Research report

Chronic melatonin treatment reverses disruption of prepulse inhibition in pinealectomized and pinealectomized-plus-ovariectomized rats

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HIGHLIGHTS

▶ Prepulse inhibition (PPI) was disrupted in pinealectomized (Px) and pinealectomized-plus-ovariectomized (Px+Ovx) rats.
▶ Chronic melatonin treatment reversed the impairments of PPI induced by Px or Px + Ovx.
▶ Novel object recognition and passive avoidance tests were not affected by chronic melatonin treatment.
▶ Melatonin increased the locomotor activity of Px and Px + Ovx rats, but reversed the locomotor hyperactivity caused by Ovx.
▶ Chronic melatonin treatment may be useful in the disorders characterized by PPI disruption.

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ABSTRACT

Although melatonin has been implicated in several neurophysiological systems, data on the relationship of melatonin with psychosis such as schizophrenia are limited and contradictory. Chronic effects of melatonin on sensorimotor gating deficits have also not been investigated yet. We investigated the neurobehavioral effects of chronic administration of melatonin in pinealectomized (Px) and ovariectomized (Ovx) rats. Px or Ovx or both operations were carried out together to the rats. The control group of rats was sham operated. A sham ovariectomy was carried out to Px rats, and vice versa. Fifth month later, melatonin (5 mg/kg) or vehicle was injected to rats for 28 days. Then, prepulse inhibition (PPI) of acoustic startle reflex, startle amplitude and startle reflex latency was measured. Locomotor activity, accelerated performance measurements, novel object recognition and passive avoidance tests were also evaluated. Px and PPI rats had impaired PPI compared to control rats. Melatonin reversed the impairments of PPI induced by Px or Px + Ovx. While melatonin treatment had no effect on locomotor activity of control rats, it significantly increased the locomotor activity of Px and Px + Ovx rats. Melatonin treatment (5 mg/kg/day, 28 days) reversed the locomotor hyperactivity caused by Ovx. Accelerated performance, passive avoidance, and object recognition responses of Px, Ovx or Px + Ovx rats were not different from the control group. Our results indicate that chronic melatonin deficiency by reason of Px results in impairment of PPI reflex and replacement of melatonin exerts beneficial effects on the impaired PPI reflex in Px and Ovx rats. Thus, melatonin may be useful in the treatment of some disorders characterized by sensorimotor gating deficits such as schizophrenia.

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1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized in the brain by the pineal gland from the amino acid tryptophan. The synthesis and release of melatonin are encouraged by darkness and suppressed by light, suggesting the involvement of melatonin in circadian rhythm and regulation of diverse body functions [1]. The levels of melatonin in the blood are highest prior to sleeping [2,3]. It acts through G-protein coupled membrane receptors, MT1 and MT2 [3]. Melatonin production and rhythmicity exhibit distinct fluctuations in psychiatric disorders [4,5]. Thus, melatonin treatment may have some beneficial effects in the treatment of mental disturbances [3] due to its anti-inflammatory [6] antinociceptive [7,8], anxiolytic [9], chemical detoxification properties [10,11] and its protective effects against oxidative stress [12–15]. Agomelatine, a naphthalene biosostere of melatonin, which is a potent MT1 and MT2 agonist and 5-HT2C receptor antagonist, has also been found to be effective in the treatment of depressive and anxiety symptoms associated with major depression [16].

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Schizophrenia is one of the most severe psychiatric disorders. It is an important neurodevelopmental disorder with approximately 1% of incidence in the population. Neurodevelopmental disorder causes a complex situation by affecting almost all brain functions [17]. Although the role of melatonin in schizophrenia has been subjected in a number of studies, some results are contradictory, and the therapeutic potential of melatonin in schizophrenia is not clear. The patients with schizophrenia do not exhibit a normal circadian pattern of melatonin secretion [18,19]. It has been suggested that pineal calcification may be responsible for the disturbance of melatonin, which appears to be a non-genetic factor in schizophrenia associated with perinatal injury [20–23]. Other studies showed that reduced nocturnal plasma melatonin levels were observed in drug-free patients or patients under medication, both with schizophrenia [24–27].

The incidence of schizophrenia is significantly higher in males than in females [28,29], male patients also have more severe schizophrenia symptoms compared to female patients [29]. Previous studies showed that ovariectomy did not have any effect on prepulse inhibition (PPI), an indicator of normal sensorimotor gating functioning, but estradiol treatment improved PPI in normal subjects and after disruption induced by apomorphine, a dopamine receptor agonist, or MK-801, an NMDA receptor antagonist [30]. Recently Cholerton et al. [31] reported that estrogen may modulate specific cognitive functions such as working memory, and verbal learning and memory. Taking together, estrogen seems to be a protective factor for schizophrenia. There is evidence that menopause is associated with a substantial decline in melatonin secretion and an increased rate of pineal calcification [32]. Thus the functioning of these two systems may be related in schizophrenia pathogenesis.

It has been suggested that lower levels of melatonin in schizophrenic patients may be related to the schizophrenia process itself [24]. Bersani et al. [18] confirmed the lack of a characteristic circadian pattern of melatonin secretion in patients with schizophrenia [18]. Thus, it has recently been hypothesized that schizophrenia may be a disorder involved in a possible dysfunction of the suprachiasmatic nucleus (SCN) [19]. Moreover a single nucleotide polymorphism (SNP) in the promoter of melatonin receptor 1A gene is significantly associated with schizophrenia and insomnia symptoms exhibited in schizophrenia patients [33]. For a recent review on the interaction between schizophrenia and melatonin please see Anderson and Maes [34].

In the light of the current literature, schizophrenia appears to be involved in reduced melatonin levels and/or abnormal melatonin secretion from the SCN, and it could be expected that melatonin treatment may have some beneficial effects on schizophrenia. However, clinical or experimental reports have shown that the effects of melatonin on the signs of schizophrenia are very limited and the studies mostly focused on the interaction between melatonin and antipsychotic drugs or immunomodulatory prospect of melatonin [3]. Hereby, the therapeutic potential of melatonin in schizophrenia is not clear.

PPI is the normal inhibition of a startle response to an intense, abrupt stimulus when it is preceded by a weak stimulus (“prepulse”). PPI represents an index of sensorimotor gating mechanisms essential to the protection of the integrity of sensory and cognitive information [35,36]. Deficits of PPI indicate the inability to filter out the unnecessary information, and they are linked to abnormalities of sensorimotor gating. Sensorimotor gating deficits have been described as an important area of information processing dysfunction in individuals with psychosis. Assessments of sensorimotor gating, as operationally measured by PPI, have become an important tool to better understand information processing impairments in schizophrenia and related disorders [37] such as abnormally low levels of PPI in patients with schizophrenia [38]. Moreover animal models of disrupted PPI by dopamine agonist, NMDA antagonist, 5-HT2 receptor agonist, or some developmental interventions, such as isolation rearing, have been shown to have good predictive validity for antipsychotic drug development and etiological research for psychotic disorders [36,37].

The main objective of the present study was to investigate a possible relationship between melatonin and sensorimotor–gating related disorders like schizophrenia. This goal was achieved by using an extensively used experimental animal model, and investigating the effects of chronic melatonin administration on PPI in pinealectomized (Px) and ovariectomized (Ovx) rats. Other behavioral tests such as locomotor activity, accelerod performance, novel object recognition and passive avoidance were also performed on the rats under melatonin treatment.

## 2. Material and methods

### 2.1. Animals, laboratory and drugs

All procedures in the present study were performed in accordance with the Guide of the Care and Use of Laboratory Animals adopted by National Institutes of Health (USA) and the Declaration of Helsinki. Local ethical committee approval was also obtained.

Adult female Wistar rats, aged 12–14 weeks old at the beginning of experiments, were used. They were placed in a quiet, temperature and humidity controlled room (22 ± 2 °C and 60 ± 5%, respectively) in which a 12:12 h light–dark cycle was maintained (lights on from 07:00 to 19:00 h). Food and water were available ad libitum. All the experiments were performed during the light phase of the light–dark cycle. All the rats were handled for 2 days before the commencement of the experiments. Melatonin was purchased from Sigma Chemical (St. Louis, MO, USA), dissolved in ethanol (96%) and further diluted in saline (0.09%NaCl, w/v) to give a final concentration of 2.5%.

### 2.2. Experimental procedure

Female rats were randomly assigned into 8 experimental groups (n = 8–9) as shown in Table 1. The whole experimental procedure was performed as summarized in the Table 2. On the first day the rats were Px or Ovx or both operations were carried out in the same session. The control group of rats was sham operated. Moreover, a sham ovariectomy was performed on Px rats, and vice versa. All the rats were housed for the next five months in their home cages. At the end of the fifth month half of the rats in each group were assigned to melatonin treatment group and the other half was assigned as the control group. Melatonin (5 mg/kg) or its vehicle was intraperitoneally (ip) injected between 16:30 h and 17:00 h. Injections were repeated daily for 28 days. On the 27th day locomotor activity was recorded for 30 min, and then rats were returned to their home cages. One hour later they were exposed to the novel object recognition test with two identical objects in the same environment of locomotor activity cages. One hour later the rats were exposed to the passive avoidance task. On the 28th day, first, accelerated performance of the rats was assessed, then novel object test and passive avoidance tests were performed. Finally, PPI of the acoustic startle reflex, startle amplitude and startle reflex latency was measured. These tests were performed successively with 30 min breaks after each test.

### 2.3. Pinealectomy and ovariectomy

The animals were ip anesthetized with a combination of xylazine/ketamine, before the operation. Both pinealectomy and ovariectomy were performed in the same session. Pinealectomy was performed as described by Hoffman and Reiter [39]. Shortly, the skin (at the top of the head) was prepared for the surgery by povidone iodine solution and cutted to expose the skull. The animal was positioned on

<table>
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<tr>
<th>Group No.</th>
<th>Surgery</th>
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n, number of animals per group; + surgery was performed.
blocks of five trials were administrated. Following trials were applied in random order within one block:

(i) Pulse alone stimulus
(ii) Prepulse (4 dB [A] SPL above background noise) + pulse stimulus
(iii) Prepulse (8 dB [A] SPL above background noise) + pulse stimulus
(iv) Prepulse (16 dB [A] SPL above background noise) + pulse stimulus
(v) No stimulus (only background noise was applied).

The pulse stimulus was a broadband noise stimulus at 110 dB [A] SPL for 40 ms, whereas all three prepulse stimuli were tone stimuli at 3 kHz frequency for 20 ms. The prepulse stimulus levels were selected at intensities which did not elicit significant startle reflex when applied alone. The prepulse stimulus was applied 120 ms prior to pulse stimulus (onset to onset). The inter trial interval varied randomly in a range of 10–30 s. This protocol approximately lasted for 20 min. PPI was defined as a decrease in the amplitude of the startle reflex in the presence of the prepulse stimulus and calculated for each of the three different prepulse intensities by using the following formula:
PPI[(%)] = 100 – [(average startle reflex in presence of the prepulse × 100)/average startle reflex without a prepulse]

2.5. Passive avoidance test

A shuttle-box apparatus (Coulbourn Instruments Inc., PA, USA) constructed from black Plexiglas was used. The cage (50 cm × 23 cm × 24 cm) consists of two connecting compartments of equal size that are separated by a sliding door. One compartment was brightly illuminated and the other compartment was totally dark. An electrically grid floor (3 mm stainless-steel rods set 10 mm apart) was used for delivery of scrambled constant current. The protocol was adapted from the previous studies [42]. Before the beginning of the experiments two pre-training trials were performed on two consecutive days. During retraining sessions the sliding door was open. Each rat was placed in the illuminated compartment and allowed for free exploration for 180 s. On the 3rd day a single training trial was applied. The rats were placed in the illuminated compartment of the apparatus as in the previous sessions and the latency to enter into the dark compartment was recorded. The door was then closed and a foot shock (0.3 mA, 3 s) was delivered to the rat, which was remained in the dark compartment for 30 s, and returned to the home cage. After 24 h from the acquisition trial, rats were placed in the illuminated compartment and allowed to step into the dark chamber. Step-through latency was recorded with a cut-off time of 5 min.

2.6. Novel object recognition test

This task was conducted in the same arenas used for locomotor activity measurements (please see below). The CCD camera connected to a digital video recording device and the whole session was recorded. The protocol was adapted from the previous studies [43]. Briefly, the locomotor activity measurement was performed for 24 h and used as the habituation trial. One hour after the completion of the habituation, two identical objects were placed in two corners of the box (approximately 5 cm from the walls) and the rats were allowed to explore the objects for 10 min. All the rats were confirmed to explore each object for at least 10 s. The testing trial was performed 24 h later. For the testing trial, one of the objects previously used was replaced with a novel object. The testing trial lasted 10 min. The duration of exploration of each object was scored by trained observers blind to the experimental treatments. Exploration was accepted as valid when the nose of the rat was directed to the object at a distance of no more than 2.5 cm and/or touching the object with the nose. Sitting on the object was not considered as exploratory behavior. Two sets of objects were used in a balanced manner. Objects were made of hard plastics differing from their shape, color and painting patterns. They were mounted on a heavy, flat stone to prevent its displacement by rats. The difference between the exploration times for novel and familiar objects during the testing trial was evaluated as novel object recognition score.

2.7. Locomotor activity and accelerated performance measurements

Locomotor activity was measured as the distance traveled (cm) in Plexiglas arena (40 cm × 40 cm × 40 cm, white walls, black floor) during 30 min. Four cages were monitored at the same time with a CCD camera (Safer, SF-2222) mounted 260 cm above from the floor and vertically aimed at the crossing of four cages. A video tracking software (Ethovision v3.1.16, Noldus Information Technology, Wagenin- gen, NL) was used to analyze the visual data. Rats were detected due to their contrast according to the black background. The parameter of distance traveled (cm) was computed with down-sampling filters (final frame-rate was 6 fps and minimum distance traveled was 1 cm) to decrease the image noise. Accelerated performance was assessed using a rotarod apparatus capable of constantly accelerating until reaching a predefined velocity in a predefined time period (Rota-mex V-EE/85, Columbus, OH). Prior to the experiment day, rats were trained to walk on the rotating rod at a constant velocity of 10–20 rpm. On the test day the system was set to increase its velocity from 0 to 60 rpm in 3 min. The time of the

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Please see text for detailed description of the procedures.

the dissection table; an incision was made in the skin and the subcutaneous tissue, bringing the lambda into view. The skullcap was opened with the aid of a micromotor, bringing the cerebral hemispheres and the superior sagittal sinus into view. The pineal gland, located under the venous sinus, was removed in one piece using forceps. Next, the bone fragment was returned to its place and the surgical layers were sutured. Then the animal was placed on its dorsal surface. Ovariectomy was performed through a midline ventral skin incision. Incisions of the muscles were made bilaterally. After the peritoneal cavity was accessed, the ovary was found. Blood vessels were ligated, and the connection between the Fallopian tube and the uterine horn were cut. The ovaries were moved out and the surgical layers were sutured. After surgery, the animals received a single dose of prophylactic antibiotic. The procedure was completed within 25 min. The process of pinealectomy was confirmed by the histological evaluation of the gland for each animal. Rats in the sham-operated group underwent similar surgical procedures without the removal of pineal gland and/or ovaries.

2.4. Prepulse inhibition of acoustic startle reflex test

PPI test was performed using an Animal Acoustic Startle Response System (AASR, Habitest Model E10-21, Coulbourn, Pennsylvania, USA) as previously described [40, 41]. This system consists of four sound proof boxes equipped with strain gage load cell platforms, and speakers with a wide sound spectrum, mounted 12 cm above the animal holders. The system was controlled by a software (Coulbourn Acoustic Startle v4.530-00) run on an IBM-compatible computer. The background noise levels were between 63 and 66 dB [A] sound pressure level (SPL) during the study. Prepulse stimulus levels, which are determined according to the background noise, were adjusted by monthly calibrations. The software recorded startle response of rats for 200 ms with a 1 ms resolution after the administration of pulse stimuli with or without a prepulse stimulus, and expressed the peak startle response as grams. Forty-eight hours before the test sessions, rats were habituated to the animal holders of the startle test system for 10 min. On the test day, rats were placed in the cages, and the test protocol was applied. These sessions were preceded by a 5-min acclimatization period, in which only the background noise was present. Then, 8
animal to fall off from the rotating and accelerating rods was measured in seconds by the built-in timer of the apparatus and evaluated as accelerated performance.

2.8. Statistics

For detecting even minor effects, the required sample sizes used in this experiment were identified using the statistical power analysis. The sample sizes of eight rats in each group necessary for a power of 0.80 were estimated using the Number Cruncher Statistical System (NCSS) software. Statistical analysis was carried out using SPSS software program, version 18.0, for Windows (SPSS Inc., Chicago, IL, USA).

The effects of Px, Ovx or both operations on locomotor activity, accelerated performance, passive avoidance and novel object recognition scores, startle amplitude and latency times were evaluated independent one-way analysis of variance (ANOVA) test followed by least significant difference (LSD) test for post hoc analysis.

PPI data were first analyzed by using a mixed design two-way analysis of variance (ANOVA) test (groups × prepulse intensity). Since there was no significant interaction effect further analyses were separately performed for each prepulse intensity level by using one-way ANOVA test followed by LSD test for post hoc analysis. Whenever a significant effect of surgical operations was found, a Student’s t-test was used to analyze the effect of melatonin treatment. The levels of statistical significance were set at p < 0.05.

3. Results

A two-way ANOVA test (group × prepulse intensity) indicated that surgical treatments had a significant effect on PPI [group effect: F(3,25) = 6.066; p = 0.003], which was independent from prepulse intensity [interaction: F(6,50) = 0.719; p > 0.05]. Further analyses revealed that Px rats had impaired PPI results compared to sham operated rats at all three prepulse intensity levels (Fig. 1A–C). Px + Ovx rats had also lower PPI levels at background +8 dB and +16 dB prepulse intensity levels (Fig. 1B and C). Moreover, melatonin treatment reversed the impairments of PPI induced by Px or Px + Ovx at background +16 dB prepulse intensity levels (Fig. 1C). There was no significant difference between the groups for their startle reflex amplitude [F(3,25) = 1.897; p > 0.05, Fig. 2A] and startle reflex latency [F(3,25) = 0.934; p > 0.05, Fig. 2B].

The learning degrees were similar among all the groups as indicated by non-significant differences, both in passive avoidance test [F(3,31) = 1.216; p > 0.05, Fig. 3A], and novel object recognition test [F(3,26) = 0.337; p > 0.05, Fig. 3B].

The distance explored by the rats during 30 min, indicating locomotor activity, was significantly different among the groups [F(2,27) = 3.892; p = 0.020, Fig. 4]. Post hoc analysis revealed that Ovx rats had a higher locomotor activity as compared to sham control, Px and Px + Ovx rats (p < 0.05, LSD test). Melatonin treatment (5 mg/kg/day, 28 days) reversed the locomotor hyperactivity caused by Ovx (p < 0.05). Melatonin treatment had no effect on control rats (p > 0.05), but significantly increased the locomotor activity of Px and Px + Ovx rats (p < 0.05).

Accelerated performance of Px, Ovx or Px + Ovx rats were not different from the sham operated group [F(3,27) = 1.299; p > 0.05, Fig. 5].

4. Discussion

The results of the present study clearly showed that both “pinealectomy” and “pinealectomy and ovarioectomy” caused some significant impairment on PPI test but not on passive avoidance and novel object exploration in rats. On the other hand ovarioectomy alone had no effect on PPI test. Impairment of PPI was reversed by replacement of chronic melatonin treatment. This has been also the first report indicating the beneficial effect of chronic melatonin administration on disrupted PPI. The reversed effect of melatonin on disrupted PPI could not be related to other non-specific effects such as sedation or muscle relaxation involved in its psychotropic properties since it did not cause any significant effect on accelerated performance or locomotor activity of the Px rats in the present study. Melatonin did not also cause any significant change on startle reflex amplitude and latency. Thus, the reversed effects of melatonin on impaired PPI were specific action. Because PPI of the acoustic startle reflex has been used to investigate human mental disorders with an attentional component, such as schizophrenia [37] and PPI disruption by several agents is a well known experimental schizophrenia model in animals, and a measurable parameter in patients with schizophrenia [35–37,44], our findings imply that there may be a relationship between melatonin deficiency and pathogenesis of schizophrenia or schizophrenia-like deficits. Our results also indicate that chronic administration
the administration of melatonin at low doses (i.e. 3 mg/kg) produced some unfavorable effects on spatial learning ability in rats [45]. While treatment with melatonin receptor antagonists during the nighttime dramatically improves memory, Px also improves nighttime memory formation and melatonin suppresses nighttime memory formation in zebrafish [46]. On the other hand, several reports indicated that melatonin improved ethanol, thinner and diabetes-induced learning and memory deficits in rats [47–49]. A recent study indicated that both melatonin and agomelatin, an antidepressant drug with melatonergic agonist and 5-HT2C antagonist properties, improved novel object recognition in rats either when administered in the morning and in the evening [50]. In the present study, we investigated the effects of pinealectomy and ovariectomy on learning and memory capabilities of rats in passive avoidance and object recognition tasks. Although we observed some reduces in passive avoidances of Ovx and Px + Ovx rats, and in the novel object exploration of Px and Ovx rats, these reductions did not reach a statistically significant level. However our study cannot rule out the possibilities such as, our test parameters might be not suitable for revealing the possible learning and memory deficits induced by Px or Ovx and some other compensatory mechanisms masked these deficits. Further studies are necessary to figure out the effects of Ovx and/or Px in learning and memory tests.

In the present study, melatonin treatment for 28 days also reversed locomotor hyperactivity induced by ovariectomy in rats.
However, melatonin did not produce any significant effect on locomotor activity of both Px and Px+Ovx rats. It is difficult to explain why locomotor activity increased significantly in only Ovx rats and melatonin reversed this effect. It may be related to an uncertain effect of Ovx on locomotor systems in rats. Further studies are required in order to clarify this statement.

The evidence that links melatonin and schizophrenia in human models is fairly weak and contradictory. Although PPI and sensorimotor gating have been used to investigate human mental disorders such as schizophrenia as an available and satisfactory model [37], the concerning reports that investigate the role of melatonin in sensorimotor gating deficits by this technique are very limited. Previously, Weil et al. [51] reported that melatonin MT1 receptor knockout mice displayed depression-like behaviors and deficits in sensorimotor gating that can be measured by PPI test. Although these authors did not report any comments involved in psychosis in their studies, the significant impairment of PPI in this mouse model provided further evidence on the role of melatonin in the pathogenesis and etiology of sensorimotor gating deficits such as schizophrenia. Our findings related to the effects of chronic melatonin treatment on impaired PPI in both Px and Px+Ovx rats are also supported by the results of Weil’s study. In a recent study, Ucar et al. [52] also investigated the effects of acutely administered melatonin on sensory gating via P50 suppression in human. In contrast to their expectations, melatonin did not increase P50 suppression. In this study, melatonin reduced P50 gating in subjects with high levels of suppression, while not affecting P50 gating in subjects with low levels of suppression. Because P50 suppression is a tool to detect sensorimotor gating deficits in schizophrenia [53], the results from Ucar et al.’s study did not support the hypothesis that melatonin administration may be useful in the treatment of schizophrenia. However, Ucar et al. [52] administered melatonin to subjects acutely and in a single dose. Chronic administration of melatonin like in the current study could be required to improve the sensorimotor gating deficits.

The beneficial effects of chronic melatonin administration on impaired PPI or sensorimotor deficits may be explained by dopaminergic and serotonergic mechanisms. Experimental studies performed on animals indicated that fetal dopaminergic system and dopaminergic D1 receptors may be associated with the process entraining the SCN [54,55]. There is also evidence suggesting that melatonin modulates striatal and limbic activity [56]. Melatonin-binding sites have been verified in some brain areas such as striatum and limbic system that have rich dopamine contents [56]. It has also been hypothesized that melatonin inhibits limbic dopaminergic activity, thus mesolimbic and mesocortical dopamine tone may increase when the melatonin secretion decreases [20,57]. These data imply that melatonin may be essential in adjustment of the dopaminergic activity in some brain areas. Thus, as a result of the decreased melatonin secretion during puberty, mesolimbic dopaminergic tone may be excessively increased, and its effect could be responsible in part for triggering the emergence of schizophrenia signs during adolescence [20]. Furthermore, in rodents, while dopaminergic agonists such as apomorphine cause impairment of PPI, dopaminergic antagonists such as haloperidole reverse this effect [40]. Therefore, beneficial effects of melatonin in the present study may be related to its regulatory action on dopaminergic tone.

Melatonin also interacts with serotonergic 5-HT2 receptors and at pharmacological doses; it acts as a 5HT2 receptor antagonist. Moreover, it has been suggested that chronic administration of melatonin–enhancing agents in conjunction with atypical antipsychotics could augment their effects on negative symptoms of schizophrenia [58]. Many atypical antipsychotic agents such as clozapine, olanzapine, risperidone and quetiapine also block 5-HT2 receptors and there is a link between their antipsychotic activity and 5-HT2 blocking activity [17,59]. Clozapine and quetiapine also reversed impaired PPI in rats [40]. It has been demonstrated that major advantage of atypical antipsychotics over the classical drugs is that they block and down-regulate 5-HT2 receptors and, therefore, may act in synchrony with the endogenous physiological mechanisms which reduce the activity of the 5-HT2 receptor [58]. Our findings regarding the effects of chronic melatonin treatment on PPI in both Px and Px+Ovx rats may be also related to its 5-HT2 receptor antagonistic property. However, we could not find any report showing a direct blocking effect or binding of melatonin on 5-HT2 receptors. On the other hand, in contrast to the above suggestion, there are several previous reports indicating that melatonin may antagonize the effects of 5-HT2 receptor blockers and it may act as a 5-HT2 receptor agonist [60–62]. As associated with the results of these reports, it has been suggested that melatonin may attenuate the effects of atypical antipsychotics and that pharmacological inhibition of melatonin secretion may enhance their therapeutic efficacy in schizophrenia [63]. Overall the data on interactions between melatonin and 5-HT2 receptors is confusing and not coherent. Thus, interaction with 5-HT2 receptors does not seem to be a good way to explain the beneficial effects of melatonin on disrupted PPI. Although presently dopamine mediating effect of melatonin is more reasonable, further studies are required to clarify the mechanism of the beneficial effect on PPI.

In conclusion, our findings demonstrate that chronic melatonin deficiency by reason of Px, results in impairment of PPI of startle reflex, and chronic melatonin administration exerts beneficial effects on the impaired PPI in both Px and Px+Ovx rats. Because PPI disruption of the acoustic startle response is known as an indicator for sensorimotor gating deficits in experimental animals and humans, melatonin may be useful in the treatment of some disorders characterized by sensorimotor gating deficits such as schizophrenia.

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The authors declare no conflicts of interests.

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