http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2018; 5(7):253-59

Research Article Doi: 10.17546/msd.433289

Effects of melatonin and agomelatine on doxorubicin induced anxiety and depression-like behaviors in rats

Hatice Aygun[1*], Serdar Savas Gul[2]

Abstract

Objective: Doxorubicin (DOX) is a chemotherapeutic agent used to treat several cancer types; however, it exhibits severe side effects in the nervous system which DOX treatment evoked neurobehavioral alterations such as anxiety and depressive-like behavior. We investigated the use of melatonin and agomelatine to prevent neurobehavioral alterations caused by DOX.

Material and Methods: Forty-nine Wistar albino rats were randomly divided into 7 groups, namely control (CON, n=7), doxorubicin (DOX, n=7), melatonin (MEL, n=7), agomelatine (AGO, n=7), melatonin + doxorubicin (MEL + DOX, n=7), agomelatine + doxorubicin (AGO + DOX, n=7) melatonin + agomelatine + doxorubicin (MEL + AGO + DOX, n=7) groups. Doxorubicin (18 mg/kg) was injected intraperitoneally (i.p) on the 5th, 6th, 7th day of the study. Animals were treated with melatonin (40 mg/kg/i.p), agomelatine (40 mg/kg/i.p), melatonin (40 mg/kg/i.p) + agomelatine (40 mg/kg/i.p), for 7 days and then doxorubicin (18 mg/kg/i.p) was injected on the 5th, 6th, 7th day. On the 8th day of the experiment, all animal evaluated open field test (OFT) and forced swim test (FST) respectively.

Results: The only DOX-treated rats exhibited the reduced exploration, grooming, and locomotor activity in the open field test and increased immobility time, reduced swimming time. Our data showed that the rats treated with DOX exhibited anxiety and depressive-like behavior. Melatonin and agomelatine treatment reduced all the parameters of DOX-induced anxiety and depressive-like behavior in rats.

Conclusions: Melatonin and agomelatine have a protective effect of against DOX-induced neurobehavioral alterations in rats.

Keywords: Doxorubicin, Melatonin, Agomelatine, Rat, Anxiety, Depression

Introduction

Cancer incidence is increasing with advancing age. It is estimated that nearly 70% of individuals over the age of 65 can get cancer by 2030 (1). Due to its persistent condition, cancer disease represents a major global health problem (2). A variety of therapeutic approaches, including antineoplastic drugs, chemotherapy, and antihormonal therapies have been used to treat cancer. Doxorubicin (DOX) is a powerful antineoplastic agent (3). The use of DOX for the treatment of various types of cancer is supported by experimental and clinical data (4,5). Although they are seen as a promising target for the development of medications, clinical and preclinical studies have shown that DOX and other antineoplastic drugs generally produce an undesirable effect in the cardiovascular system and central nervous system (6,7,8,9).

Recent animal studies revealed DOX-evoked neurobehavioral alterations such as anxiety and depression, limiting the optimization of doses in clinical trials and preclinical studies (10,11).

Agomelatine is a melatonergic M1 and M2 receptor agonist and serotonergic (5-HT2C) receptor antagonist properties (12). Agomelatine also shows a longer half-life and greater affinity for MT1 and MT2 melatonin receptors (13). Melatonin is a powerful antioxidant. In recent studies, Melatonin showed the anxiolytic effect and neuroprotective property in the experimental animal model (14,15,16).

The effect of melatonin and agomelatine against DOX-induced neurobehavioral changes has not been studied so far.

Received 12-06-2018 **Accepted** 10-07-2018 **Available Online** 30-07-2018
1 Department of Physiology Faculty of Medicine University of Gaziosmanpaşa, Tokat, TR
2 Department of Nuclear Medicine, Gaziosmanpaşa University, Faculty of Medicine, Tokat, TR
*** Corresponding Author:** Hatice Aygun **E-mail:** hatice_5aygun@hotmail.com **Phone:** +90 539 963 13 08

http://dx.doi.org/10.17546/msd.433289

Therefore, in the present study, we have investigated the possible neuroprotective effects of agomelatine alone and in combination with melatonin against DOX-induced neurotoxicity. We have determined the neurobehavioral changes (anxiety and depression), using Open Field Test (OFT) and Forced Swimming Test (FST).

Materials and Methods

Chemicals

Doxorubicin hydrochloride injection was purchased from Sandoz Pharmaceutical Industry, Turkey. Melatonin and agomelatine were commercially obtained from Sigma-Aldrich Chemicals (St. Louis, MO, USA).

Animals

Male Wistar rats (N=49; n=7 per group, aged 8-10 weeks; weighing 200–250 g, from the animal facility of the Gaziosmanpaşa University Animal Experimental Center, Tokat, Turkey, were used. The animals were housed under standard conditions of temperature (23°C±2°C) light, relative humidity (65 ± 10 %) and (12:12 h light/dark cycle) and with free access to water and food. All animals were maintained in individually ventilated Hepa filter cages. Daily health checks were carried out by the veterinarian. The animals were housed –cages for 7 days (pre-experimental period) to habituate prior to all drug injection and behavioral testing. All experimental procedures took place in the same room in which the habituation took place. Testing equipment had been installed in this room prior to the arrival of the animals. The animal room was sound-attenuated. All animal use procedures were carried out in accordance with the Regulations of Experimental Animal Administration. At the end of the experiment, all rats were killed by cervical dislocation under anesthesia. The study was approved and carried out under the strict rules structured by Institutional Animal Ethics Committee.

Experimental Design

The animals were randomly divided into seven groups of seven rats each (n=7x7):

Group I (Control) served as control groups and animals received saline for 7 days.

Group II (DOX) served as DOX groups, in which the animals received a total cumulative dose of 18 mg/kg, body weight, i.p. of DOX for 5th, 6th and 7th days.

Group III (MEL) animals received melatonin (40 mg/kg body weight, i.p.) for 7 days, dissolved in saline.

Group IV (AGO) animals received agomelatine (40 mg/kg body weight, i.p.) for 7 days, dissolved in saline.

Group V (MEL + DOX) animals received melatonin (40 mg/kg body weight, i.p.; dissolved in saline) for 7 days and were injected with DOX (cumulative dose: 18 mg/kg, i.p.) on the 5th, 6th and 7th days.

Group VI (AGO + DOX) animals received agomelatine (40 mg/kg body weight, i.p.; dissolved in saline) for 7 days and were injected with DOX (cumulative dose: 18 mg/kg, i.p.) on the 5th, 6th and 7th days.

Group VII (MEL + AGO + DOX) animals received melatonin and agomelatine (40 mg/kg body weight, i.p.; dissolved in saline) for 7 days and were injected with DOX (cumulative dose: 18 mg/kg, i.p.) on the 5th, 6th and 7th days.

Behavioral Assessment

Open Field Test

On the eighth day of the experiment, all groups were subjected to open field testing. The spontaneous locomotor activity of rats was tested on an area of 100x100 cm divided into 64 equal cuts in the open area. The movements of the animals were recorded with a video camera. Behavioral characteristics of the animals were assessed for 5 minutes on the open field. During this time, the following behavioral parameters were measured: locomotor activity (the number of squares crossed), the number of rearings and the duration of groomings. After each test, the animals were returned to their home cages, and the apparatus was cleaned with an alcoholic solution (5% alcoholic) followed by wet and dry paper towels (17).

Forced Swim Test

On the eighth day, rats were individually placed into Plexiglas cylinders (54 cm high; length, 34 cm; width 60 cm) filled with water (24.0±1 °C) to a depth of 40 cm. Test sessions were recorded by a video camera positioned directly above the cylinders (18). Rats were forced to swim for 5 min. During this time, the following behavioral parameters were measured: the time spent in immobility and swimming.

Statistical Analysis

Results are presented as the mean±standard error of the mean (SEM). The data were analyzed with One-way analysis of variance (ANOVA) used to compare key variable between groups, followed by the posthoc Tukey. Statistical significance was considered with a $p<0.05$. All statistical analyses were processed with Graph Pad Prism 7.0 software.

Results:

Open Field Test

DOX-induced anxiety-like behavior in rats was evaluated through OFT.

The DOX-treated groups and the melatonin, agomelatine, melatonin combination with agomelatine pre-co-treatment in the DOX-treated group, showed significantly decreased the number of squares crossed (Figure 1A, $p<0.001$), the number of rearings (Figure 1B, $p<0.001$), and the duration of grooming (Figure 1C, $p<0.001$) when compared to control groups (Table 1).

http://dx.doi.org/10.17546/msd.433289

The melatonin pre-co-treatment in the DOX-treated group show significantly enhanced the number of squares crossed (Figure 1A, p<0.001), the number of rearings (Figure 1B, p<0.001 and p<0.05 respectively) and the duration of grooming (Figure 1C, p<0.001) when compared to the DOX-treated group.

The agomelatine pre-co-treatment in the DOX-treated group show significantly enhanced the number of squares crossed (Figure 1A, p<0.001), the number of rearings (Figure 1B, p<0.001) and the duration of grooming (Figure 1C, p<0.001) when compared to the DOX-treated group (Table 1).

The melatonin and agomelatine combination pre-co-treatment in the DOX-treated group show significantly enhanced the number of squares crossed (Figure 1A, p<0.001), the number of rearings (Figure 1B p<0.01) and the duration of grooming (Figure 1C, p<0.001) when compared to the DOX-treated group (Table 1).

Forced Swim Test

DOX-induced depressive-like behavior in rats was evaluated through Forced FST.

The DOX-treated groups showed the significantly increased immobility time (Figure 2A, p<0.001) and decreased the swimming time (Figure 2B, p<0.001) when compared with the control group (Table 2).

The melatonin, agomelatine and melatonin combination with agomelatine pre-co-treatment in the DOX-treated group, did not show any significant changes in immobility time and swimming time when compared with the control group (Figure 2A, 2B, Table 2).

The melatonin, agomelatine and melatonin combination with agomelatine pre-co-treatment in the DOX-treated group, show significantly decreased the immobility time (Figure 2A, p<0.001; p<0.001; p<0.001 respectively) and increased the swimming time in FST (Figure 2B, p<0.01; p<0.001, p<0.001 respectively) when compared to DOX-treated groups (Table 2).

Table 1. OFT parameters show that CON (control), DOX (doxorubicin), MEL (melatonin), AGO (agomelatine). Data are presented as mean±SEM. One-way ANOVA with post-hoc Tukey test was used. (a=p<0.05, b=p<0.01, c=p<0.001) compared to the control group; (d=p< 0.05, e=p<0.01, f=p<0.001) compared to the DOX alone-treated group.

Groups	Number of squares crossed	Number of rearings	Duration of grooming
CON	85.17±2.94	21±0.89	29.5±1.52
DOX	26.5±3.64;c	5.33±0.84;c	8.66±1.02;c
MEL	90.83±2.78	22.17±1.01	30.33±1.17
AGO	89.83±4.07	23.5±0.95	31.83±1.24
MEL+DOX	57.5±3.61;c,f	8.66±0.95;c,d	18.67±0.88;c,f
AGO+DOX	6.5±3.75;c,f	10.17±1.07;c,e	20.17±0.54;c,f
MEL+AGO+DOX	62.83±3.47c,f	11.33±0.95;c,e	22.83±1.16;c,f

Table 2. FST parameters show that CON (control), DOX (doxorubicin), MEL (melatonin), AGO (agomelatine). Data are presented as mean±SEM. One-way ANOVA with post-hoc Tukey test was used. (a= p< 0.05, b=p<0.01, c=p<0.001) compared to the control group; (d= p< 0.05, e=p<0.01, f=p<0.001) compared to the DOX alone-treated group.

Groups	Immobility Time (s)	Swimming Time (s)
CON	147.3±2.57	71.5±1.97
DOX	169±1.71;c	54.5±0.88;c
MEL	139.3±3.59	75.67±3.01
AGO	136±5.27	78±3.17
MEL+DOX	142.5±2.01;f	65.17±2.28;b,e
AGO+DOX	150±1.09;f	69.33±1.78;c,f
MEL+AGO+DOX	151±1.67;f	70±1.82;c,f

http://dx.doi.org/10.17546/msd.433289

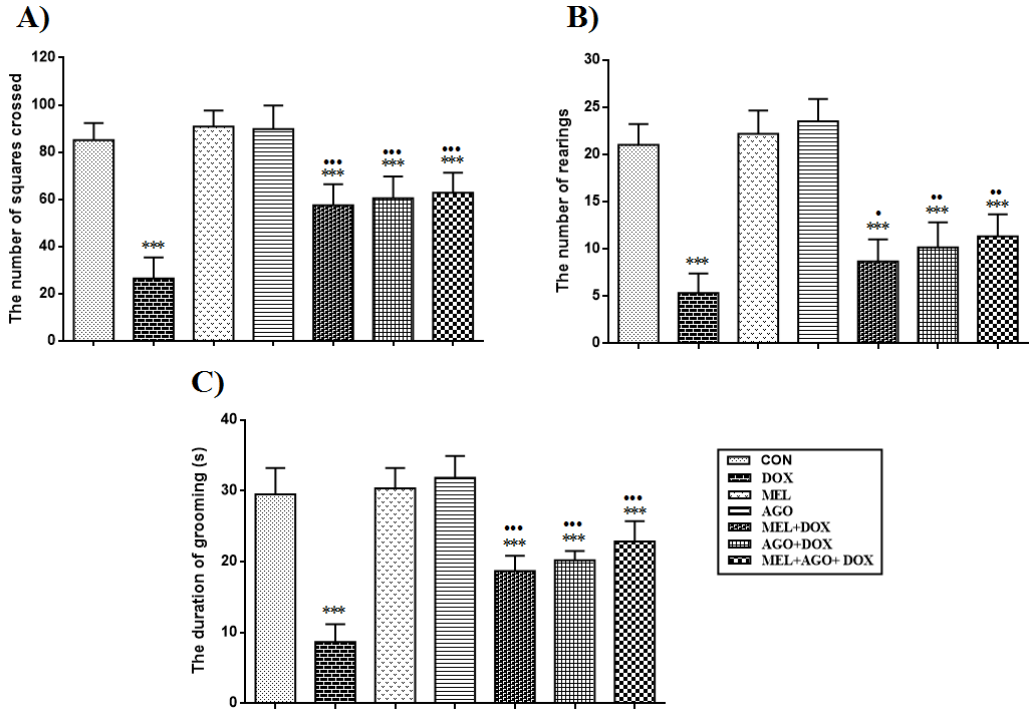

Figure 1. Melatonin and agomelatine effect on OFT parameters in DOX-pretreated rats. A) locomotor activity (the number of squares crossed) B) the number of rearings, C) the duration of groomings. Data are as mean± SEM. One-way ANOVA and Tukey test. (*=p<0.05,**=p<0.01,***=p<0.001) compared to the control group; (• =p<0.05, (•• =p<0.01), (••• =p<0.001), CON (control) compared to the DOX alone-treated group; DOX (doxorubicin), MEL (melatonin), AGO (agomelatine).

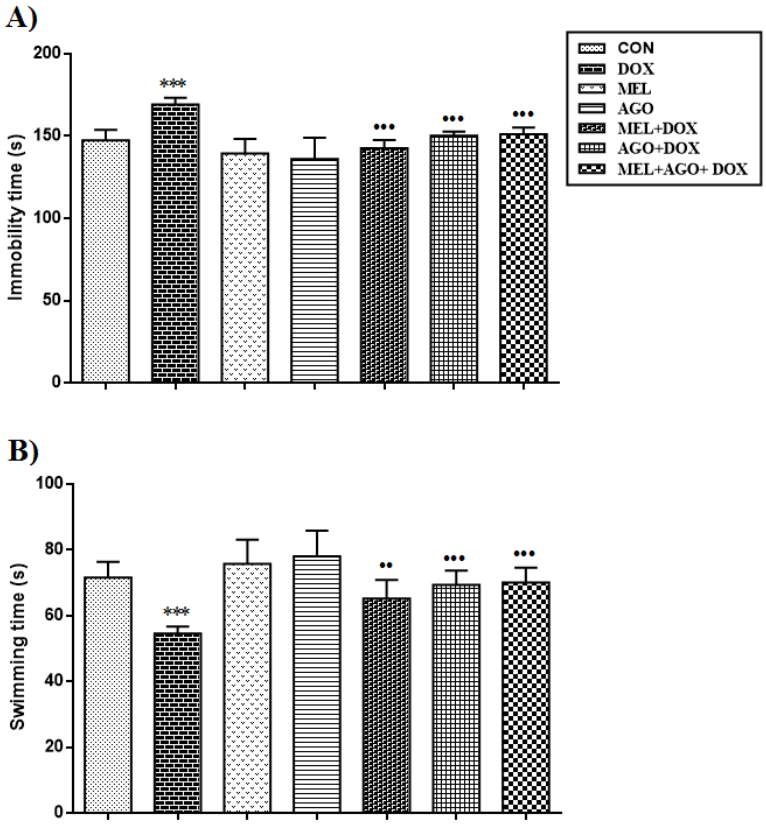

Figure 2. Melatonin and agomelatine effect on FST in DOX-pretreated rats. A) Immobility time (P < 0.05), B) swimming time. Data are as mean± SEM. One-way ANOVA and Tukey test. (*=p<0.05,**=p<0.01,***=p<0.001) compared to the control group; (• =p<0.05, (•• =p<0.01), (••• =p<0.001), CON (control) compared to the DOX alone-treated group; DOX (doxorubicin), MEL (melatonin), AGO (agomelatine).

Discussion

In the present study, it is showed that DOX injection induced the behavioral changes in anxiety and depression. Studies have shown that the affinity of agomelatine for melatonin receptor is higher than for serotonin 5-HT2C receptors. For this reason, the study was intended to compare melatonin in equal doses. Thus, we observed that whether or not there was a behavioral difference in rats when agomelatine and melatonin were administered at the same dose. Subchronic and systemic administration of agomelatine doses showed a considerable anxiolytic and antidepressive effect similar to melatonin on DOX-induced behavioral changes in rats.

OFT has been widely used to assess anxiety-like behavior in rodents. In our studies, locomotor activity (in the number of squares crossed), exploratory behavior (the number of rearings) and grooming reactions in the DOX-treated rat were lower than control rats in OFT. The decrease in locomotor activity means an increase in anxiety-like behavior. (19,20). Decreased exploratory behavior may represent an implying deficit in novelty seeking motivation, loss of interest in new situations, a symptom of anxiety and depressive disorder. Decreased number of grooming reactions seem to submissive social behavior, social neglect and maternal cannibalism, mimic a loss of interest in or pleasure from typically, a core symptom of depression (21, 22, 23, 24). The FST was chosen to test a behavioral measure of depressive-like state. Immobility time has been characterized as behavioral despair (25). In this study, treatment with the doxorubicin significantly increased immobility time and decreased the swimming time compared to control rats. According to our findings, DOX-treated rats are more anxious and depressive than control rats.

Long-term use of DOX triggers neurotoxicity and may cause neuropsychiatric diseases including anxiety and depression (26). In the OFT, DOX-treated rat showed a reduced exploratory behavior and locomotor activity. Also, it leads to the behavior changes in rats (27,28). Moreover, a single injection low dose of DOX (7 mg/kg) enhanced immobility time and decreased swimming time. Thus DOX administration could be associated with a mild depressive-like behavior.

The molecular mechanisms underlying the anxiety - depressive-like behavior in DOX-injected rats were associated with the increased brain oxidative stress and reduced total antioxidant capacity (10, 29, 30, 31, 32, 33).

Melatonin is the mainly endogenous antioxidant. It has a function to reduce the oxidative stress levels of a cell and to try to scavenge free radicals to prevent cell damage and neuronal death (34). Montilla et al. (35) found that DOX injection increased the oxidative stress, which was reduced by melatonin, in the hypothalamus and brain cortex. The antidepressant and anxiolytic effects of melatonin have been previously described in rodents subjected to the FST and OFT (36,37). In the present study, we demonstrated that an increase depressive-like behavior (significant increase immobility time and decreased swimming time) and anxiety-like behavior (significant decrease locomotor activity, exploratory behavior, and grooming reactions) in following DOX administration was significantly prevented by melatonin.

Agomelatine is a new antidepressant drug, an agonist at MT1, MT2 receptors, and antagonist at 5-HT2C receptors was the first melatonin receptor ligand showing antidepressant-like activity in animal drug screening tests (38). The affinity of agomelatine for the 5-HT2C receptor is in the micromolar range and about 100-fold less than its affinity for melatonin receptors (13). Melatonin receptors are involved in mediating anhedonic- and anxiety-like behaviors (39). Our findings demonstrate that agomelatine attenuates the DOX-related anxiety and depressive-like behavior. The repressive effect of agomelatine on the DOX-induced behavioral changes in rats was found to be similar to that of melatonin. The results of the present study point out that the antidepressant effect of agomelatine may have been by antioxidant activity. As a result, agomelatine treatment may be helpful in managing depression and showed strong efficacy in the various animal depression model (40,41). Also, it should be considered that in many studies, agomelatine might modulate depression-induced lipid peroxidation and pro-inflammatory cytokines in the brain, kidney, and liver (42,43,44). However, agomelatine stimulates cytokine production in the kidney (44).

Conclusion

The present study demonstrates that melatonin and agomelatine treatment was able to reduce DOX-induced anxiety and depressive-like behavior evaluated in the OFT and FST. Thus, the antidepressant drugs must provide therapeutic potential without the risk of adverse effects, making it a valuable tool for the treatment of depression related to the use of antineoplastic drugs.

Acknowledgments, Funding: None

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: HA, SSG: Research concept and design, data collecting, analysis and interpretation of data. **HA:** Preparation of article and revisions. All authors approved the final version of the manuscript,

Ethical issues: All Authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Pal SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clin Oncol Off J Am Soc Clin Oncol 2010; 28: 4086–4093.

2. Davison SN, Jhangri GS. The relationship between spirituality, psychosocial adjustment to illness, and health-related quality of life in patients with advanced chronic kidney disease. J Pain Symptom Manag 2013; 45: 170–178.

3. Quiles JL, Huertas JR, Battino M, Mataix J, Ramirez-Tortosa MC. Antioxidant nutrients and adriamycin toxicity. Toxicology 2002; 180: 79–95.

4. Booser DJ, Hortobagyi GN. Anthracycline antibiotics in cancer therapy. Focus on drug resistance. Drugs 1994; 47: 223-58.

5. Cutts SM, Swift LP, Rephaeli A, Nudelman A, Phillips DR. Sequence specificity of adriamycin-DNA adducts in human tumor cells. Mol Cancer Ther 2003; 2: 661–670.

6. Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. Neuropsychol Rev 2008; 18: 121–131.

7. Carvalho C1, Santos RX, Cardoso S, Correia S, Oliveira PJ, Santos MS, Moreira PI Doxorubicin: the good, the bad and the ugly effect. Curr Med Chem 2009; 16: 3267–3285.

8. Jansen CE, Dodd MJ, Miaskowski CA, Dowling GA, Kramer J. Preliminary results of a longitudinal study of changes in cognitive function in breast cancer patients undergoing chemotherapy with doxorubicin and cyclophosphamide. Psychooncology 2008; 17: 1189–1195.

9. Kwatra M, Kumar V, Jangra A, Mishra M, Ahmed S, Ghosh P, Vohora D, Khanam R. Ameliorative effect of naringin against doxorubicin-induced acute cardiac toxicity in rats. Pharm Biol 2016; 54: 637–647.

10. Merzoug S, Toumi ML, Boukhris N, Baudin B, Tahraoui A. Adriamycinrelated anxiety-like behavior, brain oxidative stress and myelotoxicity in male Wistar rats. Pharmacol Biochem Behav 2011; 99: 639–647.

11. Merzoug S, Toumi ML, Tahraoui A. Quercetin mitigates adriamycin-induced anxiety-and depression-like behaviors, immune dysfunction, and brain oxidative stress in rats. Naunyn Schmiedebergs Arch Pharmacol 2014; 387: 921–933.

12. Demyttenaere K. Agomelatine: a narrative review. Eur Neuropsychopharmacol 2011; 4: 703–709.

13. Delagrange P, Boutin JA. Therapeutic potential of melatonin ligands. Chronobiol Int 2006; 23: 413–418.

14. Aygun H, Aydin D, Inanir S, Ekici F, Ayyildiz M, Agar E. The effects of agomelatine and melatonin on ECoG activity of absence epilepsy model in WAG/Rij rats. Turkish J Biology 2015; 39: 904-910.

15. Leeboonngam T, Pramong R, Sae Ung K, Govitrapong P, Phansuwan Pujito. Neuroprotective effects of melatonin on amphetamine-induced dopaminergic fiber degeneration in the hippocampus of postnatal rats. J Pineal Res 2017; 64: 1-19.

16. Gomaa AM, Galal HM, Abou-Elgait AT. Neuroprotective effects of melatonin administration against chronic immobilization stress in rats. Int J Physiol Pathophysiol Pharmacol 2017; 9: 16–27.

17. Sáenz JCB, Villagra OR, Trías JF. Factor analysis of forced swimming test, sucrose preference test and open field test on enriched, social and isolated reared rats. Behav Brain Res 2006; 169: 57–65.

18. Molina-Hernández M, Tellez-Alcántara NP, Garcí JP, Lopez JIO, Jaramillo MT. Synergistic interaction between ketoconazole and several antidepressant drugs with allopregnanolone treatments in ovariectomized Wistar rats forced to swim. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 1337–1345.

19. Sarkisova KY, Midzianovskaia IS, Kulikov MA. Depressive-like behavioral alterations and c-fos expression in the dopaminergic brain regions in WAG/Rij rats with genetic absence epilepsy. Behav Brain Res 2003; 144: 211-226.

20. Sarkisova KY, Kulikov MA. Behavioral characteristics of WAG/Rij rats susceptible and non-susceptible to audiogenic seizures. Behav Brain Res 2006; 166: 9–18.

21. Willner P, Mitchell PJ. The validity of animal models of predisposition to depression. Behav Pharmacol 2002; 3: 169–188.

22. Kalueff AV, Lou YR, Laaksi I, Tuohimaa P. Increased anxiety in mice lacking vitamin D receptor gene. Neuroreport 2004; 15: 1271–1274.

23. Kalueff AV, Lou YR, Laaksi I, Tuohimaa P. Abnormal behavioral organization of grooming in mice lacking the vitamin D receptor gene. J Neurogenet 2005; 19: 1–24.

24. Zou J, Minasyan A, Keisala T, Zhang Y, Wang JH, Lou YR, Kalueff A, Pyykkö I, Tuohimaa P. Progressive hearing loss in mice with a mutated vitamin D receptor gene. Audiol Neurootol 2008; 13: 219–230.

25. Lopez-Rubalcava C, Lucki I. Strain differences in the behavioral effects of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology 2000; 22: 191–199.

26. Rocha PDSD, Campos JF, Nunes-Souza V, Vieira MDC, Boleti APA, Rabelo LA, Dos Santos EL, de Picoli Souza K. Antioxidant and protective effects of schinus terebinthifolius raddi against doxorubicin-induced toxicity. Appl Biochem Biotechnol 2017; 184: 869-884.

27. Konat GW, Kraszpulski M, James I, Zhang HT, Abraham J. Cognitive dysfunction induced by chronic administration of common cancer chemotherapeutics in rats. Metab Brain Dis 2008; 23: 325–333.

28. Liedke PE, Reolon GK, Kilpp B, Brunetto AL, Roesler R, Schwartsmann G. Systemic administration of doxorubicin impairs aversively motivated memory in rats. Pharmacol Biochem Behav 2009; 94: 239–243.

29. Joshi G, Sultana R, Tangpong J, Cole MP, St Clair DK, Vore M, Estus S, Butterfield DA. Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: insight into chemobrain. Free Radic Res 2005; 39: 1147-1154.

30. Joshi G, Hardas S, Sultana R, St Clair DK, Vore M, Butterfield DA. Glutathione elevation by gamma-glutamyl cysteine ethyl ester as a potential therapeutic strategy for preventing oxidative stress in brain mediated by in vivo administration of adriamycin: implication for chemobrain. J Neurosci Res 2007; 85: 497–503.

31. Tangpong J, Cole MP, Sultana R, Joshi G, Estus S, Vore M, St Clair W, Ratanachaiyavong S, St Clair DK, Butterfield DA. Adriamycin-induced TNF-α-mediated central nervous system toxicity. Neurobiol Dis 2006; 23: 127–139.

32. Tangpong J, Cole MP, Sultana R, Estus S, Vore M, St Clair W, Ratanachaiyavong S, St Clair DK, Butterfield DA. Adriamycin-mediated nitration of manganese superoxide dismutase in the central nervous system: insight into the mechanism of chemobrain. J Neurochem 2007; 100: 191–201.

33. Dubovický M. Neurobehavioral manifestations of developmental impairment of the brain. Interdiscip Toxicol 2010; 3: 59–67.

34. Bains JS, Shaw CA. Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. Brain Res Rev 1997; 25: 335-358.

35. Montilla P, Tunez I, Munoz MC, Soria JV, Lopez A. Antioxidative effect of melatonin in rat brain oxidative stress induced by adriamycin. Rev Esp Fisiol 1997; 53: 301–305.

36. Hill MN, Brotto LA, Lee TT, Gorzalka BB. Corticosterone attenuates the antidepressant-like effects elicited by melatonin in the forced swim test in both male and female rats, Prog. Neuro-Psychopharmacol. Biol Psychiatry 2003; 27: 905–911.

37. Micale V, Arezzi A, Rampello L, Drago F. Melatonin affects the immobility time of rats in the forced swim test: the role of serotonin neurotransmission. Eur Neuropsychopharmacol 2006; 16: 538–545.

38. Overstreet DH, Pucilowski O, Retton MC, Delagrange P, Guardiola-Lemaitre B. Effects of melatonin receptor ligands on swim test immobility. Neuroreport 1998; 9: 249-253.

39. Liu J, Clough SJ, Dubocovich ML. Role of the MT1 and MT2 melatonin receptors in mediating depressive and anxiety-like behaviors in C3H/HeN mice. Genes Brain Behav 2017; 16: 546-553.

40. Dagyte G, Luiten PG, De Jager T, Gabriel C, Mocaër E, Den Boer JA, Van der Zee EA. Chronic stress and antidepressant agomelatine induce region-specific changes in synapsin I expression in the rat brain. J Neurosci Res 2011; 89(10): 1646-1657.

41. Reagan LP, Reznikov LR, Evans AN, Gabriel C, Mocaër E, Fadel JR. The antidepressant agomelatine inhibits stress-mediated changes in amino acid efflux in the rat hippocampus and amygdala. Brain Res 2012; 1466: 91-98.

42. Andreasson A, Arborelius L, Erlanson-Albertsson C, Lekander M. A putative role for cytokines in the impaired appetite in depression. Brain Behav Immun 2007; 21: 147–152.

43. Cyranowski JM, Marsland AL, Bromberger JT, Whiteside TL, Chang Y, Matthews KA. Depressive symptoms and production of proinflammatory cytokines by peripheral blood mononuclear cells stimulated in vitro. Brain Behav Immun 2007; 21:229–237.

44. Demirdaş A, Nazıroğlu M, Ünal GÖ. Agomelatine reduces brain, kidney, and liver oxidative stress but increases plasma cytokine production in the rats with chronic mild stress-induced depression. Metab Brain Dis 2016; 31(6): 1445-1453.