention deficit hyperactivity disorder

Children with attention deficit hyperactivity disorder had higher levels of daytime sleepiness [42]. Currently, there is no established consensus on how to treat sleep disorders in attention deficit hyperactivity disorder. Melatonin may be an option [43] (Table 2). Initial evidence suggested that the use of melatonin in children with attention deficit hyperactivity disorder and sleep onset insomnia, a delay in dim-light melatonin onset has been reported [44]. In addition, melatonin genetic pathways have been found to be abnormal in children with attention deficit hyperactivity disorder [45,46].

Some researchers have assessed the melatonin effects on sleep

Autism	Attention deficit hyperactivity disorder
Melatonin has been used to treat sleep onset insomnia in children with autism spectrum disorders.	Melatonin genetic pathways have been found to be abnormal in children with attention deficit hyperactivity disorder.
Melatonin is effective for behavioral problems of autistic disorder.	Melatonin along with methylphenidate can partially improve symptoms of sleep disturbance.
There are relatively few side effects with autism spectrum disorders who was treated with melatonin.	Melatonin in children with attention deficit hyperactivity disorder and sleep onset insomnia, a delay in dim-light melatonin onset.

Table 2: Melatonin and neuropathy.

patterns, symptoms of hyperactivity and attention deficiency in children with attention deficit hyperactivity disorder. Children with a combined form of attention deficit hyperactivity disorder were randomly divided in to 2 groups; one group took melatonin (3 or 6mg) combined with methylphenidate (Ritalin) (1mg/kg), and the other group took placebo combined with methylphenidate (1mg/kg). Attention deficit hyperactivity disorder rating scale and sleep patterns questionnaires were completed. The results showed that melatonin along with methylphenidate can partially improve symptoms of sleep disturbance [47].

Conclusion

Although melatonin has been found and widely used since as early as 50 years ago, relationship between melatonin and mental disorders are still quite unclear, and there is little research on melatonin treatment of mental diseases. With the results from biochemical measurements in melatonin treatment of mental disorders showed that melatonin treatment of mental disorders did not have serious negative consequences melatonin will likely be widely used in the treatment of mental disorders in clinical practice. At the same time, the measurements of the effects of melatonin treatments will become more standardized and effective. We believe that in the coming years, we might have breakthrough progress in the treatment of mental disorders field by using melatonin.

Supporting Information

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