Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2019;3(3):213-219

DOI:10.30565/medalanya.556757

Effect of Prenatal Citalopram Exposure on Motor and Cognitive Functions of Rats

Prenatal Sitalopram Maruziyetinin Sıçanların Motor ve Kognitif Fonksiyonları Üzerine Etkisi

Ayşenur Zaimoğlu[1], Bahar Akyüz[1], S.Sırrı Bilge[1]*

1.University of Ondokuz Mayıs, Medical Faculty, Department of Pharmacology, Samsun, Turkey

ABSTRACT

Aim: Physicians mostly prescribe selective serotonin reuptake inhibitors in the treatment of depression in pregnancy. However, there is little information on teratogenic effects of selective serotonin reuptake inhibitors. This study aims to investigate the effects of prenatal exposure to citalopram, one of the most prescribed antidepressants, on developmental characteristics, reflex and motor functions of rat pups.
Materials and Methods: 12-14 weeks old, pregnant Sprague-Dawley rats were used in the experiments. Rats were divided into 3 groups and separated into individual cages. When treatment groups received 5 and 20 mg/kg/d citalopram by orogastric gavage from gestational days 1 to 18, control group received the same amount of saline (2 ml/kg/d). After birth duration of gestation, number of live and dead pups and gross malformation are evaluated. Eye opening, pinna detachment, incisor eruption, the development of fur and weight gain were monitored as developmental parameters. Markers for reflex development were identified as righting reflex, negative geotaxis and grip response. Motor developments and cognitive functions were established with locomotor activity test, T-maze, holeboard, Y-maze and passive avoidance test.
Results: Developmental parameters, reflex, motor and cognitive development assessments of pups were not significantly different in treatment groups compared to control group.
Conclusion: The results of the study show that prenatal exposure to citalopram has no effect on motor and cognitive functions of rat offspring.

Keywords: Depression, selective serotonin re-uptake inhibitor, rat, Citalopram, teratogenity

ÖZ

Amaç: Seçici serotonin geri alım inhibitörleri gebelikte depresyon tedavisinde sıklıkla reçete edilmektedirler. Ancak bu gruptaki ilaçların teratojenik etkileriyle alakalı literatürde yeterli bilgi yoktur. Bu çalışmanın amacı; sık reçete edilen antidepresanlardan biri olan sitaloprama prenatal dönemdeki maruziyetin, sıçan yavrularının motor ve kognitif fonksiyonları üzerine etkilerinin araştırılmasıdır.
Materyal ve Metot: Deneylerde 12-14 haftalık gebe Sprague-Dawley sıçanlar kullanıldı. Sıçanlar üç gruba ayrıldı ve ayrı kafeslerde barındırıldılar. Tedavi gruplarına, 1 ila 18. günler arasında orogastrik gavaj ile 5 ve 20 mg/kg/gün sitalopram, kontrol grubuna ise aynı miktarda tuzlu su (2 ml/kg/gün) verildi. Doğumdan sonra gebelik süresi, canlı ve ölü yavru sayısı ve brüt malformasyon değerlendirildi. Gelişimsel parametre olarak göz açma, kulak kepçesinin ayrılması, kesici diş çıkması, tüylenme ve kilo alımı değerlendirildi. Righting refleks, negatif geotaksi ve grip response refleks gelişimini değerlendirmek için yapıldı. Motor gelişim ve kognitif fonksiyonların değerlendirilmesi için lokomotor aktivite testi, T-maze, holeboard, Y-maze, ve pasif sakınma testleri yapıldı.
Bulgular: Gelişimsel parametreler, refleks, motor ve kognitif gelişim açısından tedavi grubundaki sıçanlar ile kontrol grubundaki sıçanlar arasında anlamlı bir farklılık meydana gelmedi.
Sonuç: Bu çalışma ile sitaloprama maruziyetin yavrularda motor ve kognitif fonksiyonlar üzerinde değişikliğe sebep olmadığı gösterildi.

Anahtar Sözcükler: Depresyon, seçici serotonin geri alım inhibitörleri, sıçan, sitalopram, teratojenite

Recieved Date: 22.04.2019 Accepted Date: 19.06.2019 Published (Online) Date:26.10.2019

*Corresponding Author: Prof. Dr. S. Sırrı BİLGE University of Ondokuz Mayıs, Medical Faculty, Department of Pharmacology, Samsun, +905322931464, e-mail: ssbilge@omu.edu.tr +905322931464

ORCİD: 0000-0003-2878-6968

1. Introduction

It has been shown that prenatal depression is associated with premature birth risk, low birth weight and other neonatal complications [1]. In perinatal depression, pharmacological approaches are generally accepted as standard therapy and widely use. Selective serotonin reuptake inhibitors, especially citalopram and escitalopram, are commonly used in pregnancy period [2]. Many SSRIs including citalopram can cross the placenta [3].

Current data in the literature are conflicting and inconsistent as to whether SSRIs are associated with increased risk of congenital malformation [4]. It has been observed that many monoaminergic reuptake inhibitors, including citalopram fluoxetine and venlafaxine can cause developmental morphological changes that suggesting teratogenic potential [5]. The use of paroxetine in the first trimester of pregnancy has been reported to be associated with fetal anencephaly, omphalocele development, and cardiac anomalies. On the other hand, in studies conducted at the Slone Epidemiological Birth Defects Center, it was concluded that the use of SSRIs did not increase the risk of fetal heart defects, omphalocele and craniostosis [6]. In a meta-analysis, it has been found that fluoxetine and paroxetine increased the risk of major malformation, paroxetine increased cardiac malformations, but sertraline and citalopram were not associated with congenital malformations [7]. In another meta-analysis study aimed at proving the relationship between citalopram use and congenital anomalies, citalopram was not associated with major congenital malformations or cardiac malformations [1]. However, in a cohort study of 18487 pregnant women, the use of citalopram in the first trimester was associated with an increase in the musculoskeletal defect [8].

Serotonin plays an important role in healthy fetus development during embryogenesis. SSRIs cross the placenta and block the serotonin reuptake transporter, and thus prevent the free movement of serotonin. Human studies have shown that antidepressant use during pregnancy may cause congenital malformations [8]. These drugs may also cause changes in motor and cognitive functions. There are insufficient data on the effects of developmental features and cognitive functions in offsprings exposed to citalopram on prenatal period. Therefore, the aim of this study is to investigate the motor and cognitive functions of rats prenatally exposed to citalopram.

2. Materials and methods

2.1. Animals

12-14 weeks old female rats weighing 250 to 300 g were obtained from Ondokuz Mayıs University (Samsun, Turkey) vivarium. The rats were maintained in a 12-hour light/ dark cycle in constant temperature and humidity (22 °C and 60 ± 5%) allowing food and water ad libitum. The experimental procedure was approved by the Institutional Animal Care and Use Committee of the Ondokuz Mayıs University (31.03.2015, 2015/22). All procedures and protocols were performed according to the Guide for the Care and Use of Laboratory Animals (NIH Publication 865-23, Bethesda, MD, USA)

2.2. Experimental design

Fifteen female rats were assigned to three groups each containing five animals. All animals were mated with males and pregnancy was determined by the presence of sperm in vaginal smears or vaginal plug at the vaginal opening. Pregnant rats were placed in separate cages. Rats in drug groups were treated with 5 and 20 mg/kg citalopram (Sigma, St. Louis, MO, USA) between gestational days 1 and 18. Control groups received the same amount of saline (2 ml/kg/d). Drugs and saline were administered by orogastric gavage. Pregnant rats were controlled twice a day for parturition from the 18th day of gestation to delivery. The day of birth was described as postnatal day 1 (PND 1). All experiments were conducted between 9:00 and 13:00.

2.3. Physical development

Immediately after birth, each pup was weighed and examined for anatomical anomalies. Duration of gestation and the number of dead and live pups were recorded. Then numbers of offsprings were reduced to eight rat in each cage. Body weights of the pups were measured on PND 2, 4, 7, 14 and 28. In addition, pups were monitored for physical development parameters. Days of pinna detach-

ment (unfolding of external ear), opening of eyes, incisor eruption and development of fur were recorded.

2.4. Reflex development

During lactation, offsprings were tested for neuromuscular maturation and reflex development by two blind observers.

2.4.1. Righting reflex

This test was conducted between PND 2 to 6 for the evaluation of motor function and coordination [9]. Animals were put on their backs on a flat surface and the rolling time on four limbs in contact with the surface was recorded. In the case of failure within 60 seconds duration, the test was cut off and 60 s was recorded as test time. The average test time of pups born from a mother was considered the value of that group.

2.4.2. Negative geotaxis

This test was performed at PND 3, 5, 7 and 9 to assess vestibular and proprioceptive function [10]. Rats were placed upside down on a 25-degree inclined wire mesh platform. If the animals did not turn around within 180 seconds, the experiment was terminated.

2.4.3. Grip response

This test was performed between the PND 3 and 7 to evaluate muscle strength [9]. Pups were encouraged to grab a straight rod 30 cm above wood shavings with its forepaws and support their weight. Percentage of pups that were able to hang from the rod was calculated.

2.5. Cognitive development

Pups were separated by sex on PND 23. Two male pups were selected from each group and postweaning studies were continued with these pups. It was aimed to avoid possible effects of the oestrus cycle on the activity of pups. The days of experimental program for cognitive tests is shown in Table 1.

Table 1: Experimental program of cognitive tests, holeboard test and locomotor activity.

Test	Postnatal Day (PND)
T-maze	28
Holeboard	29
Y-maze	30
Locomotor activity	31
Passive avoidance	
Training session	32
Retention session	33

2.5.1. T-maze

The test was performed on PND 28. The aim of this test is to evaluate the spatial memory [11]. The maze consists of a long arm (40 cm) and two short arms (20 cm). The arms are 10 cm wide and 25 cm high. In the first phase of trial, one of the short arms was closed and rats were placed at the end of the long arm. The rats were allowed to explore the maze for 10 minutes. After the first phase they were rested in their cages for 1 hour. In the second phase, the closed short arm was opened and rats were left in the maze and the movements were observed for 2 minutes. The number of entries into each arm and the time of spending on that arm were recorded. The ratio of the number of entries into the new arm and the amount of time spent there is calculated over the number of entries into the previous arm and the amount of time spent there.

2.5.2. Holeboard test

The test was performed on PND 29. This test was used for assessing exploratory behavior [12]. The wood board was 40 X 40 cm in size and 2 cm thick. There were 16 holes of 3 cm in diameter on it. Animals were placed sequentially in the center of the board and were observed for 5 min. The head-dip count and duration of head-dipping in seconds were recorded. A head-dip is defined as disappearing of both eyes of the rat in the hole.

2.5.3. Y-maze

The test was performed on PND 30. Spatial memory performance was evaluated according to spontaneous behavior in Y-maze [13]. The Y-shaped maze consists of three arms with a length of 40 cm, a height of 13 cm and a width of 10 cm. The arms were numbered, each animal was al-

lowed to move freely for 8 minutes leaving the maze at the end of arm 1. At the end of this period, the number of times the animals entered each arm were determined. An alternation was described as entries into 3 arms consecutively. Therefore, the calculation for the number of maximum alternations was made through finding the total number of arm entries minus two. Calculation of the percentage of alternation was done with the formula: (actual alternations/maximum alternations) X100. The most significant variation between T-maze and Y-maze tests is a delay of one hour between two tests. As a result, spontaneous exploration behavior that takes place in T-maze is not related to long-term retention, but to short-term memory, with minimum support of working memory.

2.5.4. Locomotor activity

The test was performed on PND 31. The aim was to assess the musculoskeletal system of the animals and to determine whether or not there was a movement disorder. The locomotor activity device (Ugo Basile, Varese, Italy) is a closed box with a size of 39 × 28 × 26 cm and it has stainless bars on the bottom. The apparatus automatically records every horizontal movement animal makes with movement sensors on the floor. The activity of each rat was determined for 5 min.

2.5.5. Passive avoidance test

The test was performed on PND 32 and 33. Passive avoidance test is a fear-aggravated test used for evaluating learning and memory [14]. The passive avoidance system (Ugo Basile, Varese, Italy) has two compartments: light and dark, and a guillotine gate between them. The test consists of two phases. In the training phase rats were left in the light compartment. After 30 s gate was opened and when rats innately crossed the dark side, door was closed and an electric shock (0.5 mA, 3 s) was given. Thus, rats were led to associate the dark compartment with negative consequences. Rats were rested for 24 hours in their own cages before the second test phase of the trial. In test phase rats were put into the light compartment and the passive avoidance response was evaluated. It was measured by the latency to cross through the gate. The maximum latency time was set to 300 s.

2.6. Data analysis

Statistical analysis of the data was performed using GraphPad Prism (v 5.0) software (GraphPad software, USA). Tukey-Kramer post hoc test was used followed by two-way or one-way analysis of variance. The values of the experimental groups used in the table and the text were expressed as mean ± standard error (SEM). Values $p < 0.05$ were considered as significant.

3. Results

Citalopram exposure did not show any significant difference in the duration of gestation and number of pups born alive compared to control group (data not shown). There was no significant difference in the body weights of pups in 5 mg/kg/day and 20 mg/kg/day citalopram groups compared to the control group on days 2, 4, 7, 14 and 28 (Figure 1).

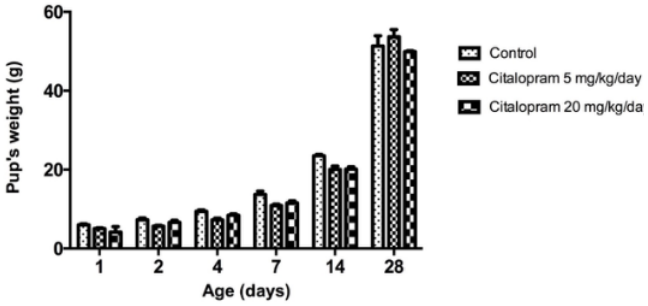

Figure. 1. Mean weight of pups during the lactation period.

Prenatal citalopram exposure was found to have no significant effect on the timing of physical features, such as pinna detachment (unfolding of external ear), opening of both eyes and ears, fur development and incisor eruption (Table 2).

Table 2: Effects of citalopram on physical maturation of the offspring of prenatally exposed rats.

Groups	Pinna detachment (days)	Incisor eruption (days)	Fur development (days)	Eye opening (days)
Control	3.7 ± 0.7	11.9 ± 0.8	8.8 ± 0.8	15.7±0.8
Citalopram 5 mg/kg	2.9 ± 0.6	11.3 ± 1	8.2 ± 0.8	15.7±0.7
Citalopram 20 mg/kg	2.8 ± 0.6	11.2 ± 0.6	8.2 ± 1	16.1±0.9

Data were expressed as means ± S.E.M.

Considering righting reflex and negative geotaxis

tests, all groups showed a decrease in time of response on the consecutive days. However, no significant difference was observed between the 5 and 20 mg/ kg/day citalopram groups compared to the control group (Figure 2 and 3).

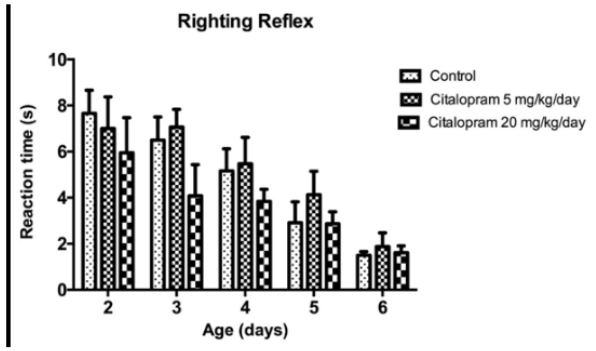

Figure. 2. Effects of prenatal citalopram exposure on righting reflex on the surface.

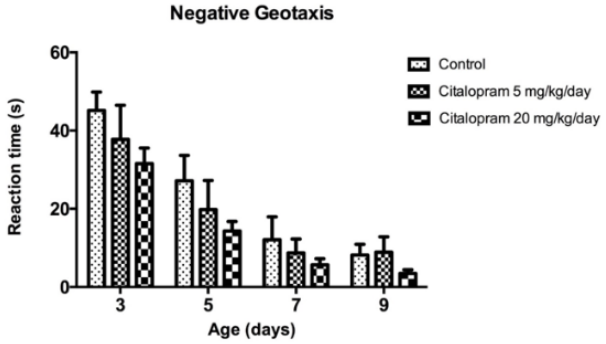

Figure. 3. Negative geotaxis in pups prenatally exposed to citalopram

In grip response test regarding to number of pups were able to hang from the rod there was no significant difference between control and drug groups. (Figure 4)

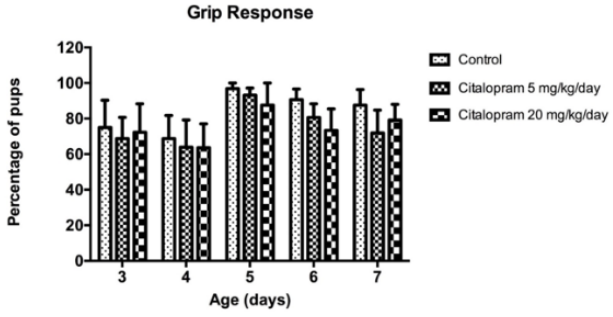

Figure. 4. Effects of prenatal citalopram exposure on grip response

Assessing of locomotor activity, explorative behavior (holeboard test) memory and learning (T-maze and passive avoidance), no significant difference was observed in rats prenatally exposed to citalopram compared to the control group (Table 3).

Table 3 : Effects of citalopram on locomotor activity, cognitive functions (T-maze, Y-maze, and passive avoidance tests), and exploratory behavior (holeboard test) of the offspring of prenatally exposed rats.

		Doses of Citalopram (mg/kg/d)		
		0	5	20
Locomotor activity	Number of move /5 min	85.7 ± 7.7	90.3 ± 4.6	89.7 ± 6.2
Y-Maze	Alternation behavior (%)	20.1 ± 3.1	17.5 ± 6.6	27.7 ± 4.4
	Number of arm entries	10.8 ± 0.5	8.1 ± 1.9	8.7 ± 1.2
T-Maze	Time spent in novel arm/time spend in previous arm (ratio)	0.54 ± 0.1	0.58 ± 0.1	0.50 ± 0.2
	Entries in the novel arm/entries in previous arm (ratio)	0.41 ± 0.16	0.59 ± 0.2	0.39 ± 0.1
Passive avoidance	Entrance latency in training session (s)	52.3 ± 4.4	57.2 ± 6.1	45.8 ± 4.6
	Entrance latency in retention session (s)	229.8 ± 13.4	230.2 ± 16.9	233.0 ± 21.5
Holeboard	Head dip (count)	12.2 ± 0.6	13.2 ± 0.9	13.0 ± 0.8
	Head dipping (s)	20.2 ± 6.3	23.3 ± 2.3	19.8 ± 2.4

Data were expressed as means ± S.E.M.

4. Discussion

Depression in pregnancy is a common mental disorder that affects both maternal and fetal health. SSRIs are the most commonly used group of antidepressants in pregnancy. It has been suggested that SSRIs and SNRIs used in pregnancy can be a risk factor for the developing brain because monoaminergic transmission is important for brain development and prenatal SSRI/SNRI usage can cause neurobehavioral and emotional changes on offsprings [15]. For this purpose, physical, motor and cognitive development of the offsprings that are prenatally exposed to citalopram, one of the most frequently used antidepressants in pregnancy, was investigated. However, information about the effects of SSRIs on the fetus is contradictory. Svirsky et al. observed that prenatal fluoxetine administration caused an increase in aggressive behavior during adulthood in male offspring and a delay in the development of maternal behavior in females but no significant change in exploration and memory [16]. A study of 68 children

with prenatal exposure to SSRIs compared to 98 children without prenatal exposure for 18 months using the Bayley developmental scale showed a slight decrease in the initial psychomotor score, which returned to normal after 18 months [17]. In a meta-analysis, it has been shown that the SSRI usage in the prenatal period, increases the risk of autism spectrum disorder in children [18].

Current study shows that citalopram administered rats did not show any significant difference in terms of gestation period and the number of live and dead pups compared to the control group. No significant difference was found between the control group and citalopram exposed group in terms of weight measurements at birth and in the consecutive days. In a prospective cohort study, birth weights of infants who were exposed to escitalopram were lower compared to the control group, but there was no difference in terms of preterm delivery, spontaneous abortion, stillbirth and major malformations [19].

In this study, there was no difference in the time of incisor eruption, fur development, eye opening and pinna detachment in the pups exposed to citalopram. Some studies based on prenatal antidepressant exposure in humans have found a significant association between various malformations and SSRIs, but some have also found that SSRIs do not cause major malformations [20, 21]. In a cohort study to evaluate the association between SSRI use and congenital malformation in pregnancy in Denmark, early use of SSRIs, especially citalopram and sertraline, in pregnancy increased the risk of septal defects [22]. Histopathologic examinations are necessary to determine malformation properly.

Righting reflex test to assess motor function and coordination, negative geotaxis test to assess vestibular and proprioceptive function, grip response test to assess muscle strength, locomotor activity to assess motor function and coordination were performed. There was no statistical difference between the control group and citalopram 5 and 20 mg/kg groups. In a prospective study evaluating intrauterine motor behavior of 96 fetuses exposed to SSRIs prenatally, exposure to SSRIs during pregnancy has been shown to effect motor development. Increased movement activity in SSRI-exposed group confirms the idea that serotonergic transmissions can enhance motor output and facilitate continuity of repetitive movements especially [23]. By contrast, according to a cohort study conducted by Handal et al., long-term prenatal SSRI exposure can cause delayed motor development [24].

Serotonin, which plays a role in cell division, differentiation, migration, and myelination in the early developmental period, also has regulatory effects on cognition, attention, learning, sleep, and stress response [25]. However, in this study, there was no difference between the rat pups exposed to citalopram and the pups not exposed in the hole-board, T maze, Y maze, and passive avoidance tests in which cognitive functions were examined. Contrary to our findings, Sprowles et al. showed that perinatal citalopram exposure weakens spatial memory in the Morris Water Maze test [26]. It is possible that the memory-related outcomes differ from ours because the exposure of the drug to the prenatal period is continued until the 20th postnatal day. In a different experimental study, following prenatal exposure to paroxetine, no difference was observed in rats' early developmental tasks such as social play or locomotor exploration activities. However, it has been suggested that there is a slight increase in anxiety and aggressive behavior predominantly in adult males [27]. Christensen et al. have examined mice prenatally exposed to paroxetine until adulthood. In adulthood, the majority of neurobehavioral and cognitive tests did not differ [28]. In another study, it was observed that rats exposed to prenatal fluoxetine reduced the social play behavior of the offspring during adolescence. In addition, they showed anxiety-like effects in the elevated plus maze test. In adult animals, social discovery is diminished and contact with other rats is decreased. These changes resemble the behavioral changes described in autistic rodents [29].

Some limitations must be considered. In our study we investigated the effect of prenatal citalopram exposure on motor and cognitive functions of rat offsprings. Besides, we assessed the effect of citalopram on duration of gestation, number of live births, physical development and gross malformation, if we could have done histopathological examination, we could have made clearer conclu-

sions about the teratogenic effect of the drug.

The results of animal studies are important in respect of teratogenicity. Because the degree of exposure can be controlled, motor and cognitive functions can be evaluated more clearly by experimental methods. Our study suggests that prenatal citalopram exposure does not cause a developmental disturbance in motor and cognitive functions in pups. In cases where the results of other experimental studies in animals related to congenital malformations are similar to our study, citalopram may be the preferred medication among SSRI group drugs which are commonly used in pregnancy.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Support: The funding was provided by Ondokuz Mayıs University (Project no: PYO. TIP.1904.15.024).

REFERENCES

1. Kang HH, Ahn KH, Hong SC, Kwon BY, Lee EH, Lee JS, et al. Association of citalopram with congenital anomalies: A meta-analysis. Obstet Gynecol Sci. 2017;60(2):145-53. doi:10.5468/ogs.2017.60.2.145
2. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58. PMID: 19185342
3. Heikkinen T, Ekblad U, Laine K. Transplacental transfer of citalopram, fluoxetine and their primary demethylated metabolites in isolated perfused human placenta. Bjog-Int J Obstet Gy. 2002;109(9):1003-8. doi: 10.1111/j.1471-0528.2002.01467.x
4. Byatt N, Deligiannidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatr Scand. 2013;127(2):94-114. doi:10.1111/acps.12042
5. Sloot WN, Bowden HC, Yih TD. In vitro and in vivo reproduction toxicology of 12 monoaminergic reuptake inhibitors: possible mechanisms of infrequent cardiovascular anomalies. Reprod Toxicol. 2009;28(2):270-82. doi:10.1016/j.reprotox.2009.04.005
6. Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell A. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007; 356:2675-2683. doi: 10.1056/NEJMoa067407
7. Myles N, Newall H, Ward H, Large M. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. Aust N Z J Psychiatry. 2013;47(11):1002-12. doi:10.1177/0004867413492219
8. Berard A, Zhao JP, Sheehy O. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. BMJ Open. 2017;7(1):e013372. PMID: 28082367
9. de Castro VL, Destefani CR, Diniz C, Poli P. Evaluation of neurodevelopmental effects on rats exposed prenatally to sulfentrazone. Neurotoxicology. 2007;28(6):1249-59. doi:10.1016/j.neuro.2007.06.001
10. Motz BA, Alberts JR. The validity and utility of geotaxis in young rodents. Neurotoxicol Teratol. 2005;27(4):529-33. doi:10.1016/j.ntt.2005.06.005
11. Deacon RM, Rawlins JN. T-maze alternation in the rodent. Nat Protoc. 2006;1(1):7-12. doi:10.1038/nprot.2006.2
12. Moreira EG, Vassilieff I, Vassilieff VS. Developmental lead exposure: behavioral alterations in the short and long term. Neurotoxicol Teratol. 2001;23(5):489-95. doi: 10.1016/S0892-0362(01)00159-3
13. Gue M, Bravard A, Meunier J, Veyrier R, Gaillet S, Recasens M, et al. Sex differences in learning deficits induced by prenatal stress in juvenile rats. Behav Brain Res. 2004;150(1-2):149-57. doi:10.1016/S0166-4328(03)00250-X
14. Sadek B, Khan N, Darras FH, Pockes S, Decker M. The dual-acting AChE inhibitor and H3 receptor antagonist UW-MD-72 reverses amnesia induced by scopolamine or dizocilpine in passive avoidance paradigm in rats. Physiol Behav. 2016;165:383-91. doi:10.1016/j.physbeh.2016.08.022
15. Dubovicky M, Csaszarova E, Brnoliakova Z, Ujhazy E, Navarova J, Mach M. Effect of prenatal administration of venlafaxine on postnatal development of rat offspring. Interdiscip Toxicol. 2012;5(2):92-7. doi:10.2478/v10102-012-0016-3
16. Svirsky N, Levy S, Avitsur R. Prenatal exposure to selective serotonin reuptake inhibitors (SSRI) increases aggression and modulates maternal behavior in offspring mice. Dev Psychobiol. 2016;58(1):71-82. doi:10.1002/dev.21356
17. Santucci AK, Singer LT, Wisniewski SR, Luther JF, Eng HF, Dills JL, et al. Impact of prenatal exposure to serotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes. J Clin Psychiatry. 2014;75(10):1088-95. doi:10.4088/JCP.13m08902
18. Kobayashi T, Matsuyama T, Takeuchi M, Ito S. Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis. Reprod Toxicol. 2016;65:170-8. doi:10.1016/j.reprotox.2016.07.016
19. Klieger-Grossmann C, Weitzner B, Panchaud A, Pistelli A, Einarson T, Koren G, et al. Pregnancy outcomes following use of escitalopram: a prospective comparative cohort study. J Clin Pharmacol. 2012;52(5):766-70. doi:10.1177/0091270011405524
20. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM, National Birth Defects Prevention S. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med. 2007;356(26):2684-92. doi:10.1056/NEJMoa066584
21. Vasilakis-Scaramozza C, Aschengrau A, Cabral H, Jick SS. Antidepressant use during early pregnancy and the risk of congenital anomalies. Pharmacotherapy. 2013;33(7):693-700. doi:10.1002/phar.1211
22. Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. BMJ. 2009;339:b3569. doi:10.1136/bmj.b3569
23. Mulder EJ, Ververs FF, de Heus R, Visser GH. Selective serotonin reuptake inhibitors affect neurobehavioral development in the human fetus. Neuropsychopharmacology. 2011;36(10):1961-71. doi:10.1038/npp.2011.67
24. Handal M, Skurtveit S, Furu K, Hernandez-Diaz S, Skovlund E, Nystad W, et al. Motor development in children prenatally exposed to selective serotonin reuptake inhibitors: a large population-based pregnancy cohort study. BJOG. 2016;123(12):1908-17. doi:10.1111/1471-0528.13582
25. Oberlander TF. Fetal serotonin signaling: setting pathways for early childhood development and behavior. J Adolesc Health. 2012;51(2 Suppl):S9-16. doi:10.1016/j.jadohealth.2012.04.009
26. Sprowles JL, Hufgard JR, Gutierrez A, Bailey RA, Jablonski SA, Williams MT, et al. Perinatal exposure to the selective serotonin reuptake inhibitor citalopram alters spatial learning and memory, anxiety, depression, and startle in Sprague-Dawley rats. Int J Dev Neurosci. 2016;54:39-52. doi:10.1016/j.ijdevneu.2016.08.007
27. Coleman FH, Christensen HD, Gonzalez CL, Rayburn WF. Behavioral changes in developing mice after prenatal exposure to paroxetine (Paxil). Am J Obstet Gynecol. 1999;181(5):1166-71. doi: 10.1016/S0002-9378(99)70102-X
28. Christensen HD, Rayburn WF, Gonzalez CL. Chronic prenatal exposure to paroxetine (Paxil) and cognitive development of mice offspring. Neurotoxicol Teratol. 2000;22(5):733-9. doi: 10.1016/S0892-0362(00)00099-4
29. Olivier JD, Valles A, van Heesch F, Afrasiab-Middelman A, Roelofs JJ, Jonkers M, et al. Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring. Psychopharmacology (Berl). 2011;217(3):419-32. PMID: 21487650

How to cite this article/Bu makaleye atıf için:
Zaimoglu A, Akyuz B, Bilge SS. Effect of Prenatal Citalopram Exposure on Motor and Cognitive Functions of Rats. Acta Med. Alanya 2019;3(3):213-219. doi:10.30565/medalanya.556757