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HEALTH SCIENCES

Schizophrenia-like behavior is not altered by melatonin supplementation in rodents

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Abstract: An emerging area in schizophrenia research focuses on the impact of immunomodulatory drugs such as melatonin, which have played important roles in many biological systems and functions, and appears to be promising. The objective was to evaluate the effect of melatonin on behavioral parameters in an animal model of schizophrenia. For this, Wistar rats were divided and used in two different protocols. In the prevention protocol, the animals received 1 or 10mg/kg of melatonin or water for 14 days, and between the 8th and 14th day they received ketamine or saline. In the reversal protocol, the opposite occurred. On the 14th day, the animals underwent behavioral tests: locomotor activity and prepulse inhibition task. In both protocols, the results revealed that ketamine had effects on locomotor activity and prepulse inhibition, confirming the validity of ketamine construction as a good animal model of schizophrenia. However, at least at the doses used, melatonin was not able to reverse/prevent ketamine damage. More studies are necessary to evaluate the role of melatonin as an adjuvant treatment in psychiatric disorders.

Key words: Schizophrenia, melatonin, behavior, animal model, ketamine.

INTRODUCTION

Schizophrenia (SZ) is a chronic psychiatric disorder that compromises many functions such as memory and thought, perception and emotions, as well as social conduct and others (Bowie & Harvey 2006, Javitt 2010). Because of their complexity and diversity, the symptoms of schizophrenia are traditionally grouped in positive, negative and cognitive (Lesch 2001). Positive symptoms can be characterized as delusions and hallucinations; Negative symptoms include affective dullness, social isolation, anhedonia, and thought scarcity and cognitive impairment such as impaired working memory, disorganization, and inattention (Bowie & Harvey 2006, Javitt 2010). Consequently, the patients have their productivity, life quality, and social functions affected.

Despite many factors and mechanisms have been proposed to understand the pathogenesis of schizophrenia, its pathology remains unknown (Van & Kapur 2009, Insel 2010). The majority of studies point to many possible etiological hypotheses of schizophrenia. The first, and most accepted, hypothesis is related to the unbalance in the neurotransmitter system, specially the dopaminergic (Kapur & Remington 2001), glutamatergic (Konradi & Heckers 2003, Kantrowitz & Javitt 2010) and GABAergic pathways (Caruncho et al. 2004, Frankle et al. 2015) and the alterations in its interactions (Carlsson et al. 2001, Menschikov et al. 2016). In addition, recent evidence on the pathogenesis of schizophrenia

includes genetic and environmental factors (McGuffin 2004), compromising of the neural development and connectivity (White & Hilgetag 2011), neuroinflammation (Tomasik et al. 2016, Trépanier et al. 2016), as well as abnormal bioenergetics (Ben-Shachar et al. 2004, Yuksel et al. 2015).

Given that drugs currently used in the treatment of schizophrenia remain far from ideal, prevention, as well as the development of alternative therapies or adjuvants, remain necessary. An emerging area in schizophrenia research focuses on the impact of immunomodulatory drugs, such as melatonin (MLT) (da Silva et al. 2017). MLT plays numerous roles that include control on the circadian rhythm acting as a neuromodulator, hormone, cytokine, and biological response mediator. It also affects the brain, immune, gastrointestinal, cardiovascular, renal, bone, and endocrine functions and acts as a natural oncostatin and anti-aging molecule (Morera-Fumero & Abreu-Gonzalez 2013). Many clinical studies have related the abnormal MLT function in the pathophysiology of schizophrenia (Bersani et al. 2003, Morera-Fumero et al. 2010, Park et al. 2011, Anderson & Maes 2012). In this sense, the application of MLT as an adjuvant treatment becomes an alternative.

Although the studies have evaluated the efficiency of MLT as a coadjutant in the schizophrenia treatment in humans (Suresh Kumar et al. 2007, Romo-Nava et al. 2014), there is still a lack of pre-clinical information about its potential as a lone agent. Thus, this study aimed to evaluate the effect of MLT administration on locomotor activity and cognition behaviors in an animal model of ketamine-induced schizophrenia. This drug is an N-methyl D-aspartate (NMDA) antagonist, repeated administration of the subanaesthetic dose of ketamine has been associated with behavioral changes like hyperlocomotion, prepulse inhibition deficits and memory loss, following alterations in glutamate or dopamine levels (Chatterjee et al. 2011).

MATERIALS AND METHODS

Ethical issues

All experiments were performed at Universidade do Extremo Sul Catarinense (UNESC), in Translational Psychiatry Lab and Inborn Errors of Metabolism Lab as a collaborator. The animals were obtained from the vivarium of UNESC and kept in cages on a 12 h light/dark cycle, with food and water available *ad libitum*. The temperature was maintained at 22±1°C. The project was approved by the Ethics Committee for Animal Experimentation of the UNESC, with the protocol numbers 045/2015-2. All the experiments were following the ARRIVE guidelines and the EU Directive 2010/63/EU for animal experiments.

Drugs

Ketamine

Ketamine was administrated (i.p.) in a dose at 25mg/kg prepared in saline 1ml/1000g of volume. The dose was used to mimic psychotic symptoms such as hyperlocomotion, stereotypic movements and cognitive deficits (Sams-Dodd 1998).

Melatonin

MLT (Sigma Chemical Co., St. Louis, Mo., USA) was administrated at 1mg/kg (MLT1) or 10mg/kg (MLT10) dissolved in 0.5% of ethanol and water, in a final volume 1ml per kilogram of weight (Subramanian et al. 2007). For the controlgroup, the same volume was administrated using ethanol and water.

Animals

One hundred and twenty (120) male Wistar (*Rattus novergicus*) rats (45 days old) weighing about 170 to 200g were used. They were randomly divided into 6 groups: water+saline, MLT1+saline, MLT10+saline, water+ketamine, MLT1+ketamine, MLT10+ketamine, according to protocols below (Figure 1).

To verify the preventive or therapeutic effect of MLT, it was used two protocols, called prevention and reversion adapted according to De Oliveira et al. (2011). In prevention protocol, animals received MLT at 1mg/kg or 10mg/kg doses or water by gavage, once a day for 14 days; between 8 and 14 days they received ketamine (25mg/kg) or saline (i.p).

In reversion protocol, animals received ketamine (25mg/kg) or saline (i.p), once a day during 14 days; between 8 and 14 days, they received MLT at 1mg/kg or 10mg/kg doses or water by gavage (Castro et al. 2011, Ozyurt et al. 2014).

After the last administration of saline or ketamine animals were subjected to behavioral tests.

Behavioral evaluation

Locomotor activity and stereotypy movements

The open-field test was performed in a box with the dimensions of 50 x 25 x 50 cm. The animals were individually placed into the box to allow for exploratory activity during the 15-minute test period, and their locomotion activity was automatically measured using a locomotion activity box fitted with laser sensors coupled to a computer (*Insight*®, Ribeirão Preto, São Paulo, Brazil). This equipment monitors locomotion activity by recording the distance covered (cm) by the animal, plus, the total evaluation time was divided (15 minutes) into 5-minute blocks

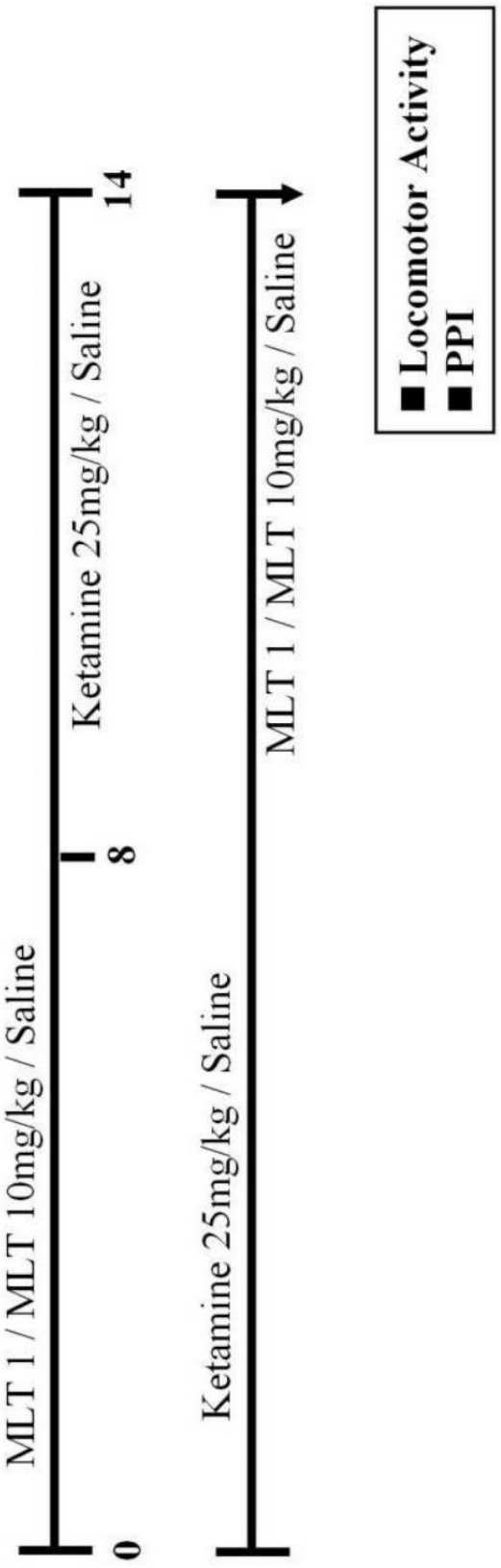

Figure 1. Experimental design.

(De Oliveira et al. 2011). The device is capable of registering several parameters of locomotion activity, and the following ones were registered in the present work: covered distance, stereotyped movements, and time spent in the center of the field. The covered distance and stereotypy are standard measures of the hallucinogenic effects of the drugs, as well as schizophrenic symptoms (De Oliveira et al. 2011). Besides, the time spent in the center of the field is a very well-known parameter of anxiety and defensive behavior, since rodents tend to avoid the center of the field, fearing the presence of a predator (Lapiz et al. 2000). However, a certain amount of time spent in the central square is normal, simply signaling the exploratory activity of the rodent (Avila-Martin et al. 2015).

Stereotypy was defined as rapid, repetitive head and forelimb movements. This parameter was analyzed at the same time and place as hyperlocomotion activity. Stereotypy is considered, by the software, as an unstable movement any time when repetitive movements are recorded in sequel readings, without alteration in animal's mass center. The possible units of measurement to be considered are mm (millimeters), cm (centimeters) and in (inches).

Prepulse inhibition (PPI)

The PPI test may be performed on humans, as well as on animals, and it is a parameter of sensorial gating (Zugno et al. 2014). It is impaired in psychiatric conditions such as EOS and schizotypal personality disorder and has shown prognostic value in children with a high risk of psychosis (Ziermans et al. 2012). The PPI test is quantified based on the protocol described by Shilling et al. (2006). Inside the PPI box (Insight ® - EP 175), which is covered by sponge for acoustic isolation, there is a cage to house the animal under test, which is located over a weighing-machine. Firstly, the animals are subjected to a habituation period of 5 minutes in this cage. The amplitude of the startle is then measured by changes in the weight detected by the weighing-machine when the rat startles. The amplitude of the weight changes (startle) is measured after the presentation of an acoustic stimulus. A 65dB background noise is constantly applied for the duration of the testing. During the testing session, the animals were introduced to 3 different types of stimulation for a total of 10 times, with these events being randomly distributed at intervals of 20 seconds: 1) 120 dB pulse for 40 ms (capable of producing a startle response); 2) pre-pulse 65, 70, or 75dB for 20 ms, 80 ms before the pulse; 3) absence of stimulus. At the beginning of each session, 10 pulses were presented to allow for the habituation of animals (this series was not considered in the calculations). The mean startle amplitude following the pulse sessions (P) as well as the mean amplitude of startle response after prepulse sessions - pulse pressure (PP) was then calculated for each animal. The percentage of inhibition promoted by the pre-pulse of the pulse induced startle response was calculated according to the following equation: prepulse inhibition (%) = 100 - [(PP/E) x 100]. Thus, 0% corresponds to no difference between the amplitude of startle after the pulse sessions and the absence of inhibition of the startle response. A negative result means that the animal's reaction increased despite the prepulse.

Statistical analysis

The results were obtained by two way ANOVA. When F values were significant, comparisons were made by the post hoc *Tukey* test. Data were expressed as mean (±) and standard error of the mean (mean ±S.E.M). The statistical significance was set to $p < 0.05$. Data were calculated by Graph

Pad Prism 6.0 software (Graph Pad Software, La Jolla, California, USA).

RESULTS

Prevention protocol

Locomotor activity

Results show the distance traveled, stereotypic movements, and length of the permanence of the animals in the center and at the periphery of the field for 15 minutes. Animals were evaluated 30 minutes and 24 hours after the last ketamine and MLT injections respectively.

Figure 2 illustrates results relating to the distance traveled and the number of stereotypic movements exhibited by the animals in the prevention protocol. It was shown that groups which received MLT1 + ketamine, MLT10 + ketamine, as well as in control group + ketamine [F (5,57) = 9.982; p<0.05] had a hyperlocomotion induction when compared to the control group. Hence, it was observed that ketamine mimicked positive symptoms in the animal model of schizophrenia. From these results, it is suggested that different MLT doses administered chronically were not capable of preventing hyperlocomotion effects induced by ketamine. Regarding the evaluation of stereotyped movements in animals treated with MLT and ketamine, respectively, the results showed that the groups that received MLT10 + saline, control group + ketamine, MLT1 + ketamine and MLT10 + ketamine, had an increased stereotypic movement when compared to the control group [F (5,57) = 11.23; p<0.05].

Length of permanence in the center and at the periphery (prevention)

Figure 3 depicts the results for the length of the permanence of the animals in the center and at the periphery after their respective treatments. The groups MLT1 + saline, MLT10 + saline and MLT1 + ketamine revealed a significant increase in the length of the permanence of the animals in the center [F (5,57) = 3.889; p<0.05].

Regarding the length of permanence at the periphery, the results showed that the groups MLT1 + saline, MLT10 + saline, and MLT1 + ketamine

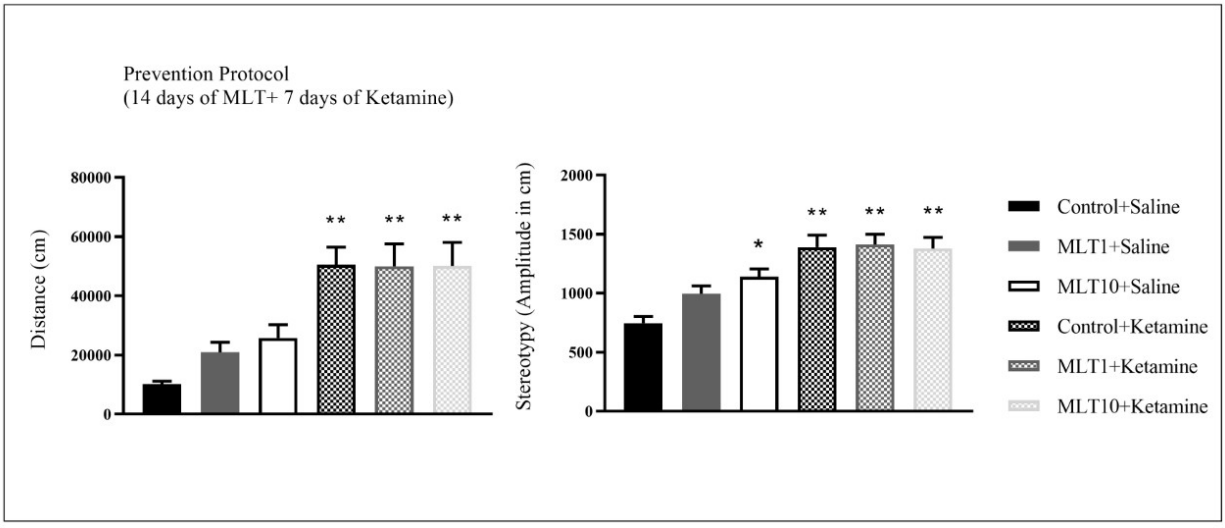

Figure 2. Effect of MLT administration (1mg/kg and 10mg/kg) and/or treatment with ketamine (25mg/kg) on locomotor activity (distance traveled and stereotypy) in the prevention protocol. The values are expressed as mean±SEM of 10-12 animals per group. **different from the control (*p<0.05).

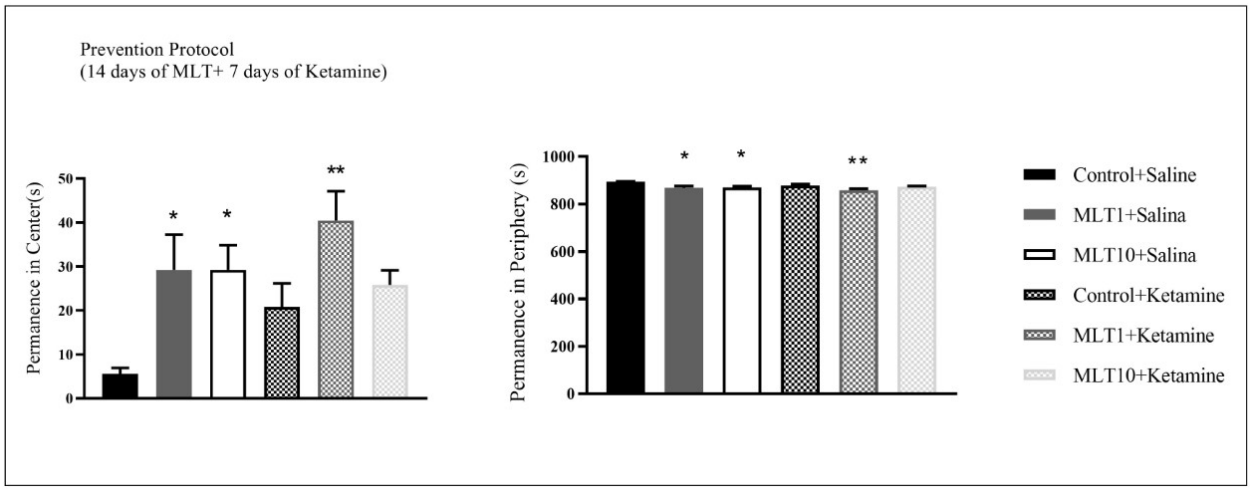

Figure 3. Effect of MLT administration (1mg/kg and 10mg/kg) and/or treatment with ketamine (25mg/kg) on locomotor activity (length of permanence in the center and at the periphery) in the prevention protocol. The values are expressed as mean±SEM of 10-12 animals per group. **different from the control (*p<0.05).

decrease the length of the permanence of these animals at the periphery [F (5,59) = 3.702; p<0.05].

Prepulse inhibition test

The results showed inhibition of prepulse interaction by the animals for 15 minutes. The animals were evaluated 30 minutes and 48 hours after the last injection of ketamine and MLT respectively.

Figure 4 illustrates the results concerning the sensory and motor effects of the animals submitted to the schizophrenia model and treated with MLT, which were obtained through the prepulse inhibition of the startle reflex (PPI). Concerning the prepulse inhibition in the intensity of (65dB) and (75dB), it was revealed that control + ketamine and MLT10 + ketamine, presented a significant alteration when compared to the control group. For the prepulse inhibition in the intensity of (70dB), control + ketamine, MLT1 + ketamine, and MLT10 + ketamine showed a decrease in PPI when compared to the control group. This finding suggests that ketamine-induced a significant deficit of PPI when compared to the control group, but MLT was not capable of preventing those effects.

Reversion protocol

Locomotor activity, distance traveled and stereotypic movements

Figure 5 represents the results of the locomotor activity (distance traveled, stereotypic movements) presented by the animals submitted to the reversion protocol. It was observed that the animals, which received ketamine + MLT1, ketamine + MLT10, as well as the ones in ketamine + control group, showed a statistically significant difference when compared to the control group, indicating that ketamine mimicked positive symptoms in the schizophrenia animal model [F (5,60)=19.578; p<0.05]. The results suggest that different doses of MLT administered chronically were not capable of preventing and/or reversing the effects of ketamine. Regarding the evaluation of stereotyped movements in animals treated with ketamine + MLT1, ketamine + MLT10, as well as the ones in ketamine + control group had an

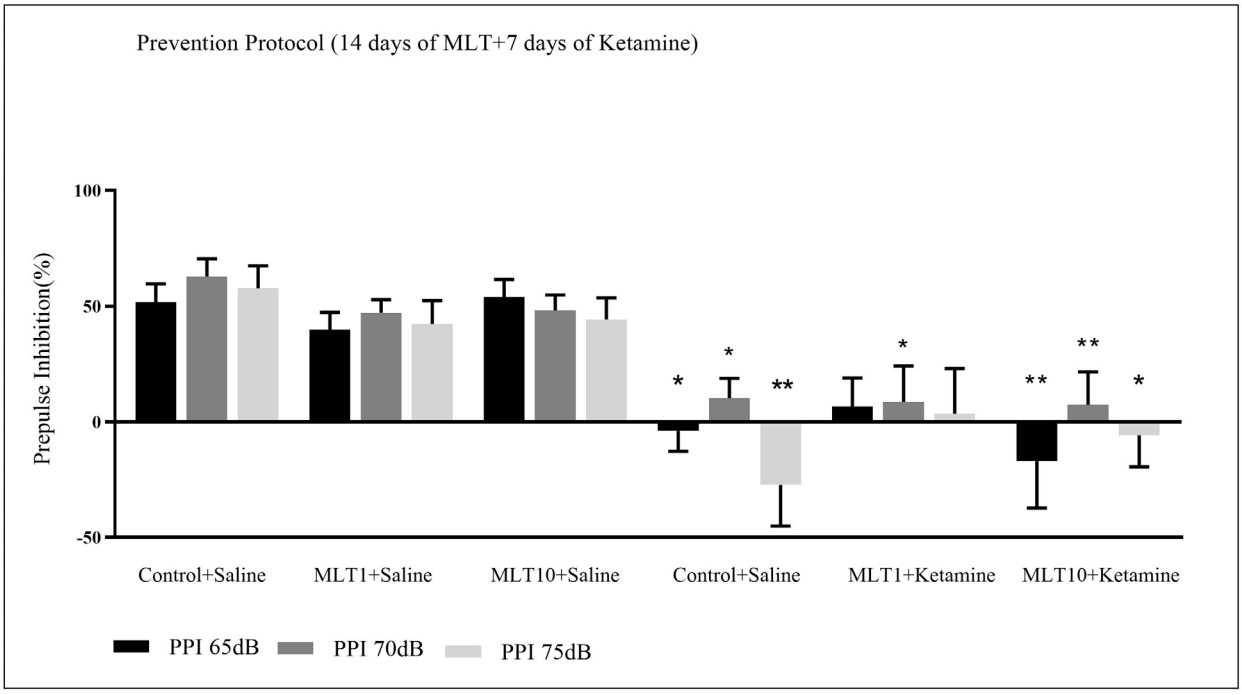

Figure 4. Effect of MLT administration (1mg/k and 10mg/kg) and/or treatment with ketamine (25mg/kg) on the prepulse inhibition in the prevention protocol. The values are expressed as mean±SEM of 10-12 animals per group. **different from the control (*p<0.05).

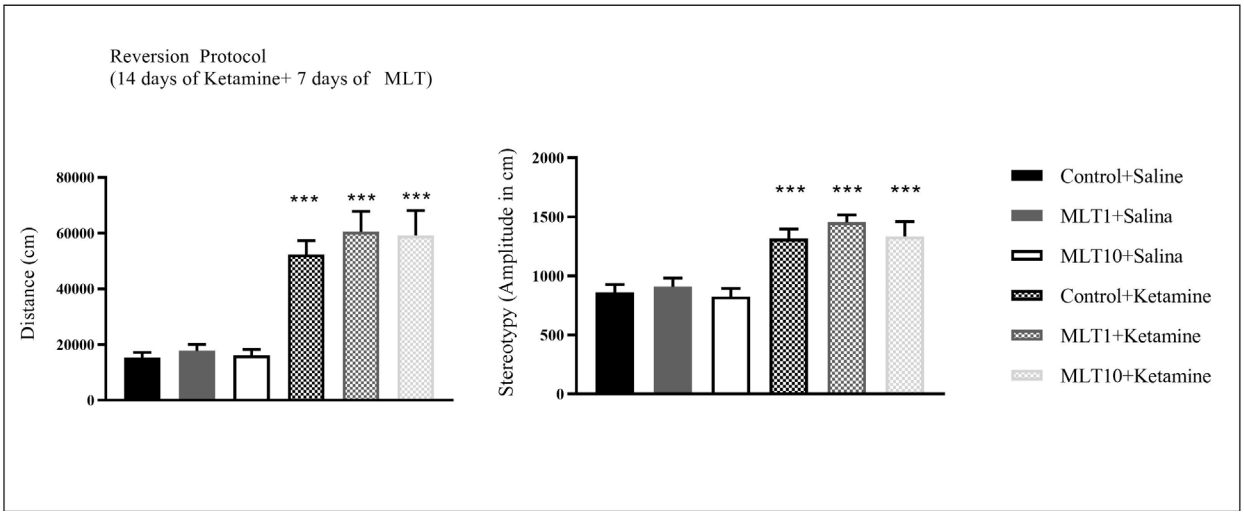

Figure 5. Effect of MLT administration (1mg/kg and 10mg/kg) and/or treatment with ketamine (25mg/kg) on locomotor activity (distance traveled and stereotypy) in the reversion protocol. The values are expressed as mean±SEM of 10-12 animals per group. **different from the control (*p<0.05).

increased stereotypic movement when compared to the control group. [F(5,60) = 11.825; p<0.05].

Length of permanence in the center and at the periphery (reversion)

Figure 6 illustrates results relating to the length of the permanence of the animals in the center [F (5,62) = 2.527; p<0.05] and at the periphery [F (5,61) = 2.111; p=0.077] of the reversion protocol. The results showed that MLT10 + Ketamine had an increase in the length of the permanence of the animals in the center [F (5,55) = 2.557; p<0.05] when compared to the control group.

Prepulse inhibition test

Figure 7 shows the results relating to the sensory and motor effects of the animals submitted to the schizophrenia model and treated with MLT that were obtained by the prepulse inhibition of the startle reflex (PPI) in the reversion protocol.

Concerning the prepulse inhibition in the intensity of (65dB) and (70dB) the ketamine group + control presented a decrease in PPI when compared to the control group, which suggests that ketamine induces a deficit in the sensory-motor profile of the animals. In the intensity of (75dB), there were no significant changes [F(10,162) = 0.452; p=0.917].

DISCUSSION

In general, in both protocols, the results of this research reveal that ketamine administration at subanesthetic doses had effects on the locomotor activity of the animals, demonstrated by increased locomotion and stereotypic movements, increased length of permanence in the center and decreased length of permanence at the periphery, which suggests an increase in the locomotor activity indexes. These results corroborate previous researches of our laboratory, which also revealed that ketamine administration (25mg/kg) in rats induced a similar behavior to those observed in schizophrenia patients. This evidence reinforces the relevance of this animal model in the study of schizophrenia (Zugno et al. 2014). The effect of ketamine is explained by the fact that it is an NMDA antagonist receptor and it is known that the glutamatergic system is integrated

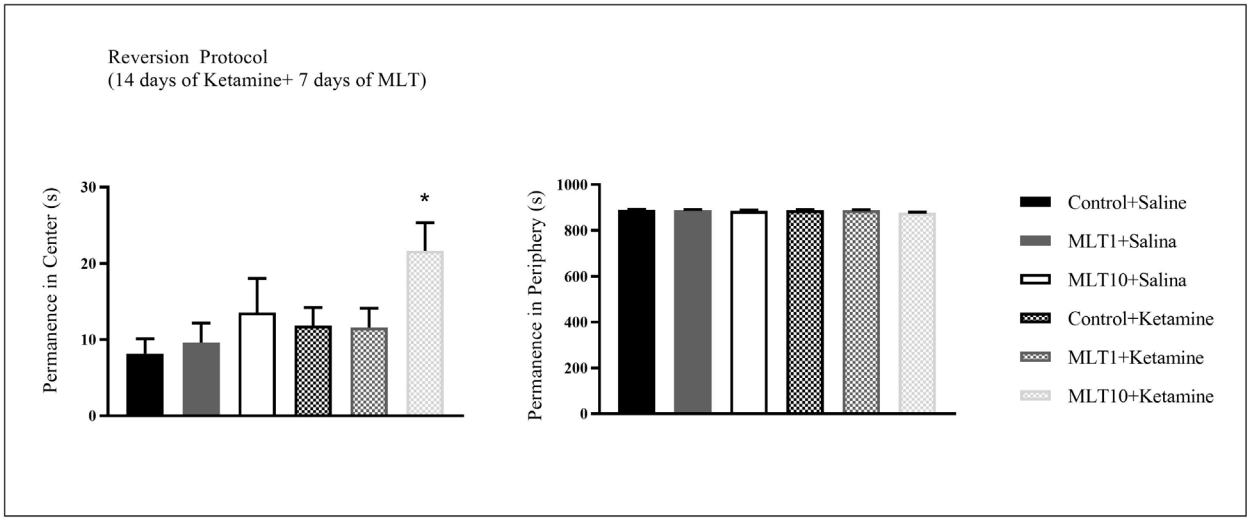

Figure 6. Effect of ketamine administration (25mg/kg) and/or treatment with MLT (1mg/kg and 10mg/kg) on locomotor activity (length of permanence in the center and at the periphery) in the reversion protocol. The values are expressed as mean±SEM of 10-12 animals per group. *different from the control (*p<0.05).

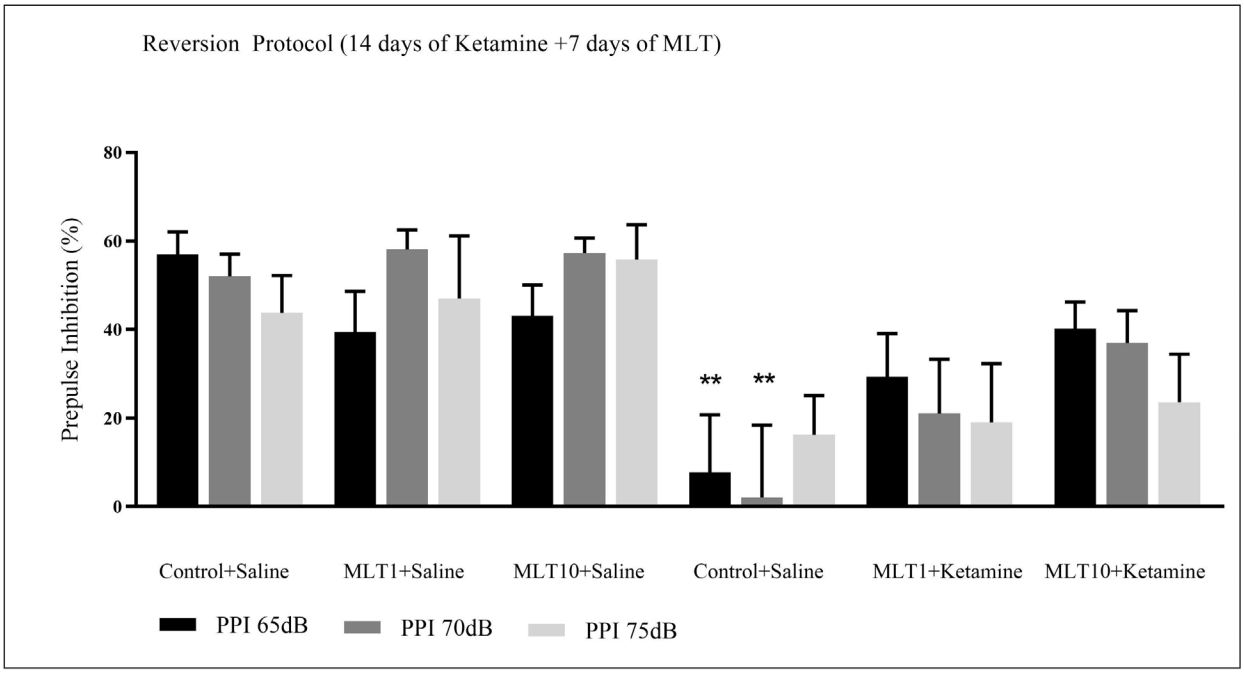

Figure 7. Effect of ketamine administration (25mg/kg) and/or treatment with MLT (1mg/kg and 10mg/kg) on the prepulse inhibition in different rat brain structures in the reversion protocol. The values are expressed as mean±SEM of 10-12 animals per group. **different from the control (*p< 0.05).

into the dopaminergic system, presenting large interactions in the Central Nervous System (CNS). Researches in animal models reveal that the administration of NMDA antagonist receptors also produces a hyperdopaminergic state in the mesocortical pathway, which is associated to the positive symptoms of schizophrenia, such a hyperlocomotion (Chaves et al. 2009).

Melatonin is known to exert an anti-excitatory effect on the brain, as demonstrated by its anticonvulsant actions that are linked to a facilitating role of melatonin on g-aminobutyric acid (GABA) transmission. An enhanced GABAergic transmission directly counteracts the influence of ketamine on glutamate and dopamine (Cardinali et al. 2008), this results in a reversal of hyperlocomotion. A recent study by Onaolapo et al. (2017) attests to these hypotheses. In this study, administration of melatonin at a dose of 5mg / kg and 10mg / kg administered for 14 days was able to reverse ketamine hyperlocomotion. However, in our study, using a similar protocol, MLT was unable to prevent/reverse ketamine-induced effects at any of the doses tested. These contrasts show that further studies in this area are needed to evaluate the actual effect of melatonin and its mechanisms.

Stereotyped behaviors are characteristic of psychiatric disorders such as schizophrenia and obsessive-compulsive disorder (Ridley 1994), and consist of various types of abnormal movements. It was shown that ketamine-induced an increase in stereotypic movements in the two protocols when compared to the control group. Although many studies demonstrate the beneficial effect of MLT in many diseases, in this study MLT was not capable of preventing or reversing the motor effects induced by ketamine in both protocols. However, MLT10 increased these effects significantly in rats which received MLT10 + saline subjected to the prevention protocol, possibly because of the anxiolytic effects of this hormone observed in some researches (Emilia et al. 2014). Some studies

reveal that MLT increases the activity of D_1 and D_2 dopamine receptors (Binfaré et al. 2010) and decreases the activity of norepinephrine receptors (Mitchell & Weinshenke 2010). MLT10 may have provoked an increased dopaminergic release and generated alterations in stereotypic movements in this neurotransmission system. These results corroborate research made by Adejoke et al. (2017), which showed that MLT5mg/kg had a beneficial effect on grooming in rats and this effect was not manifested in MLT10mg/kg. However, more studies are necessary to clarify this effect, as available evidence is insufficient to support this finding.

Perceptual and attention deficits have been observed in schizophrenia and may be related to a malfunction of the neuronal mechanisms that filter the sensory information of the environment (McGhie & Chapman 1961). Pre-pulse inhibition, in turn, is related to the symptoms of schizophrenia, as thought and distraction disorder (Turetsky et al. 2007). It is assumed that sensorimotor deficits lead to excessive overgrowth of the upper brain, resulting in cognitive disturbances and, finally, in psychosis (Perry et al. 1999). The results of our research, evaluating the PPI in three different intensities of 65, 70 and 75dB, showing that ketamine decreased the PPI in the intensities of 65dB, 70dB and 75dB in the prevention protocol; and at the intensities of 65dB and 70dB, in the reversal protocol. These results suggest that ketamine can alter this parameter.

The access to sensory-motor suppression and operational measures of PPI became an important tool for a better understanding of information-processing deficits and related disturbs (Braff et al. 2001), such as an abnormal decrease in PPI in schizophrenia patients (Caine et al. 1992). Animal models of PPI induced by dopamine agonists and NMDA antagonists have been proposed as having a good predictive validity for antipsychotic medication development and research on the etiology of psychotic disorders (Kilts 2001).

The beneficial effects of a chronic administration of MLT on the PPI and sensory-motor deficits can be explained by dopaminergic and serotoninergic mechanisms. MLT binding sites have been found in some brain regions, such as the striatum and the limbic system, which are rich in dopaminergic content (Zisapel et al. 1983). There is also the hypothesis that MLT inhibits limbic dopaminergic activity. Thus, mesolimbic and mesocortical dopamine content may increase when MLT secretion decreases (Sandyk & Kay 1991, Zisapel et al. 1983). These data indicate that MLT may be essential in adjusting dopaminergic activity in some brain areas. Moreover, in rodents, whereas dopamine agonists as apomorphine cause PPI impairment, dopamine antagonists, such as haloperidol, revert this effect (Uzbay et al. 2010). However, in our study, MLT at both doses was not able to reverse and/or prevent ketamine damage. Studies with this parameter and other intensities and/or doses are required.

So, although many studies have evaluated the efficacy of MLT as a coadjutant in the treatment of schizophrenia in humans, there is still a dearth of preclinical information about its potential as a single agent. The results are still conflicting with each other and therefore more studies in animal models are necessary to understand the real effects of melatonin in schizophrenia.

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Alexandra Ioppi Zugno, Arlindo Afonso and Lara Canever conceived of the presented idea. A.Z. developed the theory and performed the computations. Gustavo Mastella, Amanda K Godoi, and Isabela Hubbe verified the analytical methods. Gustavo Mastella, Amanda K. Godoi, Isabela Hubbe, Patricia Wessler, Laura Bischoff and Alex Victor Bialecki carried out the experiment. Arlindo Afonso and Felipe Pacheco supervised the findings of this work. Alexandra Zugno, Lara Canever and Felipe Pacheco wrote the article and finalized the data analysis. All authors discussed the results and contributed to the final manuscript.